Methodology for Multireader Assessment of MR Imaging Features of Gliomas in Clinical Trials

caBIG cancer Biomedical Informatics Grid ™

Adam E. Flanders, Erich Huang, Max Wintermark, Dima Hammoud, Manal Nilcolas-Jilwan, P. Raghaven, Chad Holder, Scott Hwang, Robert Clifford, John Freymann, Justin Kirby, Daniel L. Rubin, Eliot Siegel, C. Carl Jaffe, Ken Buetow.

Thomas Jefferson University Hospital, Philadelphia, PA, National Cancer Institute, Bethesda, MD, University of Virginia, Charlottesville, VA, National Institute of Health, Bethesda, MD, Emory University, Atlanta, GA, SAIC- Frederick, Inc., Frederick, MD, Stanford University, University of Maryland, Boston University School of Medicine, Boston, MA.

Disclosure

- Geron Inc. – consultant.
- DoD grant recipient.

Background

- Multicenter research trials that incorporate *imaging* present unique challenges;
  - Due to variations in imaging protocols
  - Lack of controlled terminologies
  - No standard-based markup or annotation.
  - Limited options for systematic federated image review.
  - Absence of uniform data collection methods.
  - Absence of quality control standards.
  - Many others......

Enter caBIG

caBIG ® Cancer Biomedical Informatics Grid ®

- Fewer than 5% of cancer patients are enrolled in clinical trials.
- Since 2004 the Cancer Bioinformatics Grid has focused on the concept of leveraging informatics tools to lower barriers for patient access to clinical trials.
- *Imaging workspace* in caBIG is focused on developing tools that exploit quantitative and qualitative features of clinical imaging as a biomarker for diagnosis and treatment response.

caBIG Core Technology Descriptions

The National Biomedical Imaging Archive (NBIA) provides the central storage for medical images so that they can be easily accessed from a local version of radiology workstation from any geographic location.

The Imaging Middleware provides the grid data transfer support designed to meet the special needs of imaging data such as data file size.

The Clear Canvas workstation and Annotation Imaging Markup (AIM) data service are used by radiologists to capture tumor characteristics. The tumor characteristic data is saved in a data service that can be queried from a local version of the workstation or through the web portal of the data integration software.
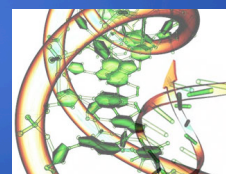
The caIntegrator software provides a web accessible analysis across the tumor characteristic, genomic, and clinical data. It can also link the researcher back to each image from which a tumor characteristic is derived.

TCGA - The Cancer Genome Atlas Study

The Cancer Genome Atlas — *Understanding genomics to improve cancer care*

- TCGA is a five-year program to chart the genomic changes involved in more than 20 types of cancer.
- To date, TCGA has achieved comprehensive sequencing, characterization, and analysis of the genomic changes in glioblastoma multiforme and ovarian cancer.
- Cancers selected for study were chosen based on specific criteria that include:
  - Poor prognosis and overall public health impact
  - Availability of human tumor and matched-normal tissue samples that meet TCGA standards for patient consent, quality and quantity
- *Large collection of GBMs collected and processed through this effort.*

TCGA Informatics Opportunity

- TCGA fosters cross cutting initiatives to compare features of light microscopy (pathology markup) and genomics/proteomics.
- Exploiting synergies between all initiatives to improve ability to forecast survival & response.
- *Opportunity* to integrate MR imaging features into ongoing work to forge new novel discoveries.

Clinical Features

Imaging Features

Genomic Features

Pathologic Features
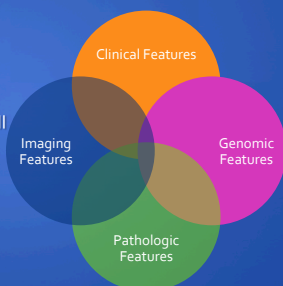
Purpose

- Develop a method for collaborative imaging assessment of the baseline glioblastoma MR images that have been contributed to the TCGA collection.
- Leverage the informatics tools developed by caBIG.
- Set the stage for discovery of new relationships between imaging and the other "omics" in glioblastoma.
- Model for imaging assessment in clinical trials.

Immediate Challenge

- Technologic infrastructure available from caBIG.
- Large glioma dataset from TCGA with:
  - Rich genomic/proteomic features
  - Clinical parameters
  - Pathologic categorization
- No baseline clinical imaging included.
- Absence of a taxonomy or controlled terminology for primary brain tumors (aka a BI-RADS for brain).
- No domain experts to evaluate imaging.

Our Charge

- Assemble "a team".
- Capture the baseline MR imaging studies from the originating sites corresponding to the glioma repository at TCGA.
  - UCSF
  - Henry Ford Hospital
  - Emory University
- Develop a taxonomy for MR features of gliomas.
- Recruit motivated domain experts (neuroradiologists) from various institutions.
- Train the neuroradiologists on the proper use of the taxonomy.

