Challenges and Novel Approaches in Glioma Treatment

Mina Lobbous, MD
Department of Neurology
Division of Neuro-Oncology
University of Alabama at Birmingham

Disclosure

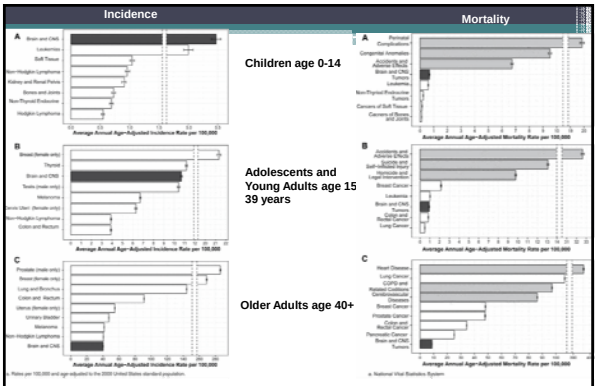
- No conflict of interest

Objectives

- Overview of updates WHO classification for Gliomas
- Current treatment modalities for gliomas
- Novel approaches and future directions.

Gliomas

- **Etiology:**
  - No lifestyle exposure is linked to glioma susceptibility (Glioma SE)
  - Ionizing radiation in children
- **Impact:**
  - Second leading cause of cancer death for young men age 20-40
  - Second most common malignancy of children, leading solid cancer and leading cause of cancer death in children
  - 5-year survival less than 4% for GBM
  - Public health cost of disease and treatment among highest in oncology.
    - *Projections of the Cost of Cancer Care in the United States: 2010-2020*, ranks brain cancer as the most expensive in terms of annualized net cost for care per patient ($140,000 for initial care)
  - Years of life lost greater than 20 years per person
    - UK: British J Cancer (2005) 92:241-245 #1 of 17 cancer sites
    - US: SEER 2002 #4 of 22 cancer sites



From: CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2009–2013
Neuro Oncol. 2016;18(suppl_5):v1-v75. doi:10.1093/neuonc/now207
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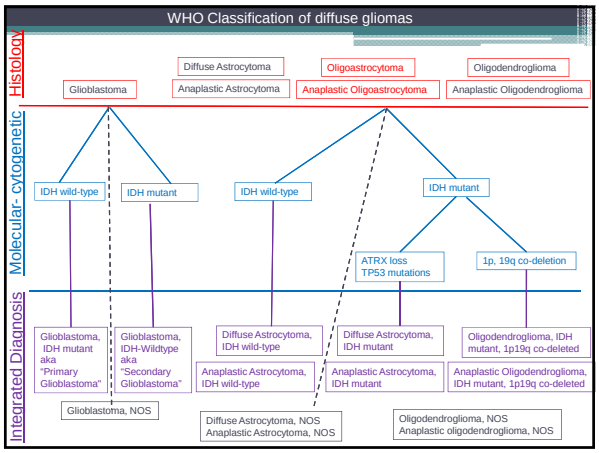
Astrocytoma

WHO Grade	WHO Designation	Histological Criteria
I	Pilocytic Astrocytoma	
II	Diffuse Astrocytoma	One criterion: usually nuclear atypia
III	Anaplastic Astrocytoma	Two criteria: usually nuclear atypia and mitotic activity
IV	Glioblastoma	Three criteria: nuclear atypia, mitosis, endothelial proliferation and/or necrosis

	WHO grade	**A**typia	**M**itoses	**E**ndothelial Proliferation	**N**ecrosis	Average Survival
Astrocytoma	II	+	+/-	-	-	6-8 years
Anaplastic Astrocytoma	III	+	+	+/-	-	2-3 years
Glioblastoma	IV	+	+	+	+	1-2 year



Glioma Grading and Natural History

Median Survival (Range)

