The Wave of the Future:
Glioblastoma Multiforme (GBM)
and Diffusion Tensor Imaging (DTI)

Whitney Feltus, MS IV
Wake Forest School of Medicine
Gillian Lieberman, MD
Objectives

- **Our Patient**
- **Overview of GBM**
  - The basics
  - MRI Findings
  - Treatment
- **Diffusion Tensor Imaging**
  - Introduction
  - How it works
- **Diffusion Tensor Imaging for Treatment of GBM**
  - Surgery
  - Radiation
- **Post-Treatment Evaluation Using DTI**
  - Response
  - Injury
  - Progression vs Pseudopropagation
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  – Progression vs Pseudoprogression
Our Patient
Clinical Presentation

- **History of Present Illness:**
  A 63 year-old left-handed male from an outside hospital presented to the emergency department with a 1-week history of slurred speech, memory loss, and decreased concentration. All other review of systems were negative.

- **Past Medical History:** Hepatitis C, Appendectomy in (1958), Hernia repair (1985)

- **Family History:** Non-contributory

- **Social History:** The patient lives with his wife, has two children and works as a manager at manufacturing firm. He quit smoking in 2004 and denied use of alcohol

- **Physical Exam:** Vital signs were stable. There were no physical exam findings including neurological deficits.

- **Imaging:** CT scan at OSH revealed 3.8 cm mass in left frontal lobe
Our Patient

Head CT Unlabeled

C- axial CT
PACS, BIDMC
Our Patient

Head CT Labeled

4 cm circular, hypodense, intra-axial mass in the left posterior-inferior frontal lobe

Surrounding edema

Right-ward shift of septum pellucidum
Our Patient

Enhancing Mass on CT Angiogram

4 cm ring-enhancing, heterogenous mass
Our Patient
Hospital Course

– Admitted to the neurosurgery unit and started on dexamethasone for cerebral swelling and dilantin for seizure prophylaxis
– Received an MRI of the head for further evaluation of the lesion and surgical planning
– Underwent tumor resection and found to have biopsy proven glioblastoma multiforme, WHO grade IV
Objectives

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Overview of Glioblastoma Multiforme

Origins: **Rudolph Virchow**

“Father of Pathology”

German pathologist

First named gliomas in 1830’s

One of first to study brain tumors at the microscopic level

(13 October 1821 – 5 September 1902)

Image adopted from:
http://www.sciencephoto.com/image/229103/350wm/H4220150-Rudolf_Virchow_German_pathologist-SPL.jpg

Andreas M. Stark, et al. (2005)
Spongioblastoma multiforme - 1926

“It is from this group doubtless that the generally unfavorable impression regarding gliomas as a whole has been gained. It is not only the largest single group in the series...but at the same time is one of the most malignant...In the five unoperated cases, the average duration of life from the onset of symptoms was only three months, which speaks well on the whole for the average survival period of twelve months for those surgically treated.”

Lassman A, et. al. (2005)
Overview of Glioblastoma Multiforme
Classification, Epidemiology, Prognosis

**Classification:**
- Most common primary brain and glial tumor
- WHO Grade IV astrocytoma
- Highly aggressive and invasive

**Epidemiology:**
- Incidence: 2-3 cases/100,000/yr in the U.S. and Europe
- Male > Female
- 6th or 7th decade

**Prognosis:**
- Dismal
- Survival
  - Median: 14 months with treatment
  - 5-year: 3%
- Poor Prognostic Indicators:
  - Older age
  - Histological features
  - Poor Karnofsky performance status
  - Unresectable tumors
  - Unmethylated MGMT promoter

Overview of Glioblastoma Multiforme
Clinical Presentation

**Signs/Symptoms**
- Headache, seizures, focal neurological deficits

**Tumor Location**
- Cerebral hemispheres (Temporal lobe)
- Bihemispheric → across corpus callosum
Overview of Glioblastoma Multiforme

Clinical Presentation

### Table 1
Tumor location in 267 adult patients with GBM

<table>
<thead>
<tr>
<th>Tumor location</th>
<th>n = 267</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supratentorial</td>
<td>265</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>70</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>46</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>23</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>9</td>
</tr>
<tr>
<td>Multilobular</td>
<td>117</td>
</tr>
<tr>
<td>Infratentorial</td>
<td>2</td>
</tr>
<tr>
<td>Brain stem</td>
<td>2</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>0</td>
</tr>
</tbody>
</table>

