Innovative Multimodal Imaging Techniques in Brain Tumor Clinical Trials

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CTSI: Neuroimaging: A Short Course on Modern Imaging Modalities in Clinical Invest.
11 April 2014
Disclosures

- MedQIA, LLC - Paid Consultant
- Genentech/Roche - Paid Consultant & Grant Support
- Tocagen - Consultant
- Amgen - Consultant
- Boston Scientific - Consultant
- ACRIN - Paid Consultant
- Siemens - Paid Consultant & Grant Support
- Celgene - Paid Consultant
- Pharmacyclics - Consultant
- National Brain Tumor Society - Paid Consultant & Grant Support
- National Institutes of Health - Grant Support
- Olea Medical - Consultant
Basics of Brain Tumor Biology
Brain Tumor Biology

- Mutations can cause protein structure alterations, resulting in a cascade of molecular changes (signaling)
- These can cause further issues and downstream effects
  - *Uncontrolled Proliferation*
  - *Metastases*
  - *Metabolic Dysfunction*
• Cancer arises from normal cells

• **Benign**
  • Non-cancerous tumor. Slow growing.
  • Can transform to a malignant tumor

• **Malignant**
  • Cancerous.
  • Invades and destroys nearby tissue and infiltrates/metastasizes
Brain Tumor Biology

Clonal Genetic Model of Cancer
Brain Tumor Biology

- WHO = World Health Organization
- **Grade:**
  - How abnormal cells look under the microscope
  - How quickly they are likely to grow or spread
  - I-IV from least to most malignant/differentiated
    - I: “Well differentiated” (low Grade)
    - II: “Moderately differentiated” (Intermediate Grade)
    - III: “Poorly differentiated” (High Grade / Malignant)
    - IV: “Undifferentiated” (High Grade / Malignant)
Brain Cancer - Gliomas

- Brain Cancer **Does Not Metastasize** *(No Staging, Only Grading)*
- Neuroblastomas & Epidemoma
- Oligodendrogliomas
  - *Oligodendroglioma (WHO II)*
  - *Anaplastic Oligodendroglioma (WHO III)*
- Astrocytomas
  - *Astrocytoma (WHO II)*
  - *Anaplastic Astrocytoma (WHO III)*
- Mixed Gliomas
  - *Astrocytoma and Oligodendroglioma*
- Glioblastoma (GBM) - WHO IV
Brain Cancer Incidence

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Malignant</th>
<th>Non-Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children (0-14)</td>
<td>3.64</td>
<td>1.50</td>
</tr>
<tr>
<td>Children (0-19)</td>
<td>3.33</td>
<td>1.93</td>
</tr>
<tr>
<td>Adults (20+)</td>
<td>8.85</td>
<td>18.53</td>
</tr>
<tr>
<td>All Ages</td>
<td>7.27</td>
<td>13.77</td>
</tr>
</tbody>
</table>

† Rates per 100,000 and age-adjusted to the 2000 United States standard population

Central Brain Tumor Registry United States, 2012

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Brain Cancer Incidence

Astrocytomas and Glioblastomas account for 75% of all gliomas

- Glioblastoma: 54.4%
- All Other Gliomas: 1.9%
- Oligoastrocytic Tumors: 3.3%
- Pilocytic Astrocytoma: 5.1%
- Anaplastic Astrocytoma: 6.0%
- Oligodendroglioma: 6.1%
- Diffuse Astrocytoma: 9.1%
- Glioma Malignant, NOS: 7.3%
- Ependymal Tumors: 6.8%

ICD-O-3 codes = 9380-9384, 9391-9460, 9480
Brain Cancer Histology

Infiltration of high-grade astrocytoma into adjacent brain tissue
Preoperative situation

- > 40 mm from tumor edge: 1:1000
- 20 - 40 mm from tumor edge: 1:100
- 20 mm brain adjacent to tumor: 1:10
- 40 mm tumor: 1:1

- 0.2% tumor cells
- 1.8% tumor cells
- 6% tumor cells
- 92% tumor cells

Ratio of tumor cells to total cells
Percentage of tumor cell population

Wilson, 1990
Cancer Phenotypes

• Key Phenotypes/Characteristics of Glioblastoma
  • Uncontrolled Proliferation (positive feedback)
Cancer Phenotypes