Astrocytoma

- **Grade I: >10 years (curative)**
  - **Benign histopathological features**
  - **Pilocytic astrocytoma (PA), pleomorphic xanthroastrocytomas (PXA), subependymal giant cell astrocytomas (SEGA)**
- **Grade II: 6.5 years (5-8 years)**
  - **Nuclear atypia**
- **Grade III: 3 years**
  - **Nuclear atypia + mitosis**
- **Grade IV: 12-18 months**
  - **Nuclear atypia**
  - **Mitosis**
  - **Endothelial proliferation and/or necrosis**

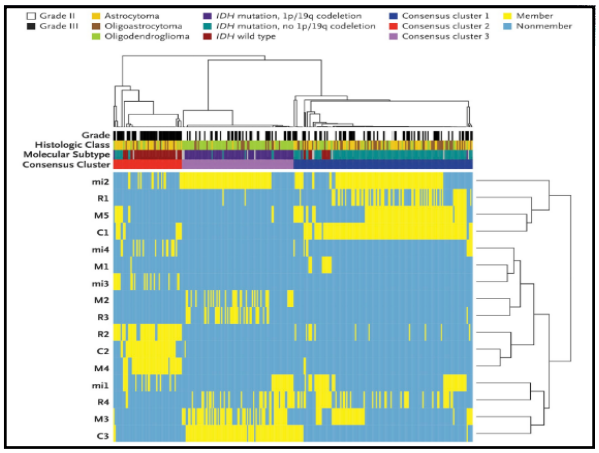
Oligodendroglioma

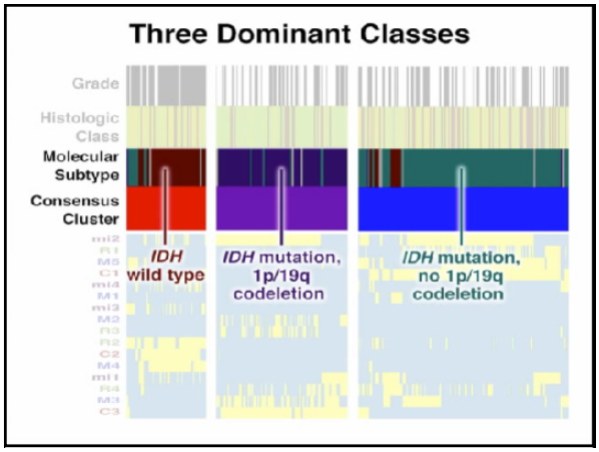
- **Low Grade: 15 years (8-20 years)**
- **Grade III Anaplastic: 5 years**

DeAngelis LM. N Engl J Med 2001;344:114-123.
Van den Bent MJ, et al. Crit Rev Oncol Hematol 2008;66:262-272.

Low Grade Gliomas WHO II

- This includes astrocytomas, oligodendrogliomas, or mixed oligoastrocytomas (term no longer used).
- Most commonly occur in children and young adults; biphasic age distribution
  - 1st peak around ages 6-12 years
  - 2nd peak between 3rd and 5th decades
- Between 50–80% present with seizure (infiltration rather than compression)
- They are called "low-grade" but they are NOT benign
  - Median OS is around 6.5–8 years
- Very heterogenous group with varying clinical behavior
  - Good prognostic signs include: age <40 years, seizures at presentation and no additional neurological deficits, KPS ≥70, MMSE >26/30
  - Poor prognostic signs include: tumor diameter >5–6 cm and the presence of contrast enhancement

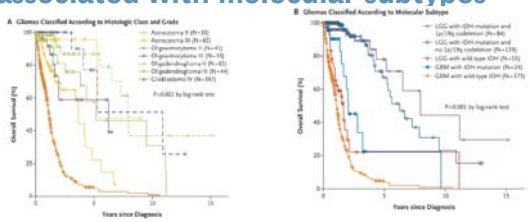




LGG molecular classification

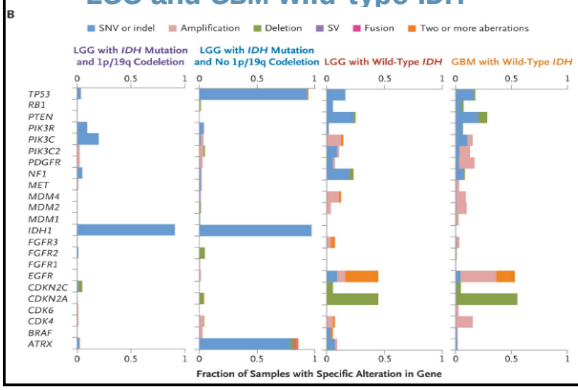
1. IDH + 1p/19q codeletion
2. IDH mutant
3. IDH wild-type

