GLIOBLASTOMA: WHERE ARE WE NOW?

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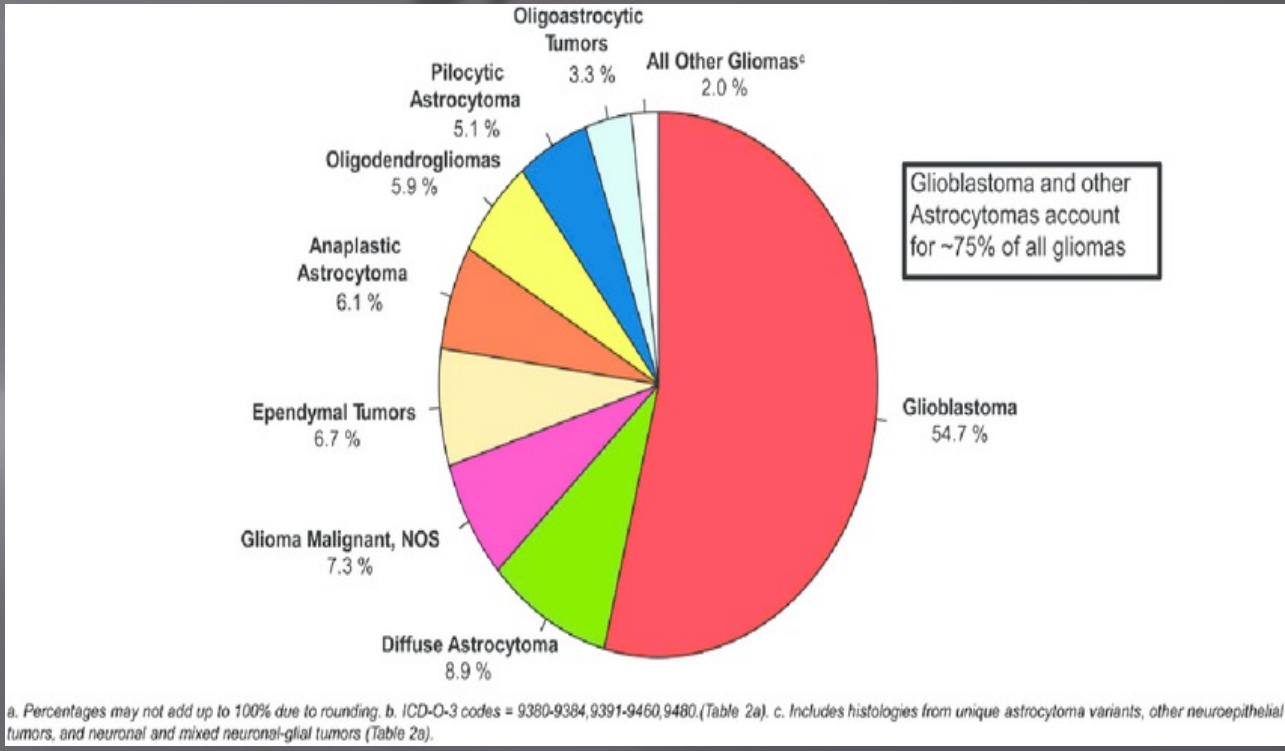
GBM Epidemiology

- Most common primary malignant brain tumor in USA & European countries.
- GBMs comprise 16% of all primary brain and CNS system neoplasms and 77-81% of all high grade gliomas.
- Average age-adjusted incidence rate is 3.20-4.64/100,000 population.
- GBMs account for 1.4% of all cancers & 2.4 cancer deaths/year in the US alone.
- 10,000 new cases of GBM & 4,000 of Grade III gliomas diagnosed each year.
- Higher incidence in men.



de Groot, J.F. (2015). High-grade gliomas. *Continuum. 21(12): 332-344*.

Glioblastoma

- Highly malignant primary CNS tumor
- Originates from the supportive glial cells-glioma
- Rare metastasis to other parts of the body
- Two types of GBM
    a. Primary GBM: accounts for 90% of all GBM
    b. Secondary GBM: develops from astrocytic, oligodendroglioma

GBM Epidemiology

- Median age onset primary GBM-62 yrs with onset as early as 55 secondary GBM 45 yrs.
- Secondary GBM seen in younger patients
- Anaplastic astrocytoma- 51 yrs; Anaplastic oligodendroglioma- 48 yrs.
- High grade gliomas can occur in all ages including children.
- Exclusively occur in the brain but can appear in brain stem, cerebellum and spinal cord.
- Gliomas of lower WHO grade can recur, progress or transform- referred to as secondary GBM.