### Table 2
Initial symptoms

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>n = 267</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemiparesis</td>
<td>109</td>
</tr>
<tr>
<td>Signs of increased intracranial pressure</td>
<td>92</td>
</tr>
<tr>
<td>Aphasia</td>
<td>86</td>
</tr>
<tr>
<td>Seizures</td>
<td>54</td>
</tr>
<tr>
<td>Neuropsychological deficits</td>
<td>53</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>41</td>
</tr>
<tr>
<td>Ataxia</td>
<td>24</td>
</tr>
<tr>
<td>Cranial nerve dysfunction</td>
<td>24</td>
</tr>
<tr>
<td>Dizziness</td>
<td>24</td>
</tr>
<tr>
<td>Others</td>
<td>12</td>
</tr>
<tr>
<td>None (= incidental)</td>
<td>5</td>
</tr>
</tbody>
</table>
Overview of Glioblastoma Multiforme

Cell Biology: Glial Cells

Glial cell
Support cells in the brain and maintain homeostasis

Table 2–2 Nomenclature and Principal Functions of Glial Cells.

<table>
<thead>
<tr>
<th>Glial cells</th>
<th>Oligodendrocytes</th>
<th>Microglial cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macroglia</td>
<td>Myelin formation in CNS</td>
<td>Immune surveillance of the CNS</td>
</tr>
<tr>
<td></td>
<td>Regulate ionic environment; reuptake of neurotransmitters; guidance of growing axons</td>
<td></td>
</tr>
<tr>
<td>Astrocytes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microglia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Image adopted from:
Overview of Glioblastoma Multiforme

Cell Biology: Astrocytes

Astrocytes

Types:
- Protoplasmic: delicate, branched, in gray matter
- Fibrous: contain glial fibrils, usually not branched

Location:
- Surround blood vessels and overlay surface of the brain below the pia

Function:
- Structural support for blood brain barrier formed by vessels
- Ion balance (K+) in extracellular space
- Role in neurotransmission?
- Repair

Waxman SG. (2010)
Overview of Glioblastoma Multiforme:
Pathology

Heterogeneous Patterns:
Variable micro- and macroscopic findings from one area of the tumor to the next
Overview of Glioblastoma Multiforme

Pathology: **Gross Anatomy**

- **Gross Anatomy**
  - Firm & white
  - Soft & yellow (necrosis)
  - Cystic degeneration
  - Hemorrhage

Image adopted from: http://library.med.utah.edu/WebPath/jpeg5/CNS136.jpg

Saunders W B. (2009)
Overview of Glioblastoma Multiforme

Pathology: Microanatomy

- Poorly differentiated
- Polymorphic
- Elongated/irregular
- Hyperchromatic nuclei
- Eosinophilic

Vascular proliferation and pseudopalisading necrosis separates GBM from anaplastic astrocytoma


Saunders W B. (2009)
Overview of Glioblastoma Multiforme

Pathology: Microvascular and Endothelial Proliferation

• Hypoxia induces production of VGEF
• Cells pile up and bulge into lumen of vessels (Tufts)
• Tufts form glomeruloid body (black arrows)

Image adopted from:

Saunders W B. (2009)
Overview of Glioblastoma Multiforme

Pathology: Necrosis

- Hypercellularity and rapid cell turn-over
- Cells along margin of necrotic tumor form pseudopalisades
  - Palisade = fence or row of wooden poles
  - Pseudopalisade = elongated nuclei gathered in a row due to necrosis

Saunders W B. (2009)
Overview of Glioblastoma Multiforme

Pathology: Glial Fibrillary Acidic Protein

- Intermediate filament (IF) of cells expressed in the CNS and elsewhere
- Function:
  - May play role in maintaining structure and shape of astrocytes (Eng et al. (2000))
  - Cell communication
  - Mitosis?
- Good marker for GBM

Saunders W B. (2009)
Overview of Glioblastoma Multiforme

Pathogenesis: Molecular Genetics

- **Gene Amplification:**
  - MDM2
    - Inhibitor of p53
  - Epidermal growth factor receptor (EGFR)
    - Stimulation and growth of tumor cells by:
      » Inc tyrosine kinase activity, activation of RAS and PI-3 kinase pathways

- **MGMT (DNA repair gene)**
  - May have methylation of promoter gene
  - Alters responsiveness to DNA alkylating chemotherapy drugs

Saunders W B. (2009)
Overview of Glioblastoma Multiforme

The Diagnosis and Evaluation of GBM Using Magnetic Resonance Imaging (MRI)
Overview of Glioblastoma Multiforme

MRI: An Overview of Magnetic Resonance Imaging

- MRI is the standard for characterizing brain lesions
  - Gadolinium contrast allows better visualization of active lesions
    - GBM is an aggressive tumor that causes breakdown of the blood brain barrier (BBB)
    - Disruption of the (BBB) allows contrast to leak into tissues
    - Higher grade tumors have a higher degree of enhancement