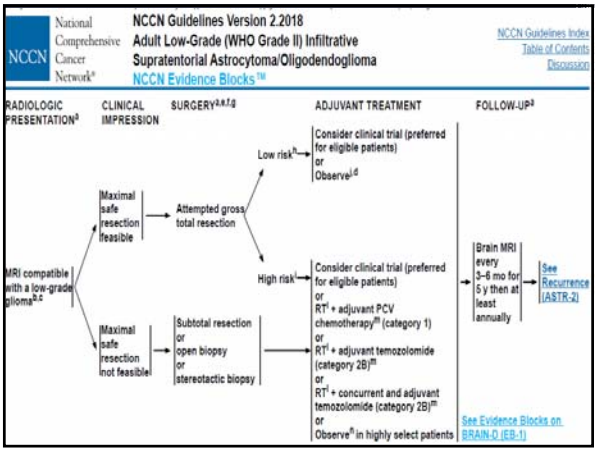
Clinical characteristics and outcomes associated with molecular subtypes



- LGG wild-type median survival 1.7 years, intermediate between GBM IDH mutated (median survival 2.1 years) and GBM wild tpe (median survival 1.1 years)
- LGG with IDH+1p/19q : median survival 8 years
- LGG with IDH mutation only: median survival 6.3 years

LGG and GBM wild-type IDH

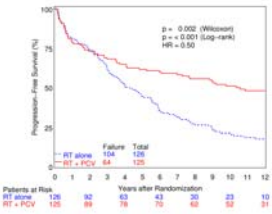




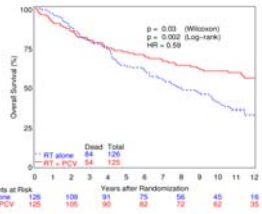
Treatment of Low-grade Gliomas (LGG)

- Standard treatment options for diffuse astrocytomas (WHO grade II) include the following:
  - Surgery alone
  - Surgery followed by radiation therapy
  - Surgery followed by chemotherapy
  - Surgery followed by radiation therapy and chemotherapy

Progression-Free Survival



Overall Survival



Phase III study of radiation therapy with or without procarbazine, CCNU, and vincristine (PCV) in low grade glioma. RTOG 9802 with Alliance, ECOG and SWOG

	RT Alone	RT + PCV
Median	7.8 years	13.3 years
5-year	63.1 %	72.3%
10-year	40.1%	60.1%

PCV, procarbazine, lomustine, and vincristine.
Buckner JC, et al. ASCO Meeting Abstracts 2014;32:2000.

- Patients with grade II glioma:
  - with less than gross total tumor resection or who are >40 years of age
  - RT + PCV prolongs both progression-free and overall survival compared with RT alone
    - Median survival is increased by 5.5 years
    - Five-year and 10-year survival are increased by 9% and 20%, respectively

PCV, procarbazine, lomustine, and vincristine.
Buckner JC, et al. ASCO Meeting Abstracts 2014;32:2000.

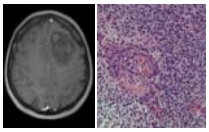
Key Points and Implications for Patient Care

- Important role for surgical resection
- Observation for gross total resection
  - Age cut off?
- Radiation therapy alone is not adequate for high-risk low-grade glioma
- Chemotherapy considerations

High Grade Gliomas

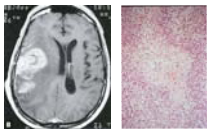
Anaplastic Astrocytoma

- Grade III glioma
- (30–40 yo)
- Often recurs as higher-grade tumor
- Median survival 36–48 months

