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.
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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
Clonal Genetic Model of Cancer

Normal → Mutation → Benign Tumour → Primary Cancer

ONC/ TSG

Drug resistance

Genetic plasticity

Metastasis

Gene

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Nature Reviews | Genetics

Fienberg, Nature Genetics, 2006
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

CBTRUS Statistical Report: NPCR and SEER Data from 2004-2008

Glioma Malignant, NOS 7.1%
Ependymoma 5.8%
Oligodendroglioma 6.4%
Pilocytic Astrocytoma 5.2%
Protoplasmic and Fibrillary Astrocytoma 1.8%
Anaplastic Astrocytoma 6.7%
All Other Astrocytoma 8.8%
All Other Glioma 4.3%
Astrocytomas and glioblastomas account for 76% of all gliomas*
Glioblastoma 53.9%

*ICD-O-3 codes = 9380-9384,9391-9460,9480

Central Brain Tumor Registry United States, 2012
Cancer Phenotypes

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

- Key Phenotypes/Characteristics of Glioblastoma
  - Uncontrolled Proliferation (positive feedback)
  - Hypoxia (HIF-1α)
  - Invasion - Migration
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Cancer Phenotypes

Key Phenotypes/Characteristics of Glioblastoma

- Uncontrolled Proliferation (positive feedback)
- Hypoxia (HIF-1α)
- Invasion - Migration
- Vascular Proliferation - Angiogenesis
- Excretion of Growth Factors and Signaling Molecules
Cancer Phenotypes

• Key Phenotypes/Characteristics of Glioblastoma
  • Uncontrolled Proliferation (positive feedback)
  • Hypoxia (HIF-1α)
  • 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**”
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• 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)
    • OS GTR = 14 mo vs. STR = 11 mo (Sanai, Neurosurg, 2008; Fadul, Neurology, 1988)
  • High Grade Gliomas cannot be cured with surgery
    • Goal is to diagnose, relieve mass effect, and achieve GTR (Ryken, J Neuroonc, 2008)
• Radiation Therapy

  • External Beam Radiation Therapy (XRT) significantly prolongs survival
    • Surgery Alone ~ 3-4 mo OS; Surgery + RT ~ 7-12 mo OS (Buatti, J Neuroonc, 2008; Stupp, N Eng J Med, 2005; Walker, J Neurosurg, 1978)
    • 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
• 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
  • 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%
Current Therapies for Brain Tumors

• 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)
• 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
Current Therapies for Brain Tumors

• 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 patient's 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)**
Current Therapies for Brain Tumors

Phenotype/Clinical Characteristic

Imaging

Outcomes

UT Houston Medical Center

B.M. Ellingson, Ph.D., Dept. of Radiological Sciences, David Geffen School of Medicine at UCLA, 2013
• Magnetic Resonance Imaging (MRI)
  • Standard MR Techniques
    • T2/FLAIR
      • Edema
      • Non-enhancing (infiltrating) tumor
    • T2 Relaxometry
      • Edema
  • Diffusion MRI
    • Cellularity, Proliferation, Invasion
  • Dynamic Contrast-Enhanced (DCE) MRI
    • Vascular Permeability
  • Dynamic Susceptibility-Contrast (DSC) MRI
    • Blood Volume, Blood Flow
  • Contrast-Enhanced T1-Weighted
    • Abnormal Vasculature
    • Proliferative Tumor
• Positron Emission Tomography (PET)
  • $^{18}$F-FDG PET
    • Glucose Metabolism
  • $^{18}$F-FLT PET
    • DNA Synthesis / Proliferation
  • $^{18}$F-FDOPA PET
    • Amino Acid Uptake/Transport/Metabolism
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Standard MRI - T2/FLAIR/Relaxometry

Mobile H₂O

Immobile H₂O

Long T2 (Bright)

Short T2 (Dark)
Standard MRI - T2/FLAIR/Relaxometry

*T2-Weighted Edema*
Standard MRI - T2/FLAIR/Relaxometry

*T2-Weighted*

*Infiltrative Tumor*
Standard MRI - T2/FLAIR/Relaxometry

*T2-Weighted*  
*FLAIR*
Standard MRI - T2/FLAIR/Relaxometry

T2  FLAIR  Double IR
Advanced Neuroimaging Protocol for Clinical Trials

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Standard MRI - T2/FLAIR/Relaxometry

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

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Differential Quantitative T2 Mapping (DQT2)

Ellingson, J Neuroonc, 2012
Differential Quantitative T2 Mapping (DQT2)

Pre-Bev  Post-Bev  Pre-Bev  Post-Bev
Differential Quantitative T2 Mapping (DQT2)
• Magnetic Resonance Imaging (MRI)
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Diffusion MRI

Ellingson et al., Concepts in MR, 2008
Diffusion MRI is a Cellularity Biomarker

Ellingson & Cohen-Adad, Chpt. 3.1: Diffusion-Weighted Imaging in
Diffusion MRI is a Cellularity Biomarker