- Advanced uses:
  - Functional, hemodynamic, metabolic, cellular, cytoarchitectural alterations
  - Tumor grade using and cellularity using diffusion sequences
  - Staging & Prognosis
  - Evaluate treatment response and tumor progression

Cha s, et al. (2006). Update on Brain Tumor Imaging: From Anatomy to Physiology.
Overview of Glioblastoma Multiforme

MRI: MRI vs CT

MRI gives:

- better visualization of cellular activity within the lesion
- sharper borders of tumor for more precise measurements
- increased differentiation of edema vs lesion
Overview of Glioblastoma Multiforme

MRI: T1-Weighted Imaging Overview

The Basics of T1-Weighted Imaging

Fat = hyperintense (bright)

Lesions, inflammation, fluid collections = hypointense (dark)

Overview of Glioblastoma Multiforme

MRI: A Comparison of T1-Weighted Imaging with and without Gadolinium Contrast

<table>
<thead>
<tr>
<th>MRI Sequence Type:</th>
<th>T1 Pre-contrast</th>
<th>T1 Post-contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Function</td>
<td>Assess for intratumoral hemorrhage, surrounding edema (Clark J, et al. (2012))</td>
<td>To define active lesions Can detect smaller, satellite lesions</td>
</tr>
<tr>
<td>GBM Findings</td>
<td>- Hypointense lesion - Surrounding vasogenic edema</td>
<td>- Ring-enhancing, heterogeneous lesion - Central area of necrosis</td>
</tr>
</tbody>
</table>
Overview of Glioblastoma Multiforme

MRI: T1-Weighted Imaging of Our Patient Unlabeled
Overview of Glioblastoma Multiforme

MRI: T1-Weighted Imaging of Our Patient Labeled

pre-C axial T1 MRI
PACS, BIDMC

post-C axial T1 MRI
PACS, BIDMC

3.8 cm homogeneous, hypointense mass

Ring-enhancement with central area of heterogenous enhancement

* Central area of necrosis

Satellite lesion detected

edema

* Central area of necrosis
Overview of Glioblastoma Multiforme

MRI: T1-Weighted Imaging of Our Patient

Another view of the frontal lobe lesion

pre-C sagittal T1 MRI
PACS, BIDMC
Overview of Glioblastoma Multiforme

MRI: T2-Weighted Imaging Overview

• **Basics:**
  - Water and fluid are bright on T2
  - Used to assess for edema or infiltrative tumor
    Clark, et al. (2012)

• **GBM Findings:**
  - Vasogenic edema
  - Central area of necrosis

Axial T2-Weighted MRI
PACS, BIDMC
Overview of Glioblastoma Multiforme

MRI: FLAIR (Fluid Attenuated Inversion Recovery)

- **FLAIR Basics:**
  - Inversion recovery pulse sequence
  - Nulls signal from water of CSF and maintains hyperintensity of T2
  - Improves lesion detection


- **GBM Findings:**
  - More hyperintense signaling due to higher grade of tumor
  - Surrounding vasogenic edema (hyperintense)
  - Central necrosis (hypointense) better visualized than on T2
Overview of Glioblastoma Multiforme
MRI: Diffusion Weighted Imaging

- **DWI Basics:**
  - Measures diffusibility of water molecules in and out of tissues
  - Areas of decreased diffusion will appear bright
  - Apparent Diffusion Coefficient (ADC) takes into account direction, mainly diffusion of molecules along one vector

- **GBM Findings:**
  - Increased areas of cellularity restrict diffusion of water molecules and appear bright on DWI

Overview of Glioblastoma Multiforme

MRI: MR Spectroscopy

- **Basics:**
  - Analysis of chemical composition of brain lesions
  - Used to distinguish tumors from other lesions and measure cellular activity

- **Measures:**
  - N-acetylaspartate (NAA)
    - Product of glutamate breakdown
    - Neuronal marker
    - Decreased in astrocytomas due to replacement of viable neuronal tissue by malignant cells
  - Choline
    - Component of cell membranes
    - Increased in astrocytomas due to increased cellularity
  - Creatinine
    - Maintains energy-dependent systems in the brain
    - Decreased in astrocytomas due to increased metabolism