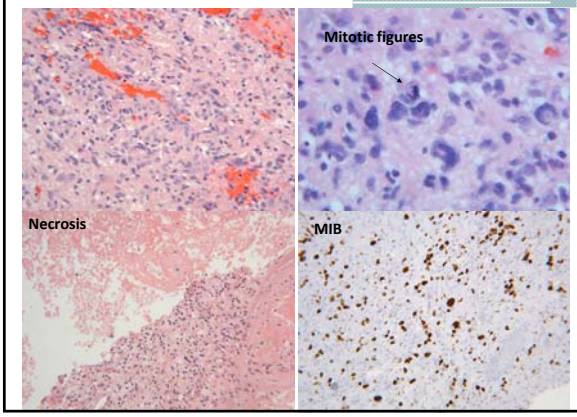


Glioblastoma

- Most aggressive,
- Histology:
  - Grade IV, poorly differentiated
  - Necrosis, vascular endothelial hyperplasia, frequent mitoses, cellular atypia
  - Neovascularization and pseudopallisading
- Most common in older adults - peak 55–65 yr
- Rapid growth ; size may double every 10 days

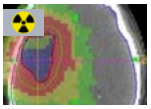


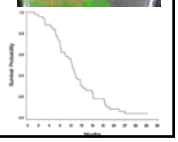
Neuropathology



Malignant Glioma Conventional Therapy

- **Surgery**
  Histopathologic diagnosis
  Benefit of cytoreduction
- **Radiation therapy**
  External beam to ~6,000 cGy
- **Chemotherapy**
  Nitrosourea-based regimens





REVIEW

Glioma Extent of Resection and Its Impact on Patient Outcome

Nader Sanai, M.D.
Brain Tumor Research Center,
Department of Neurological Surgery,
University of California at San Francisco,
San Francisco, California

Mitchel S. Berger, M.D.
Brain Tumor Research Center,
Department of Neurological Surgery,
University of California at San Francisco,
San Francisco, California

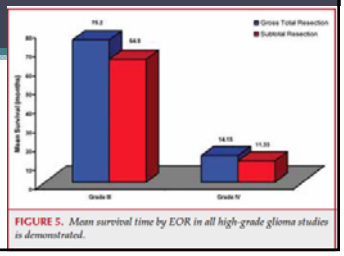
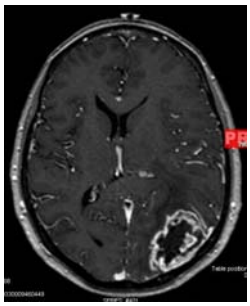
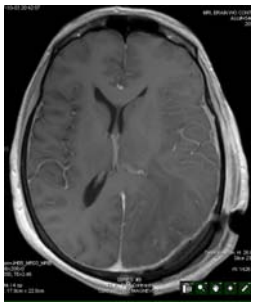
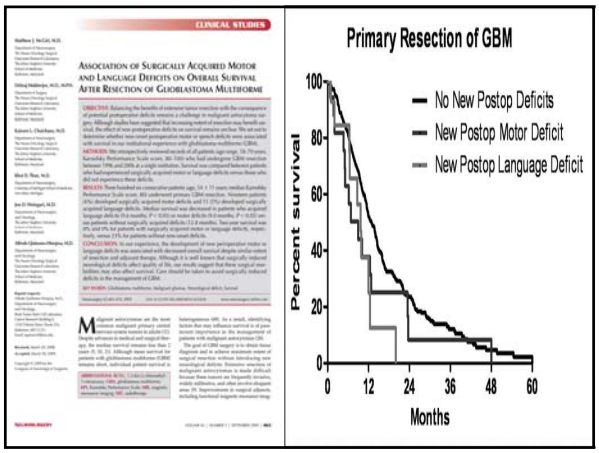


FIGURE 5. *Mean survival time by EOR in all high-grade glioma studies is demonstrated.*