- Key Phenotypes/Characteristics of Glioblastoma
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  - Hypoxia (HIF-1α)
  - Invasion - Migration
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  - Vascular Proliferation - Angiogenesis
Cancer Phenotypes

• Key Phenotypes/Characteristics of Glioblastoma
  • Uncontrolled Proliferation (positive feedback)
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  • Invasion - Migration
  • Vascular Proliferation - Angiogenesis
  • Excretion of Growth Factors and Signaling Molecules
Cancer Phenotypes

• Key Phenotypes/Characteristics of Glioblastoma
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  • Invasion - Migration
  • Vascular Proliferation - Angiogenesis
  • Excretion of Growth Factors and Signaling Molecules

• GOAL: Detect & Quantify these Phenotypes/Behaviors
Biomarkers

- **Definition of Biomarkers**

  
  “A characteristic that is **objectively measured** and evaluated as an **indicator of normal biological processes**, pathogenic processes, or pharmacologic **responses to a therapeutic intervention**”

---

**Mutation**

**Genome/Proteome**

**Signal Pathway**

**Phenotype/Clinical Characteristic**

**Imaging Characteristic**

**Outcomes**
Biomarkers

• Definition of Biomarkers

• “A characteristic that is **objectively measured** and evaluated as an **indicator of normal biological processes**, pathogenic processes, or pharmacologic **responses to a therapeutic intervention**”
**Surgical Resection**

- Extent of Resection (biopsy vs. resection) affects OS
  - High grade gliomas: GTR 2-yr survival 19%, STR = 0% (Ammirati, *Neurosurg*, 1987)
  - OS GTR = 13 mo vs. STR = 8.8 mo (Lacroix, *J Neurosurg*, 2001)

- **High Grade Gliomas cannot be cured with surgery**
  - Goal is to diagnose, relieve mass effect, and achieve GTR (Ryken, *J Neuroonc*, 2008)
Current Therapies for Brain Tumors

• **Radiation Therapy**
  - External Beam Radiation Therapy (XRT) significantly prolongs survival
    - Dose 4500 cGy ~ 13 week OS; 6000 cGy ~ 42 week OS
      - Administered 5 days per week in 1.8-2.0 Gy Fractions
  - Interstitial Brachytherapy
    - Implantation of radioactive seeds
    - Limited value and rarely used -- results in substantial radiation necrosis
  - Experimental RT
    - Proton beam therapy; Neutron Capture Therapy
    - Radiosensizers
Current Therapies for Brain Tumors

- **Chemotherapy (Anti-neoplastic Agents)**
  - Adjuvant chemo >6-10% increase in 1 year survival rates (Fine, *Cancer*, 1993; Stewart, *Lancet*, 2002)
  - Temozolomide (TMZ) -- * Current standard of care
    - Orally active alkylating agent approved by FDA in 2005
      - PFS 6.9 mo vs 5 mo; OS 14.6 mo vs. 12.1 mo; 2 yr survival rate 26% vs 10%
Current Therapies for Brain Tumors

• RT+TMZ followed by adj TMZ significantly improves OS (Stupp, N Eng J Med, 2005)
  • PFS 6.9 mo vs 5 mo; OS 14.6 mo vs. 12.1 mo; 2 yr survival rate 26% vs 10%

Overall Survival

Stupp, N Eng J Med, 2005
• Chemotherapy (Anti-neoplastic Agents)
  • Nitrosoureas: (BCNU; carmustine & carmustine wafers [Gliodel])
    • Approved by FDA in 2002
    • Increased survival 13.8 mo vs. 11.6 mo (Westphal, Acta Neurochir, 2006)
    • Lots of toxicity & other issues (CSF leaks, increased ICP)
Current Therapies for Brain Tumors