ADC Map

Edema

Necrosis

Viable Tumor (Dark)
Diffusion MRI is a Cellularity Biomarker

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Diffusion MRI is a Cellularity Biomarker

ADC Before RT

ADC After RT
Diffusion MRI is a Cellularity Biomarker

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

**Pre-Tx FLAIR**
**Post-Tx FLAIR**
**Pre-Tx T1+C**
**Post-Tx T1+C**
**fDM**

**PFS = 247 Days**
**OS = 247 Days**

**PFS = 258 Days**
**OS = 662 Days**

**PFS = 438 Days**
**OS = 1613 Days**

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

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

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

Proliferation

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

T1+C

Proliferation

Cell Proliferation

[1/yr]

0

10

Ellingson, J Neuroonc, 2012
• Magnetic Resonance Imaging (MRI)
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Brain Tumor Contrast Enhancement

Normal Vasculature

Neovasculature
Serial T1-Weighted Images
Dynamic Contrast Enhanced (DCE)-MRI

\[ \text{Gd Bolus} \rightarrow \text{Plasma} \quad C_p(t) \quad \xrightarrow{K_{\text{trans}}} \quad \text{EC Space} \quad C_e(t) \quad \xleftarrow{k_{ep}} \quad \text{Kidneys} \]

Signal Intensity vs. Time

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Dynamic Contrast Enhanced (DCE)-MRI

\[ S \propto \frac{\sin \theta (1 - e^{-TR/T1})}{(1 - \cos \theta \cdot e^{-TR/T1})} \]
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

Gd Bolus

Plasma $C_p(t)$

$K_{\text{trans}}$

EC Space $C_e(t)$

$k_{ep}$

Kidneys

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

0

0.05
Advanced Neuroimaging Protocol for Clinical Trials

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Dynamic Susceptibility Contrast (DSC)-MRI

Standard DSC Method:

$\Delta R^2$ or $\Delta R$

CBV

Signal

Time (sec)

Time (sec)

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Dynamic Susceptibility Contrast (DSC)-MRI
Dynamic Susceptibility Contrast (DSC)-MRI

![Dynamic Susceptibility Contrast (DSC)-MRI Image]

- **Time**
- **Signal Intensity**

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Dynamic Susceptibility Contrast (DSC)-MRI

$T_1+C$  

$rCBV$
Dynamic Susceptibility Contrast (DSC)-MRI

\[ T_1 + C \]

\[ rCBV \]
Dynamic Susceptibility Contrast (DSC)-MRI

$T1+C$

$rCBV$
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Standard MRI - Contrast Enhancement

**Pre-Contrast**

**Post-Contrast**

Pre-contrast images show the baseline state of a brain scan without any contrast enhancement. Post-contrast images illustrate the enhanced visibility of certain areas after administering contrast material, which can help in identifying lesions or abnormalities more clearly.

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Standard MRI - Contrast Enhancement

B.M. Ellingson, Ph.D., Dept. of Radiological Sciences, David Geffen School of Medicine at UCLA, 2013
Standard MRI - Contrast Enhancement

Post-Bevacizumab Volume

CE-ΔT1w, HR = 0.46; P < 0.001***
Conventional, HR = 0.51; P = 0.002**

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Positron Emission Tomography (PET)
Positron Emission Tomography (PET)

T2-Weighted MRI

$^{18}$F-FDOPA PET (Dopamine)
Positron Emission Tomography (PET) Parametric Response Maps
Positron Emission Tomography (PET) Parametric Response Maps

Pre-Treatment

First Post-Treatment Follow-Up

Post-Contrast T1-Weighted

$^{18}$F-FDG PET

$^{18}$F-FDG PET PRM

Ellingson, PET Clinics, 2013 (In Press)
Positron Emission Tomography (PET) Parametric Response Maps

T2-Weighted

$^{18}$F-FDOPA PET

$^{18}$F-FDOPA PET PRM

Ellingson, PET Clinics, 2013 (In Press)
Positron Emission Tomography (PET) Parametric Response Maps

T2-Weighted

$^{18}$F-FLT PET

$^{18}$F-FLT PET PRM

Ellingson, PET Clinics, 2013 (In Press)
Advanced Neuroimaging Protocol for Neuro-Oncology

- **Magnetic Resonance Imaging (MRI)**
  - T2/FLAIR
    - Edema & Infiltrating tumor
  - T2 Relaxometry
    - Edema / Density
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Challenges in a Multi-Center Clinical Trial

• Image Standardization
Challenges in a Multi-Center Clinical Trial

• Image Standardization

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Challenges in a Multi-Center Clinical Trial

• Quality Control
Challenges in a Multi-Center Clinical Trial

- Scanner Variability

![Graphs showing ADC values for CSF and NAWM across different MRI scanners.](image-url)