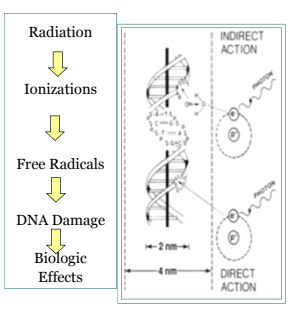
GTR

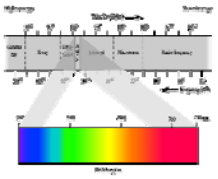




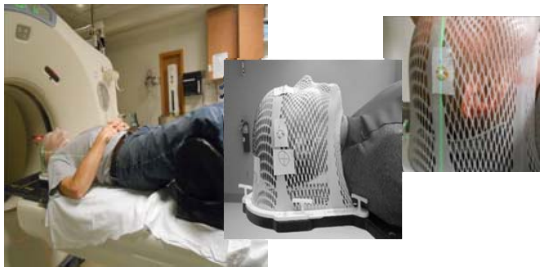


Radiation therapy

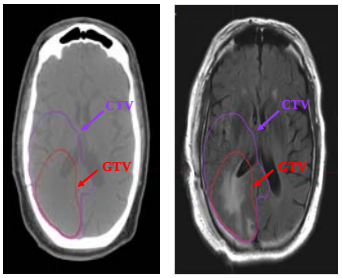




CT Simulation = 3D



Radiation Planning for Gliomas



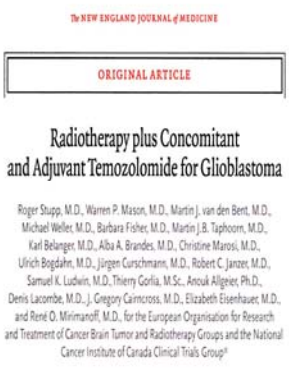
GTV = Gross Target Volume
- **Includes the radiographic disease**

CTV = Clinical Target Volume
- **Includes microscopic disease or region at risk of recurrence, not typically radiographically visible**

Chemotherapy for Gliomas (HGG)

FDA Approvals
- June, 1996: Carmustine wafer for recurrent GB
- January, 1999: Temozolomide for anaplastic astrocytoma
- February, 2003: Carmustine wafer for newly diagnosed GB
- March, 2005: Temozolomide for newly diagnosed GB
- May, 2009: Bevacizumab for progressive GB
- April, 2011: Tumor treatment fields for recurrent GB
- October, 2015: Tumor treatment fields in combination with temozolomide for newly diagnosed GB

- **"RT + TMZ → TMZ" vs. RT alone**
  - RT (60Gy)+TMZ (75 mg/m2) + TMZ (150-200 mg/m2, 5/28d) X6 mo.
- PFS = **6.9** mo. vs. **5** mo.
- OS = **14.6** mo. vs. **12.1** mo.
- Increased 2-yr. survival from **~10.4% to 26.5%**
- **FDA approved in 2005**



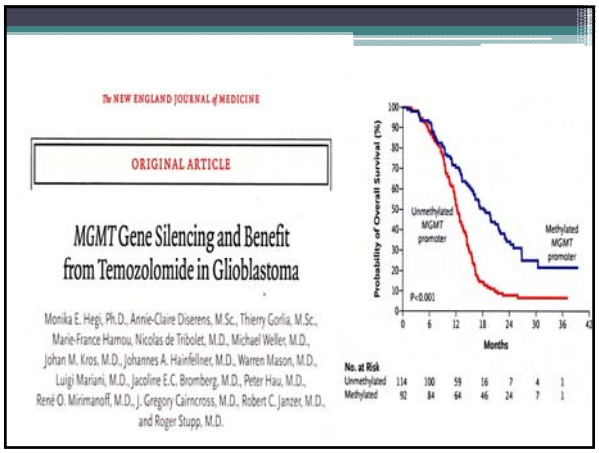
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

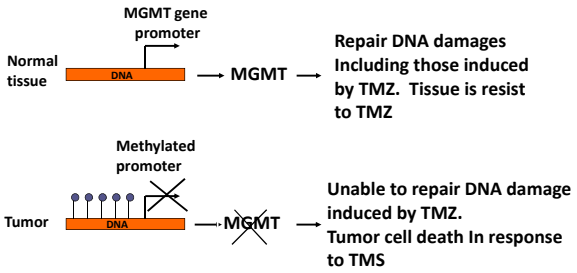
Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