Overview of Glioblastoma Multiforme

MRI: MR Spectroscopy Graphs in Normal Brain Tissue vs GBM

Overview of Glioblastoma Multiforme

MRI: MR Spectroscopy Example in Low-Grade Astrocytoma

Fig 4. A 59-year-old woman with right superior frontal mass initially diagnosed as low-grade astrocytoma. 
A. Axial postcontrast T1-weighted image shows an ill-defined nonenhancing mass within the right superior frontal lobe. 
B. Axial FLAIR image demonstrates homogenous T2 prolongation within the mass and a single-voxel proton-spectroscopic imaging within the center of the mass reveals a marked increase in lactate (Lac) and choline (Cho) metabolites and a decrease in N-acetylaspartate (NAA) metabolite. 
C. 3D, lactate-edited, proton spectroscopic imaging of the same tumor location confirms the presence of lactate metabolite within the tumor. Re-evaluation of the tissue specimen revealed a few mitotic figures and vascular hyperplasia, and the tumor was upgraded to anaplastic astrocytoma. 
D. Serial axial postcontrast T1-weighted images during 1-year period show emergence of subtle enhancement at the posterior surgical margin at 9-month follow-up (black arrow), which rapidly progresses into an aggressive grade IV astrocytoma (black arrow).

MR Spectroscopy Graph of Comparison Case 3

Overview of Glioblastoma Multiforme Surgery, Radiation, and Chemotherapy for the Treatment of GBM
Overview of Glioblastoma Multiforme

Treatment: Surgery

Does the extent of resection correlate with increased survival in patients with glioblastoma multiforme?
The effect of extent of resection on time to tumor progression and survival in patients with glioblastoma multiforme of the cerebral hemisphere

Methods:
• Retrospective study
• N = 92
• Measure pre- and post-operative tumor volumes
• End point: variables affecting time to tumor progression and overall survival

Results:
• Variables that had significant impact on TTP:
  • Pre-operative Karnofsky Performance Status (p<.05), chemotherapy (p<.05), percent of resection (POR) (p<.001), volume of residual disease (VRD) (p<.001)
• Variables that had significant impact on overall survival:
  • Age (p<.05), preop KPS (p = .05), postop KPS (p<.005), POR (p<.0005), VRD (p<.0001)

Overview of Glioblastoma Multiforme

Treatment: Surgery

- **EFFECT OF PERCENT OF RESECTION (POR) ON TIME TO TUMOR PROGRESSION**
- **EFFECT OF POSTOPERATIVE TUMOR VOLUME (VRD) ON TIME TO TUMOR PROGRESSION**
- **EFFECT OF PERCENT OF RESECTION (POR) ON SURVIVAL**
- **EFFECT OF POSTOPERATIVE TUMOR VOLUME (VRD) ON SURVIVAL**

A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection and survival
Lacroix M, et al. (2001)

Methods:
• Retrospective, multivariate analysis
• N = 416
• Volumetric data by MRI collected prospectively
• End point
  • Predictors of survival: age, KPS, extent of resection, degree of necrosis and enhancement on preop MRI

Results:
• Survival and extent of resection:
  • Resection $\geq 98\%$ = median survival 13 months (95% confidence interval [CI] 11.4-14.6 months)
  • Resection $< 98\%$ = median survival 8.8 months (95% CI 7.4-10.2 months; $p < 0.0001$)
• Survival and KPS:
  • KPS (0-5), and tumor necrosis on MR imaging
    • significantly longer survival in patients with lower scores (1-3) who underwent aggressive resections
    • slightly longer survival with higher scores (4-5).

Overview of Glioblastoma Multiforme

Treatment: Radiation Therapy

- **Improved survival with radiation treatment**

- **Dose : 60 Gy + 10 Gy boost**
  - 2 Gy fx 5d/wk for 6 wks

- **No benefit of whole brain radiation vs limited-volume RT**

- **No benefit of radiosurgery**
Overview of Glioblastoma Multiforme

Treatment: Chemotherapy

- East
- West
- North

Bar chart showing distribution across quarters and geographical locations.
Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Randomized, multicenter phase III trial to compare radiation therapy alone vs radiation + temozolomide

Stupp R, et al. (March 2005). NEJM

The European Organisation for Research and Treatment of Cancer (EORTC) Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada (NCIC) Clinical Trials Group

• Methods:
  – Phase III, Randomized control trial
  – N = 573 patients from 85 centers randomized with newly diagnosed biopsy proven GBM
  – Assignments:
    • Radiotherapy alone (fractionated focal irradiation in daily fractions of 2 Gy given 5 days/wk for 6 weeks for total of 60 Gy)
      – 287 patients
    • Radiotherapy + temozolomide (75 mg/m2/day, 7 days/week, for duration of radiotherapy + 6 cycles of adjuvant temozolomide 150 – 200 mg/m2 for 5 days during each 28-day cycle)
      – 286 patients

  – End Point: overall survival
Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma
Randomized, multicenter phase III trial to compare radiation therapy alone vs radiation + temozolomide
Stupp R, et al. (March 2005). NEJM

The European Organisation for Research and Treatment of Cancer (EORTC) Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada (NCIC) Clinical Trials Group