• Other Chemotherapy (Anti-neoplastic Agents)
  • Lomustine (CCNU)
    • Alkylating agent
  • 5-FU
    • Transformed into different cytotoxic metabolites, resulting an apoptosis
  • Vorinostat
    • Histone deacetylase inhibitor
  • Irinotecan (Camptosar)
    • topoisomerase inhibitor -- prevents DNA from unwinding
  • Topotecan (Hycamtin)
    • topoisomerase inhibitor
  • Vincristine (Oncovin)
    • leurocristine (VCR) - vinca alkaloid -- mitotic inhibitor
  • Temsirolimus (Torisel)
    • mTOR inhibitor - blocks growth and division
• Anti-Angiogenic Agents (Reduces Blood Vessels)
  • Bevacizumab (Avastin) -- VEGF
    • Humanized monoclonal antibody that inhibits VEGF-A.
    • FDA Approval for recurrent GBM in May 2009
    • Increases 6 month PFS (Vrendenburgh, Clin Cancer Res, 2007; J Clin Onc, 2007)
  • Cediranib (AZD2171)
    • Tyrosine kinase inhibitor, VEGF inhibitor
  • Sorafenib
    • Tyrosine kinase inhibitor, VEGF inhibitor
  • Cetuximab
    • EGFR inhibitor
  • Erlotinib
    • Tyrosine kinase inhibitor, EGFR
Current Therapies for Brain Tumors

• **Immunotherapy**
  
  • **Dendritic Cell Vaccine**
    
    • Creates a vaccine from patient-specific tumor cell proteins + dendritic cells from the patients blood. Dendritic cells mediate T-cell immune response to the remaining tumor
  
  • **Rindopepimut (CDX-110)**
    
    • Immunotherapy that targets tumor specific oncogene EGFRvIII
  
  • **Retroviral Vectors (Toca511)**
    
    • Retrovirus that delivers genetic instructions to produce cytosine deaminase inside cancer cells. CD then converts 5-FC (an antifungal) to 5-FU (cytotoxic)
  
  • **Alloreactive Cytotoxic T Lymphocytes (AlloCTL)**
• Poor survival is largely due to ineffective therapies
  • Blood Brain Barrier (BBB) penetration
  • Treatment resistance
  • Tumor infiltration

• Need for imaging biomarkers that can:
  • Detect treatment response and early failure
  • Quantify changes in biological processes within the tumor
  • Spatially localize regions of growing or responding tumor
Standard Neuroimaging Protocol for Clinical Trials

• Magnetic Resonance Imaging (MRI)
  • Standard MR Techniques
    • T2/FLAIR
      • Edema
      • Non-enhancing (infiltrating) tumor
  • Contrast-Enhanced T1-Weighted
    • Abnormal Vasculature
    • Proliferative Tumor
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T2-Weighted Imaging

Mobile $\text{H}_2\text{O}$

*Free Mobile Water*

- Structured water
  - Hydrophobic surface

Bound water
- Rotationally bound (dipolar)
- Rotationally bound (ionic)

Immobile $\text{H}_2\text{O}$

*Irrotationally bound (dipolar)*
*Irrotationally bound (ionic)*

Shorter T2

Long T2 (Bright)

Short T2 (Dark)
T2-Weighted Imaging

• **T2-Weighted MRI**
  • MRI sequence with a long TE (80-120ms) and long TR (>4s)
  • Related to rotational mobility of water molecules
  • Mobile water = Long T2 = Bright Areas
  • $T2_{edema} > T2_{tumor} > T2_{normal\ brain}$

\[
\frac{M_{xy}}{M_0} = e^{-TE/T2}
\]

Long T2 = More Signal = Bright
T2-Weighted Imaging

T2-Weighted

Edema
T2-Weighted Imaging

Infiltrative Tumor
T2-Weighted Imaging
T2-Weighted FLAIR Imaging

- T2-Weighted FLAIR MRI
  - “Fluid Attenuated Inversion Recovery” - FLAIR
  - Inversion Recovery (IR) preparation nulls MR signal from CSF
T2-Weighted FLAIR Imaging

T2-Weighted

FLAIR
T2-Weighted FLAIR Imaging

T2-Weighted

FLAIR

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T2-Weighted FLAIR Imaging

- T2-Weighted FLAIR MRI
  - Sensitive to both Edema and Non-Enhancing tumor
Double Inversion Recovery (DIR)

T2

FLAIR

Double IR
Advanced Neuroimaging Protocol for Clinical Trials

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T2 Relaxometry

TE = 10ms  TE = 100 ms  TE = 200 ms

T2 [ms]

0  500
T2 Relaxometry

- Possible surrogate for “edema” and “non-enhancing tumor”
- T2 measurements do not vary significantly across field strength

1.5T GE

1.5T Siemens

3T Siemens
T2 Relaxometry

- $T_{2\text{edema}} > T_{2\text{tumor}} > T_{2\text{normal brain}}$
Differential Quantitative T2 Mapping (DQT2)
Differential Quantitative T2 Mapping (DQT2)