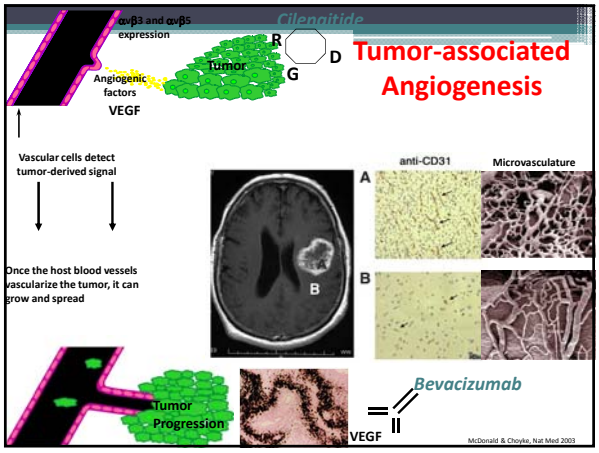
Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D., Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirimanoff, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group*

NEJM (2005) 352:987-996.



Inactivation of the methylguanine methyl-transferase (*MGMT)* by promoter methylation

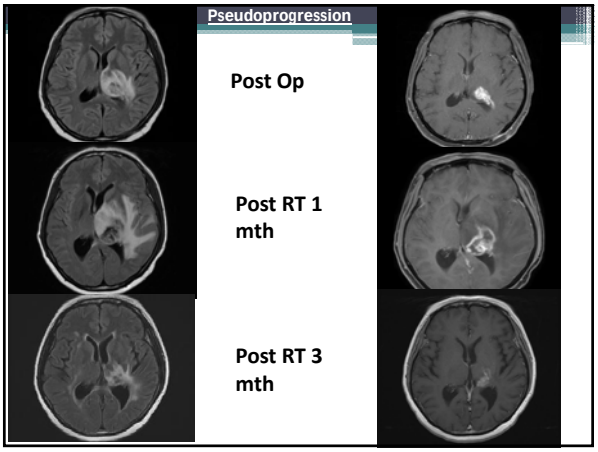




Response Assessment in Neuro-oncology (RANO)

- Consideration of the following:
  - Status of enhancing disease (post contrast T1)
  - Assessment of nonenhancing (T2/FLAIR) disease
  - Corticosteriod use
  - Performance and clinical status
- Categories
  - Complete Response
  - Partial Response
  - Stable Disease
  - Progressive Disease

J Clin Oncol 28: 1963-1972



Tumor Treating Fields (Optune)

- External, non-invasive, wearable, portable, patient controlled
- Intermediate frequency 100-300 kHz
- No half-life (requires continual use)
- Reaches deep tissues without attenuation of energy
- Does not stimulate nerves or muscles
- Does not heat tissue
- Personalized transducer array layout maximizes TTFields to the tumor (NovoTAL program)

Recurrent Glioblastoma

- OS 8-10 months
- FDA approved : CCNU, Avastin, Optune
- NCCN guidelines → consider clinical trial

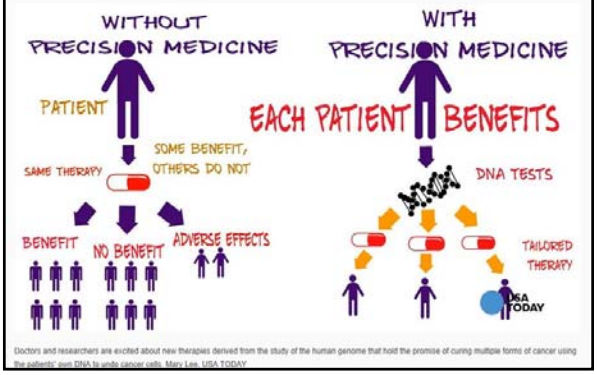
Clinical trial directions

- **Immunotherapy**
  - Cell
  - Vaccine
  - Immunecheckpoint inhibitors (ICI)
- **Personalized therapy**
  - Molecular profiling
  - Feed into Phase I studies or basket studies, umbrella studies
- **Oncolytic or modified viruses**
  - Polio, Herpes, Adeno, Retro, Mumps