VASARI Featureset

- Pre-existing validated featureset which had been used successfully for a similar pilot project using REMBRANDT glioma data.
- Comprehensive inventory of all glioma MR imaging features & method for scoring these features.
- Requirements:
  - Features had to be "innate" to domain experts.
  - Not cognitively challenging or ambiguous.
  - Applied reliably after minimal training.
- Multiple iterations, tested, validated and re-applied.
- Presented at ASNR 2009.

Defining Rich Set of Qualitative and Quantitative Image Biomarkers

- Community-driven ontology development project
  - Collaboration with ASNR
- Imaging features (26 features / 4 categories)
  - Location of lesion
  - Morphology of lesion margin (definition, thickness, enhancement, diffusion)
  - Morphology of lesion substance (enhancement, PS characteristics, focality/multicentricity, necrosis, cysts, midline invasion, cortical involvement, T1/FLAIR ratio)
  - Alterations in vicinity of lesion (edema, edema crossing midline, hemorrhage, pial invasion, ependymal invasion, satellites, deep WM invasion, calvarial remodeling)

Qualitative/Semi-quantitative Features Familiar to Neuroradiologists

MRI Featureset
1. Infiltration
2. Enhancement
3. Nodularity
4. Necrosis
5. Edema
6. nCET
7. Diffusion
8. Hemorrhage

Well-marginated, Non-enhancing

TCGA Scoring of Images

TCGA Scoring of Images

Methods

1. Clinical MR exams for 78 TCGA gliomas were anonymized, indexed and stored in the NBIA central archive.
2. 6 Neuroradiologists from three institutions recruited and trained to use the VASARI featureset.
   - Training set and "mock" evaluations used to test software, connectivity and agreement.
3. VASARI/AIM enabled version of Clear Canvas installed at all three sites.

Methods

4. "Reads" of all 78 studies were coordinated using a master worklist hosted at NCI.
   - Staggered reads provided three evaluations for each study.
   - Each neuroradiologist assigned a bolus of exams to be scored by a given date.
5. Assigned studies were queried/retrieved locally to each CC workstation from NBIA using caGRID.
6. Six neuroradiologists concurrently scored the MR studies using the featureset and transmit scores to AIM instance at Emory.
7. 6084 data entries collected in 30 days.
8. QC and analysis.

Agreement

- Agreement highest for anatomic features:
  - Side: k=0.943, 95% CI 0.915-0.982
  - Location: k=0.837, 95% CI 0.807-0.902
- Other features with good agreement:
  - Proportion enhancing tumor: k=0.656, 95% CI 0.596-0.757
  - Presence of satellites: k=0.663, 95% CI 0.591-0.780
  - Diffusivity: k=0.730, 95% CI 0.664-0.828
- Only three features showed low agreement (k<0.4):
  - Calvarial remodeling: k=0.366, 95% CI 0.124-0.626
  - Cortical involvement: k=0.167, 95% CI 0.157-0.335
  - Definition of non-enhancing margin: k=0.374, 95% CI 0.347-0.514

Kappa statistic of Berry & Miekle

Utilizing the NCI Semantics and Technologies To Support Phenotype/Genotype Clinical Analysis

Image + Image Annotation Data + Genomic & Clinical = Analytic Results
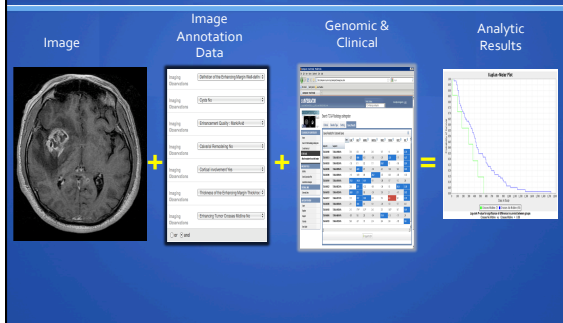
Summary

- Tools developed through the NCI caBIG development effort enabled a practical solution for multicenter/ multireader image evaluation.
- Data collected utilizing these methods are amenable to cross-correlative analysis with other data repositories (e.g. genomics/proteomics).
- Poised to process and score up to 500 additional new brain tumors.
- Incorporating physiologic data (perfusion, DTI).
- Very rewarding cross-collaborative effort.
- Always looking for additional participants!
- Success of this project can serve as a model for similar assessments in the imaging arm of the TCGA project.

Additional TCGA Glioma Presentations at ASNR 2011

- Relationship between MR Imaging Features, Gene Expression Subtype, and Histopathologic Features of Glioblastomas.
  - (17e) Adult Brain: Neoplasms, **Paper 273**
  - Tuesday; Starting at 12:21 PM
  - Room 602/603/604
- Associations Between MR Imaging and Genomic Features of Glioblastomas
  - (47c) Epilepsy, Brain Neoplasms, Paper 563
  - Thursday, Starting at 2:11 PM
  - Room 666 - 609
- Prediction of Glioblastoma Multiforme (GBM) Patient Survival Using MRI Image Features and Gene Expression
  - (47a) Brain: Neoplasms II, Glioma, Paper 537
  - Thursday, Starting at 1:39 PM
  - Ballroom 6 B/C

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