Outcome Survival

- Remains poor
- Majority of patients 2.5 years
- <5% will survive 5 years or greater
- Mean survival rate 15 months despite aggressive management

GBM Risk Factors

- Efforts to identify specific associations of Gliomas with environmental and occupational exposure have largely been inconclusive and underpowered.
- Pesticides
- Vinyl chloride
- Smoking,
- Petroleum refining and synthetic rubber.
- Use of cell phone
- Prior history of head trauma
- Infections have not been proven to cause brain tumors- but may be helpful in preventing progression.
- ***Neurofibromatosis***

GBM Risk Factors/Li-Fraumeni Syndrome

- First described by Fredrick Li & Joseph Fraumeni in 1969.
- First associated with sarcoma & other diverse tumors.
- Associated with many other types of cancers including brain tumors.
- Inherited in autosomal dominant manner.
- Patients with LiFraumeni syndrome tend to develop cancers earlier than would be expected.

Where we have been?

- First discovered glioma as a glial tumor by Rudolf Virchow in 1865
- GBM long & prolific life.
- Hundreds of different types of clinical trials.
- Outcome survival rates dating back to 1960's 6mos-18mos.
- RT therapy first used 1960's-1970's demonstrated increased survival by 2mos.

Surgical Resection

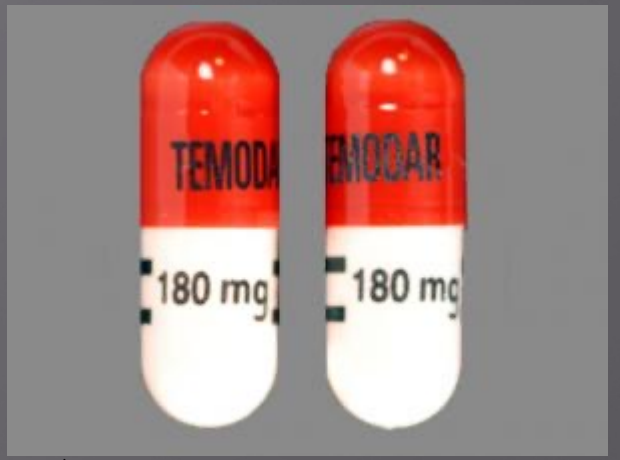
- 1960's recognized as beneficial; although some NS still treated patients with conservative/supportive treatment
- Gross total resection vs biopsy-doubles survival rates by 11-12 mos
- Very dependent on whether tumor is located in eloquent area of brain
- Surgery + RT + Chemo (various heterogeneous chemotherapy) improved MS to 14 mos

Radiation Therapy

- Various dosages employed
  - 60 Gy improved MST by 6 months
  - 6000 rads *WB/RT + surgery increased 6 mos survival rate 2-3x that in control group
- Radiosensitizers
  - Misonidazole + Metronidazole- studies demonstrated no consistent benefit.
- Alterations in RT regimen-no significant improvement in MS
  - Dose escalations >60 Gy
  - Hyperfractionation or accelerated superfractionated RT
  - Brachytherapy
  - Neutron vs Photon boosts
  - Radioactive targeting agents
  - Stereotactice radiosurgery with linear accelerator or gamma knife

*WB/RT: Whole brain RT.

Chemotherapy



- Nitrosurea Agents
  - Systemic BCNU-RTC demonstrated marginal improvement in MS (2 mos)
  - Other nitrosureas studied including CCNU and Semustine (older CCNU)
  - Universally remained standard of care up for adjuvant chemotherapy into the 1990's
  - Gliadel (BCNU) delivered locally to resection cavity MS increased by 2 mos
- Alkylating Agents/TMZ
  - 2005 single study by Stupp et al demonstrated benefit of Temozolomide
  - Given concomitantly after surgical resection along with RT (6 weeks)
  - Followed by adjuvant therapy up to 12 cycles
  - Increasing long-term survival rates up to 3 years

Survival Rates

- Glioblastoma-14-16 months
- Grade III gliomas-survival rates primarily dependent on histology but…3-5 years for anaplastic astrocytoma; 15 years for oligodendroglioma
- Clinical prognostic factors include age, performance on Karnofsky Performance Status Scale and ***histology***