• Results
  - Median follow-up 28 months:
    • Median survival 14.6 months with radiation + temozolomide
    • Median survival 12.1 months with radiation therapy alone
  - Unadjusted hazard ratio for death in radiotherapy + temozolomide = .63 (95% CI, 0.52 to 0.75; P<.001)
  - 2-yr survival rate = 26.5 % with Concurrent therapy, 10.4 % with radiotherapy alone

Figure 1. Kaplan–Meier Estimates of Overall Survival According to Treatment Group.
The hazard ratio for death among patients treated with radiotherapy plus temozolomide, as compared with those who received radiotherapy alone, was 0.63 (95 percent confidence interval, 0.52 to 0.75; P<.001).
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Diffusion Tensor Imaging

Image adopted from:
http://4.bp.blogspot.com/_4ify7vDXrDs/TVHNmBs9bI/AAAAAAAAG_0/5P4rfZn5I60/s640/brain_2_pathways.jpg
A 2 or 3D view of white matter fiber tracks (WMT) in the brain

Uses color-coding and tractography to visualize tracts extending in multiple directions

Measures diffusion of water molecules along the white matter axis to reconstruct the image

Diffusion Tensor Imaging

Introduction: How is it used?

- Detect of brain injury
  - Ischemia vs penumbra
  - Tumor infiltration
  - Axonal degeneration
- Define anatomy
  - Localize eloquent areas of the brain
- Obtain more precise coordinates of lesions
- Evaluate for treatment response and side effects
Diffusion Tensor Imaging

Introduction: How does it work?

Basic Principles:

1. Diffusion ➔
2. Measurement ➔
3. Image reconstruction
Diffusion Tensor Imaging

1. Diffusion: Why use diffusion for imaging?

- Not affected by magnetic field of MR
- No interference with diffusion process
- High resolution imaging of deep and superficial organs

Le Bihan D, et al. (2001)
Diffusion Tensor Imaging

1. Diffusion: Why water?

- Convenient
- Easily follows white matter tracts in healthy brain
- Interact with tissue components
- Insight to structural and geometric properties of white matter tracts
- Sum of interactions in a voxel represent distribution and displacement of water molecules

Le Bihan D, et al. (2001)
Diffusion Tensor Imaging

1. Diffusion: Concepts of Diffusion

**Brownian motion**: Random movement of molecules (gas or liquid) due to collisions in surrounding medium
Movement of molecules also based on temperature or their thermal energy

**Fick’s first law of diffusion**: Diffusion occurs down the concentration gradient
Magnitude of diffusion proportional to concentration gradient

**Apparent Diffusion Coefficient (ADC)**: Represents diffusion in one direction (cm$^2$/s or mm$^2$/s); High diffusion give low signal

Water exchange (movement) occurs intra- and extracellularly in tissues
Diffusion of water limited by:
- Shape of surrounding structure
- Tissue cellularity

De Figueiredo E, et al. (2011)
Diffusion Tensor Imaging

1. Diffusion: **Isotropy vs Anisotropy**

**Isotropy:**
Diffusion of molecules **EQUALLY** distributed in all directions
- Net movement is same

**Anisotropy:**
**UNEQUAL** distribution
- Net movement is not same

* Direction of molecules (water) take into account shape of surrounding structure
* Proportional to elliptical shape (FA)

De Figueiredo E, et al. (2011)
Diffusion Tensor Imaging

1. Diffusion: Anisotropy in White Matter

Apply Brownian motion:
- Restriction of movement perpendicular to axon
  » Water will quickly collide with sides of fibers (myelin sheath and endoneurium)

Apply Ficks Principle:
- Ease of diffusion is parallel (along axis) to axon

White matter tracts are anisotropic in an ellipsoid shape
- Get linear movement (vector) of water molecules parallel to axon

De Figueiredo E, et al. (2011)
Diffusion Tensor Imaging

1. Diffusion: Anisotropy in White Matter

Diffusion is faster parallel to white matter tracts

2. Measurement of Diffusion: **Quick Definitions**

**Tensor**:
Mathematical model describing the linear relationship between vectors, scalars, and other tensors.

**Scalar**:
Real number related to vectors in space; can be multiplied to produce another vector.

**Fractional Anisotropy**:
Scalar measurement of anisotropy
- Between 0 and 1
- 0 = isotropic, 1 = diffusion along one axis and fully restricted in all other directions

Diffusion Tensor Imaging

2. Measurements: Diffusion Tensor

Diffusion ($D$) related to **direction** and **magnitude** of diffusion

**Direction = Eigenvectors**
Principle eigenvector parallel to main axis of WMT

**Magnitude = Eigenvalues** ($\lambda_1, \lambda_2, \lambda_3$)

Diffusion Tensor Imaging

2. Measurements: Eigenvalues

Eigenvalues

Used to calculate scalar measurements such as FA, $p$, $q$, $L$

1. $P =$ pure isotropic diffusion
2. $q =$ pure anisotropic diffusion
3. $L =$ magnitude of diffusion tensor