Pre-Bev  Post-Bev  Pre-Bev  Post-Bev
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Diffusion MRI

\[ S = S_0 \cdot e^{-b \cdot \text{ADC}} \]
Diffusion MRI

A

B

C

0 1000 2000 3000 4000 5000
0 200 400 600
b-value [s/mm²]

b-value [s/mm²]

b = 0 s/mm²
b = 50 s/mm²
b = 100 s/mm²
b = 250 s/mm²
b = 500 s/mm²

b = 750 s/mm²
b = 1000 s/mm²
b = 2500 s/mm²
b = 3500 s/mm²
b = 5000 s/mm²

MR Signal Amplitude [s.u.]

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Diffusion MRI is a Cellularity Biomarker

Ellingson, JMRI, 2010
Diffusion MRI is a Cellularity Biomarker

ADC Map

- Edema (high ADC)
- Necrosis (high ADC)
- Viable Tumor (low ADC)
Diffusion MRI is a Cellularity Biomarker
Diffusion MRI is a Cellularity Biomarker

ADC Before RT  ADC After RT
Diffusion MRI is a Cellularity Biomarker

A. Percent Progression Free

- ADCL > 1.0 um²/ms
- ADCL < 1.0 um²/ms

B. Percent Survival

- ADCL > 1.0 um²/ms
- ADCL < 1.0 um²/ms

Radiotherapy + TMZ
Surgery
MRI (~10 wks after RT)
Adjuvant TMZ
Progression

Post-Contrast T1-Weighted
T1 Subtraction Map
Enhancing Tumor
ADC Map

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Diffusion MRI is a Cellularity Biomarker

Functional Diffusion Mapping (fDMs)
Diffusion MRI is a Cellularity Biomarker

Ellingson, Neuro Onc, 2012
Diffusion MRI is a Cellularity Biomarker

Ellingson, Neuro Onc, 2012
Cell Invasion, Motility, and Proliferation Level Estimate (CIMPLE) Maps

\[
\frac{d}{dt} ADC(t) = \rho \cdot ADC(t) + D \nabla^2 ADC(t)
\]

Proliferation

Invasion
Cell Invasion, Motility, and Proliferation Level Estimate (CIMPLE) Maps

T1+C

Proliferation

Cell Proliferation [1/yr]

0 → 10

Ellingson, J Neuroonc, 2012
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• Cancer tissues have low extracellular pH and high intracellular pH
• Acidosis drives malignant processes
• Cancer cells often use glutamine (amino acid) for fuel
• Therefore, CEST imaging of glutamine may be sensitive to tumor cells
Chemical Exchange Saturation Transfer (CEST)

- Use a soft RF pulse to saturate spins on macromolecular $^1$H that are undergoing chemical exchange with water
pH-Weighted MRI of Cancer Using Glutamine CEST

• CEST signature for glutamine (“amine protons” at +2.8ppm wrt water) is sensitive to low pH
  • Abundance of free 1H in solution at low pH available for exchange
  • Reduction in exchange rates, leading to better z-spectra
pH-Weighted MRI of Cancer Using Glutamine CEST

PATIENT #1

Baseline 7/24/13
Recurrence 9/24/13

T1+C

pH-Weighted MRI

PATIENT #2

Pre-RT 8/21/13
Post-RT 10/14/13

CEST Asymmetry @ 28ppm

+5%
-5%
pH-Weighted MRI of Cancer Using Glutamine CEST

Post-Contrast T1-Weighted

Pre-RT 7/30/13
Mid-RT 8/26/13
Post-RT 9/23/13
Recurrence 10/23/13

pH-Weighted MRI

CEST Asymmetry @ 28ppm

-5%
+5%
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Brain Tumor Contrast Enhancement

**Normal Vasculature**

**Neovasculature**
Brain Tumor Contrast Enhancement

**Normal Vasculature**

**Neovasculature**
Brain Tumor Contrast Enhancement

Serial T1-Weighted Images

Time
Dynamic Contrast Enhanced (DCE)-MRI

\[ Gd \text{ Balus} \]

\[ \text{Plasma} \]

\[ K^{trans} \]

\[ k_{ep} \]

\[ \text{EC Space} \]

\[ C_e(t) \]

\[ C_p(t) \]

\[ \text{Kidneys} \]
Dynamic Contrast Enhanced (DCE)-MRI

\[
\begin{align*}
\text{Plasma: } C_p(t) & \rightarrow \text{EC Space: } C_e(t) \\
\text{Kidneys: } & \text{Gd Bolus: }
\end{align*}
\]

