Imaging-genomic Analysis of TCGA/TCIA Diffuse Lower Grade Gliomas by Molecular Subtype

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with TCGA Glioma Phenotype Research Group

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Cancer of the Brain and CNS

- 120 different types of brain tumors
- #2 leading cause of cancer death among children and young adults
- 612,000 people in the U.S. living with the diagnosis of central nervous system or primary brain tumors
- 66,290 cases of primary brain tumors expected to be diagnosed this year
- 4 brain tumor treatments approved by the FDA (do not discriminate)

Source: Central Brain Tumor Registry of the United States (CBTRUS) www.cbtrus.org
Glioma: Cancer of glial cells

Astrocytoma (WHO Grade II/III)

Oligoastrocytoma (WHO Grade II/III)

Oligodendroglioma (WHO Grade II/III)

Glioblastoma (WHO Grade IV)

Image from: NIH/National Institute of Neurological Disorders and Stroke (NINDS)
Molecular markers in glioma

Mutation of Isocitrerase Dehydrogenase (IDH1/2)

Co-deletion of Chr 1p and Chr 19q

Role of IDH (Labussiere et al, 2010)

Case TCGA-DU-6393, visualized at www.cbioportal.org
IDH/Codel vs Histology/Grade

Brat et al (to appear)
Biology Follows IDH/Codel Molecular Subtypes

IDH Mut-Non-codel
TP53
ATRX
Gain of CCND2, MYC, Loss of AGXT

IDH Mut-Codel
TERT
CIC
NOTCH1
FUBP1

IDH WT
CDKN2A loss
EGFR gain/mut
PTEN mut
MDM4 gain

Brat et al (to appear)
The Cancer Imaging Archive (TCIA)

http://www.cancerimagingarchive.net/

http://xnatview.org/ (guest)
9 Neuroradiologists + 26 Features
(LGG-VASARI set)

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Is there necrosis?
Is there edema?
Is there contrast enhancement?
What is the maximal area?
Is the shape ovoid or irregular?
Etc…

TCGA-DU-6401
Axial T1 post-Gad contrast
Are there neuro-imaging features associated with the IDH/Codel-defined molecular subtypes?
Radiogenomic Study Set (n=70)
IDH-mut/codel tumors are likely to be centered in the frontal lobe.

75% of IDH-mut/codel tumors are in the frontal lobe vs other locations (FET p=0.026).

IDH-mut/non-codel were split 41% frontal and 41% temporal lobes.
Other IDHmut Associated Features

- IDHmut-codel tumors were more likely to have:
  - T1/FLAIR signal cross the midline (FET p=0.007)
  - Have presence of hemorrhage (FET p=0.009)
  - Have presence of cysts (FET p=0.066)

- IDHmut-non-codel tumors were least likely to have presence of satellites (FET p=0.030)
IDHwt tumors tend to be more infiltrative

IDH-mut-codel
TCGA-CS-4943 (T1 ~ FLAIR)

IDH-wt
TCGA-CS-4941 (T1<<FLAIR)

FLAIR region likely to be larger than T1 (FET, p=0.003)
IDH-wt tumors are less likely to have well defined non-enhancing regions

- IDH-mut-non-codel: Well-defined NER
- IDH-wt: Poorly-defined NER

56% IDH-mut/Codel and 76% IDH-mut/Non-codel vs. 32% for IDH-wt (FET, p=0.027)
IDHwt tumors tend to be smaller

**IDH-mut-codel**
TCGA-DU-5871 (57.6 cm²)

**IDH-wt**
TCGA-DU-6404 (21.5 cm²)

Mean: 23.0 cm² vs 39.7 cm² maximal area (t-test p<0.001)
Features of GBM were not more common in IDH-wt tumors

TCGA-06-0189 (GBM) T1 Post-gad

Enhancing Component

- MUT
- WT

(FET p=0.286)

Necrotic Component

- MUT
- WT

(FET p=0.931)
Bi-clustering finds sets of samples with consistent imaging characteristics

Cluster 6: GrIII/IDH-wt
- Enhancing region
- Irregular shape
- Poorly-defined NER
- Ependymal contact
- Corpus callosum invasion
- Not frontal center
- No cysts
- No calvar remodeling
Conclusions

• Several MR imaging features are associated with LGG molecular classes
• IDH-wt LGG does show association with aggressive features
• IDH-wt LGG is not likely under-diagnosed GBM
• Imaging patterns are present
• Further work needs to be done to determine if the associations in MR Imaging have clinical implications or other genomic associations
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