$\text{ADC} = D = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}$

$FA = \frac{3}{2} \sqrt{\frac{(\lambda_1 - \bar{\lambda})^2 + (\lambda_2 - \bar{\lambda})^2 + (\lambda_3 - \bar{\lambda})^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$

Diffusion Tensor Imaging


Apply Tensor to White Matter:
Measurement of diffusivity in at least 6 different directions (ADC’s) with same point of origin

Visualized as an ellipsoid

Represented by a 3x3 matrix of numbers (diagonalization) to:
- Estimate **diffusivity** in any direction based on diameter (uses x,y,z axis)
- Determine direction of maximum diffusivity (Diffusion Tensor)

Diffusion Tensor Imaging


Diffusion tensor proportional to strength of anisotropy (FA)

Tensor directionality related to integrity of white matter

Reduced anisotropy can be due to disruption of white matter tracts (invading tumor, radiation damage)

Image Obtained From:
http://www.sciencedirect.com/science?_ob=MiamiCaptionURL&_method=retrieve&_eid=1-s2.0-S0166223612000720&_image=1-s2.0-S0166223612000720-gr3.jpg&_ba=&_fmt=full&_orig=na&_issn=01662236&_pii=S0166223612000720&_acct=C00002969&_version=1&_urlVersion=0&_userid=582433&md5=b86a6a8085f84a5e6c1351b0b7f17cd
Mean Diffusivity (Tensor Size):
Lower signal with greater diffusivity: water molecules spread out within a given space;

FA (Tensor Shape):
Higher signal with lower diffusivity and greater flow of molecules along an axis.

Images obtained from:
Diffusion Tensor Imaging

3. Image Reconstruction: Data Acquisition

- Measurement in small voxels (1.8 x 1.8 x 3mm)
- Uses echo-planar imaging (fast acquisition)
- Pulse field gradients applied \(\rightarrow\) variation in diffusion measurements
  - Pulse field gradient = short, timed pulse with spatial-dependent field intensity
- Detect diffusion anisotropy (encoded in MRI signal)
- Only molecular displacements along direction of the gradient are visible
Diffusion Tensor Imaging

3. Image Reconstruction: Tractography

View of WMT directions in the Brain using 2D or 3D color-coded maps

- **Blue** = CST (projection or cranial-caudal)
- **Red** = corpus callosum (commissural or medial-lateral)
- **Green** = intrahemispheric (association or anterior-posterior)
Diffusion Tensor Imaging

3. Image Reconstruction: Tractography of Corpus Callosum

Fig 3. A. Illustration shows the anatomic relationships of several WM fiber tracts in the coronal plane. Circled tracts are those further illustrated in this review. The corpus callosum is “sandwiched” between the cingulum superomedially and the superior occipitofrontal fasciculus inferolaterally. The superior longitudinal fasciculus sweeps along the superior margin of the claustrum in a great arc. The inferior occipitofrontal fasciculus lies along the inferolateral edge of the claustrum. (Reproduced with permission from reference 20.)

B. Directional map corresponding to A. The paired cingula are easily identified in green (yellow arrows) just cephalad to the red corpus callosum (thick white arrow). White arrowheads indicate superior occipitofrontal fasciculus; thin white arrows, inferior occipitofrontal fasciculus. Like the corpus callosum, the commissural fibers of the anterior commissure are left-right oriented toward the midline, resulting in the characteristic red (open arrows) on this DTI map. Further lateral, the fibers diverge and mingle with other tracts; they are no longer identifiable with DTI, but can be traced with tractography.
Diffusion Tensor Imaging

3. Image Reconstruction: Tractography of Corticospinal Tract

Image Obtained From: http://www.ajnr.org/content/25/3/356.full.pdf+html
Objectives

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  – Surgery
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Diffusion Tensor Imaging for the Treatment of GBM
Our Patient: Hospital Course

The patient received a functional MRI (fMRI) and diffusion tensor imaging for neurosurgical planning.
Diffusion Tensor Imaging for GBM Treatment
Surgical Planning and Resection: **Current Practice**

- **Neuronavigation and Intraoperative MRI**
- **Benefits:**
  - Provides minimally invasive approach to tumor resection
  - More precise resection of tumor
  - Avoid critical structures or eloquent areas of the brain

Li ZX, et al. (2006).