- \( K^{\text{trans}} \) and \( k_{ep} \)

Dependent on Contrast Agent Concentration & Compartmental Volume Fraction

“Contrast Wash Out”

“Contrast Wash In”

- Permeability (P)
- Vessel Surface Area (S)
- Flow Rate (F)

Time

Signal Intensity
Dynamic Contrast Enhanced (DCE)-MRI

\[ K_{\text{trans}} = 0 \text{ min}^{-1} \]

\[ K_{\text{trans}} = 0.048 \text{ min}^{-1} \]
Dynamic Contrast Enhanced (DCE)-MRI

\[ \text{Gd Bolus} \]

\[ K^{\text{trans}} \]

\[ k_{ep} \]

\[ \text{Plasma} \quad C_p(t) \]

\[ \text{EC Space} \quad C_e(t) \]

\[ \text{Kidneys} \]
Dynamic Contrast Enhanced (DCE)-MRI

\[ C_p(t) \xrightarrow{K_{trans}} EC \xrightarrow{k_{ep}} C_e(t) \]

\[ \text{T2-Weighted} \quad \text{Post-Contrast T1w} \quad \text{K}_{\text{trans}} \]

[Diagram showing the flow of Gd Bolus through Plasma, EC Space, and Kidneys, with color maps for T2-Weighted, Post-Contrast T1w, and K_{trans}]
Advanced Neuroimaging Protocol for Clinical Trials

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Perfusion MRI is a Vascularity Biomarker

Standard DSC Method:

$\Delta R_2^*$ or $\Delta R_2$

CBV

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Perfusion MRI is a Vascularity Biomarker

**DSC Time Series**

**T1+C**

**rCBV**
Perfusion MRI is a Vascularity Biomarker

\[ T_{1+C} \]

\[ rCBV \]
Perfusion MRI is a Vascularity Biomarker

$T_1+C$

$rCBV$
Perfusion MRI is a Vascularity Biomarker
Perfusion MRI is a Vascularity Biomarker

A. High Pre-Treatment Atlas-Defined Hypervascular Volume (> 2.35 cc)
Low Pre-Treatment Atlas-Defined Hypervascular Volume (< 2.35 cc)

B. High Post-Treatment Atlas-Defined Hypervascular Volume (> 0.14 cc)
Low Post-Treatment Atlas-Defined Hypervascular Volume (< 0.14 cc)

C. Small Decrease in Atlas-Defined Hypervascular Volume (< 80% Decrease)
Large Decrease in Atlas-Defined Hypervascular Volume (> 80% Decrease)

A. Percent Progression Free vs Progression-Free Survival (Days)
P = 0.0027

B. Percent Progression Free vs Progression-Free Survival (Days)
P = 0.0025

C. Percent Progression Free vs Progression-Free Survival (Days)
P = 0.0672

A. Percent Survival vs Overall Survival (Days)
P = 0.0654

B. Percent Survival vs Overall Survival (Days)
P = 0.0304

C. Percent Survival vs Overall Survival (Days)
P = 0.0483

David Geffen School of Medicine
UCLA Health System

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Standard MRI - Contrast Enhancement

**Pre-Contrast**

**Post-Contrast**
Standard MRI - Contrast Enhancement

Pre-Contrast T1w MRI

Post-Contrast T1w MRI

Normalized Raw Subtraction Map

CE-ΔT1w Map

Difference in Normalized Signal Intensity (Day 2 - Day 1)

1.0
0.5
0.0
0.0
Standard MRI - Contrast Enhancement

FLAIR  Pre-Contrast  Post-Contrast  T1 Subtraction

A

B

C
**Post-Bevacizumab Volume**

- CE-$\Delta$T1w, HR = 0.46; P < 0.001***
- Conventional, HR = 0.67; P = 0.041*

**Post-Bevacizumab Volume**

- CE-$\Delta$T1w, HR = 0.46; P < 0.001***
- Conventional, HR = 0.67; P = 0.041*

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Advanced Neuroimaging Protocol for Neuro-Oncology

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