Implications for Patient Care

- Obtain MGMT status and consider role of TMZ in unmethylated patients.
- Use of Optune device during maintenance TMZ dependent upon compliance and motivation.
- Management of the elderly or low KPS patient with hypofractionated RT +/- TMZ.
- Clinical trial consideration:
  - Be aware of ALC and factors depressing (RT, TMZ, steroids).
  - Next generation sequencing data

Precision Medicine targets multiple cancers



Doctors and researchers are excited about new therapies derived from the study of the human genome that hold the promise of curing multiple forms of cancer using the patients' own DNA to undo cancer cells. Mary Lee, USA TODAY

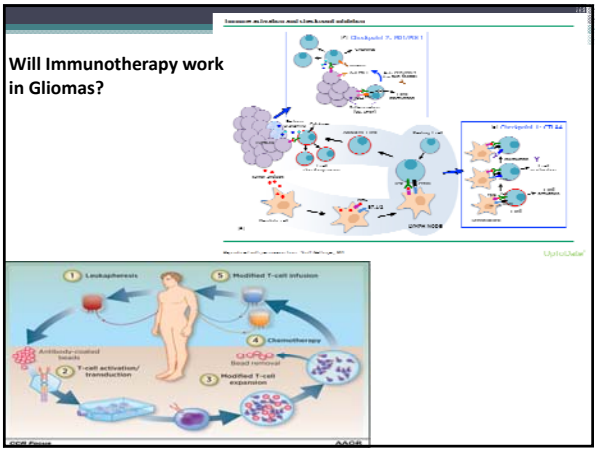
Table 1. Genomic alterations and example targeted therapies in glioblastoma

Gene	Alteration or target	Target frequency in glioblastoma[a] (%)	Candidate therapy (drug example)
Growth factor receptors			
EGFR	Deletion (EGFRvIII), mutation, translocation and/or amplification	55	EGFR vaccine or antibody-drug conjugate (rindopepimut, ABT-414)
KIT	Amplification, mutation	10	KIT inhibitor (imatinib)
PDGFRA	Amplification	15	PDGFR inhibitor (dasatinib)
FGFR1, FGFR3	Translocation (e.g. FGFR3-TACC3)	3	FGFR1/3 inhibitor (JNJ-42756493)
MET	Amplification, translocation	3	MET inhibitor (cabozantinib)
MAPK and PI3K/mTOR signaling pathways			
PTEN	Deletion, mutation	40	AKT inhibitor, mTOR inhibitor (voxtalisib)
PIK3CA	Amplification, mutation	10	mTOR inhibitor, PI3K inhibitor (buparlisib)
NF1	Deletion, mutation	14	MEK inhibitor (trametinib)
BRAF	Mutation (BRAF V600E)	2	BRAF inhibitor (vemurafenib), MEK inhibitor (trametinib)
Cell cycle pathways			
MDM2	Amplification	10	MDM2 inhibitor (AMG232)
TP53	Wild-type (no mutations)	60	MDM2 inhibitor (AMG232)
CDK4/6	Amplification	20	CDK4/6 inhibitor (ribociclib)
RB1	Wild-type (no mutations)	90	CDK4/6 inhibitor (ribociclib)
Others			
IDH1	Mutation	6	IDH1 inhibitor (AG120)
MYC, MYCN	Amplification	5	Bromodomain inhibitor (OTX-015)

Challenges facing targeted therapy in glioblastoma

- None of the recurrent genomic variants in glioblastoma has been strongly associated with clear prognostic and predictive value
- Inter- and intra-tumor genomic heterogeneity
- Limited opportunities for re-operation
- BBB, most tested agents weren't primarily designed for intracranial neoplasms. BBB becomes significant barrier in the infiltrative non-enhancing areas of the tumor.

Will Immunotherapy work in Gliomas?



Questions?