Image obtained from: [http://www.featurefilmstory.com/brainlab1.gif](http://www.featurefilmstory.com/brainlab1.gif)
Diffusion Tensor Imaging for GBM Treatment Surgery: Is There Utility of DTI in Surgical Planning and Resection?
Clinical evaluation and follow-up outcome of diffusion tensor imaging-based functional neuronavigation: a prospective, controlled study in patients with gliomas involving pyramidal tracts
Wu Js, et al. (2007) Shanghai, China

• Methods
  – Prospective Randomized-Controlled Trial
  – 238 patients initial imaging diagnosis cerebral gliomas involving pyramidal tract randomized: Study (n = 118) and control (n=120)
  – Study underwent DTI and 3D MRI for PT mapping
  – End points: gross total resection, post-op motor deterioration, 6-month KPS, Median survival, estimated hazard ratio
Clinical evaluation and follow-up outcome of diffusion tensor imaging-based functional
neuronavigation: a prospective, controlled study in patients with gliomas involving
pyramidal tracts
Wu Js, et al. (2007) Shanghai, China

• Results
  – **Gross total resection (HGG):** Control = 33.3%, trial = 74.4 %
    (p<.001)
  – **Post operative motor deterioration:** Control = 32.8%, trial = 15.3%
    (P<.001)
  – **6-month KPS:** Control = 74 +/-28 , study = 86 +/-20 (p<.001)
    overall; 53 +/- 32 vs 77+/- 27 for HGG (P<.001)
  – **Medial survival:**
    • Control = 14 months (95% confidence interval, 10.2-17.8 mo)
      (p = .048)
    • Study (81 HGG) = 21.2 months (95% CI, 14.1-28.3 mo)
  – **Estimated hazard ratio for effect of DTI-based functional neuronavigation**
    • .57, representing 43% reduction in risk of death
Diffusion Tensor Imaging for GBM Treatment Surgery: The Role of DTI in Surgical Planning

• Preservation of eloquent areas of brain
  – Corticospinal tract
    • Ohue S, et al. (2012)
  – Language (brocas area, wernickes area, arcuate fasciculus

• Coordinates of tumor
  – Smaller craniotomy
  – More gross total resection with 3D planning

• Survival benefits??
Diffusion Tensor Imaging for GBM Treatment Surgery: The Role of DTI in Surgical Planning
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Tracks

Blue = Cranial-Caudal (Corticospinal Tract)

Green = Intrahemispheric projections (Arcuate Fasciculus)

Red = Communicating tracts between hemispheres (Corpus Callosum)

Combined fMRI for location of eloquent areas of the brain (language, motor)

3D Diffusion Tensor MRI, posterior view

PACS, BIDMC
Diffusion Tensor Imaging for GBM Treatment
Radiation Therapy

• Problem
  – Radiation side effects
    • Radiation to normal tissue
    • Radiation necrosis
      – Cognitive decline, seizures, personality changes, neurological deficits
  – Tumor progression/recurrence after treatment
    • Residual tumor cells

• Solution
  – Focus radiation to targeted lesion
  – More radiation dose to tumor and less to normal tissue
Diffusion Tensor Imaging for GBM Treatment
Is There a Role for DTI in Radiation Planning?
Diffusion Tensor Imaging: Possible Implications for Radiotherapy Treatment Planning of Patients with High-Grade Glioma

Jena R, et al. (2005)

• Methods
  – N = 7 patients with HGG
  – Compare standard planning with plans based on DTI
  – Standard plans used 2.5 cm clinical target volume (CTV) margin added to the GTV
  – DTI-based plans: CTV generated by adding 1 cm margin to the IHV (image-based high-risk volume)
  – Estimates on normal tissue complication probability (NTCP) calculated
  – End Point: Level of dose escalation that could be achieved using DTI-based plans

• Results
  – DTI use resulted in non-uniform margins added to the GTV to encompass areas at high risk tumor involvement
  – 6/7 cases: IHV encapsulated by standard CTV margin
  – DTI reduce size of planning-target volume (PTV) (mean 35%, range 18-46%) in all cases
  – Resulted in escalation does (mean 67 Gy, range 64-74) with NTCP


Image adopted from:
http://ac.els-cdn.com/S0936655505002037/1-s2.0-S0936655505002037-main.pdf?_tid=ba91d3e0-12e5-11e2-a37a-00000aacb35d&acdnat=1349879046_274507c69f9a08070c8b90335dcb4f14

Fig. 2 – Display from image registration software showing successful registration of both the fractional anisotropy map (green) and T2-weighted MRI (red) to the planning CT data set (grey).
Diffusion Tensor Imaging for GBM Treatment 
Radiation Therapy: The Role of DTI in Treatment Planning


Fig. 3 - A fractional anisotropy map has been overlaid onto a planning CT in the treatment-planning system to enable delineation of target volumes based on diffusion tensor imaging.

Fig. 4 – Planning CT showing delineation of target volumes. CTV_s, standard CTV, grown by adding a 2.5-cm margin to the GTV; CTV_i, individualised CTV, grown by adding a 1 cm margin to the IHV_DTI; GTV, gross-tumour volume. IHV_DTI, area of abnormality seen on DTI scan; note that in this case, the CTV_i coincides with the CTV_s at its maximum extent.

Image adopted from:

http://ac.els-cdn.com/S0936655505002037/1-s2.0-S0936655505002037-main.pdf?_tid=ba91d3e0-12e5-11e2-a37a-00000aacb35d&acdnat=1349879046_274507c69f9a08070c8b90335dcb4f14
Fig. 8 — The reduction in planning-target volume for the diffusion tensor imaging-based plans relative to the standard volume.


Image adopted from:
http://ac.els-cdn.com/S0936655505002037/1-s2.0-S0936655505002037-main.pdf?_tid=b91a93e0-12e5-11e2-a37a-00000abc35d&acdnat=1349879046_274507c69f9a08070c8b90335dcb4f14
Diffusion Tensor Imaging for GBM Treatment
Radiation Therapy: The Role of DTI in Treatment Planning

• DTI could provide more accurate definition of tumor margins and infiltration

• Need more randomized studies to evaluate benefits of using DTI for radiation therapy treatment planning
Objectives

- Post-Treatment Evaluation Using DTI
  - Response
  - Injury
  - Progression vs Pseudoprogression
Post-Treatment Evaluation of GBM using DTI
Overview

• What happens after treatment?
  – Response
  – Radiation-induced damage
  – Pseudoprogression
  – Progression
  – Tumor recurrence
Post-Treatment Evaluation of GBM using DTI
Response: White Matter Tracts Post-Chemotherapy

Gerstner E R, et al. (2011)

Figure 1 Tractography in a glioblastoma patient before and 4 months after receiving cediranib showing the reemergence of white-matter tracts with treatment.

Post-Treatment Evaluation of GBM using DTI

Radiation-Induced Injury: Damage to White Matter Tracts

Radiation-induced injury to white matter tracts can be assessed using DTI

Nagesh V, et al. (2008)

Image adopted from:
Post-Treatment Evaluation of GBM using DTI
Radiation-Induced Injury: Necrosis vs Tumor Progression

Progression vs Pseudoprogression

Pseudoprogression: A subacute response to radiation therapy that can present as increased enhancement or expansion of the site of the lesion on post-treatment imaging

Hygino da Cruz L, et al. (2011)
Post-Treatment Evaluation of GBM using DTI
Radiation-Induced Injury: Progression vs Pseudopropgression

Current Limitations of Imaging to Assess Necrosis vs tumor progression:

The imaging characteristics of radiation injury and tumor infiltration are similar as radiation can cause breakdown of the blood brain barrier (BBB) and leakage of contrast into the resection bed.

Hygino da Cruz L, et al. (2011)
Post-Treatment Evaluation of GBM using DTI

Radiation-Induced Injury: Progression vs Pseudoprogession

Current Limitations of Imaging to Assess Necrosis vs Progression:

There can be discoordinate findings between images and sequences.

Hygino da Cruz L, et al. (2011)

Post-Treatment Evaluation of GBM using DTI
Radiation-Induced Injury: Progression vs Pseudoprogession

Use of DTI Post-Radiation

– Correlation between primary tumor site and area of progression using water diffusion
  • Priya A, et al. (2008)
– Compare differences in ADC and fractional anisotropy

The utility of DTI for GBM post-radiation response is a topic of debate
  • Alexiou G, et al. (2009)
Summary

• Our Patient
• Overview of GBM
  – Glioblastoma Multiforme is the most common primary brain tumor
  – Very aggressive with poor prognosis
  – There are multiple MRI sequences used to diagnose and evaluate properties of the tumor
  – Surgical resection and chemoradiation therapy can prolong survival
• Diffusion Tensor Imaging
  – Model of white matter tracts
  – Can assess anatomy and damage
• Diffusion Tensor Imaging for the Treatment of GBM
  – Used in surgery planning and resection
  – Possible use in radiation planning to improve targeted therapy
• Post-Treatment Evaluation Using DTI
  – Can possibly assess response to treatment, radiation injury and progression vs pseudoprogression
Acknowledgments

- Dr. Rafael Rojas, Neuroradiology, Beth Israel Deaconess
- Dr. Gillian Lieberman, Radiology, Beth Israel Deaconess
- Dr. Michael D. Chan, Radiation Oncology, Wake Forest
- Claire Odom, Department of Radiology, Beth Israel Deaconess
References

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