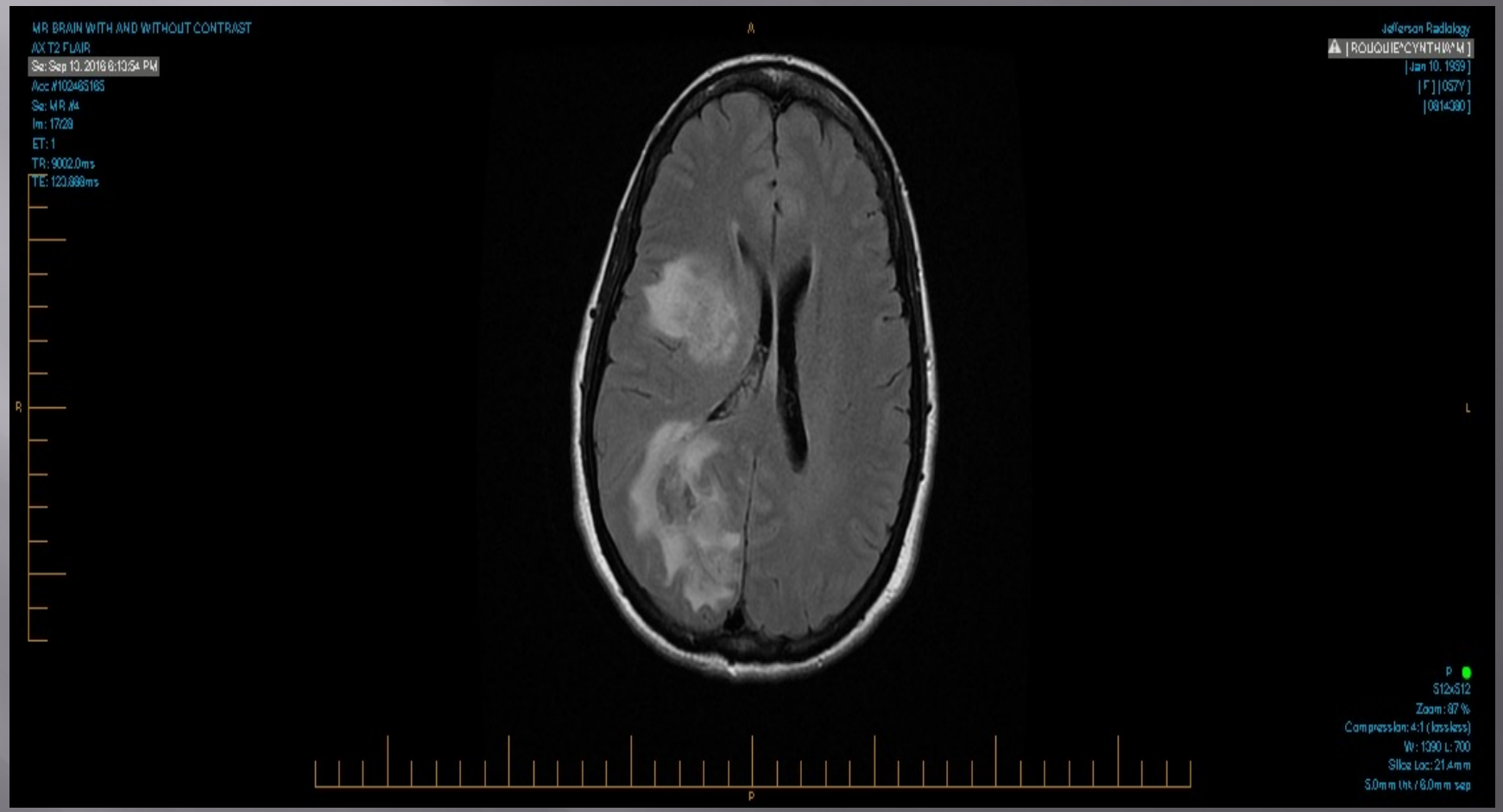
Do not repeat the tactics which have gained you one victory, but let your methods be regulated by the infinite variety of circumstances (Sun Tzu 6.28)

Where are we now?

Case Presentation 1

- CR is a 58 year-old right handed woman presented July, 2016 with unremitting right sided HA, left VF disturbances described as flashes. Decreased peripheral vision OS. Spinning & lights left VF. Episodic & not associated with other seizure like symptoms.
- No other motor or sensory symptoms at initial presentation.
- Visual disturbances continued to worsen hampering her ability to drive.
- Headaches worsened & were associated with nausea but no vomiting.
- MRI scan performed September 2016 demonstrating tumor in right temporal/occipital region.
- Brain bx performed 2016 in OSH
- Pathology: AA WHO Grade III. No molecular/genetic testing performed (insufficient tissue sampling).

CR Case Presentation 1
Initial MRI 9/2016



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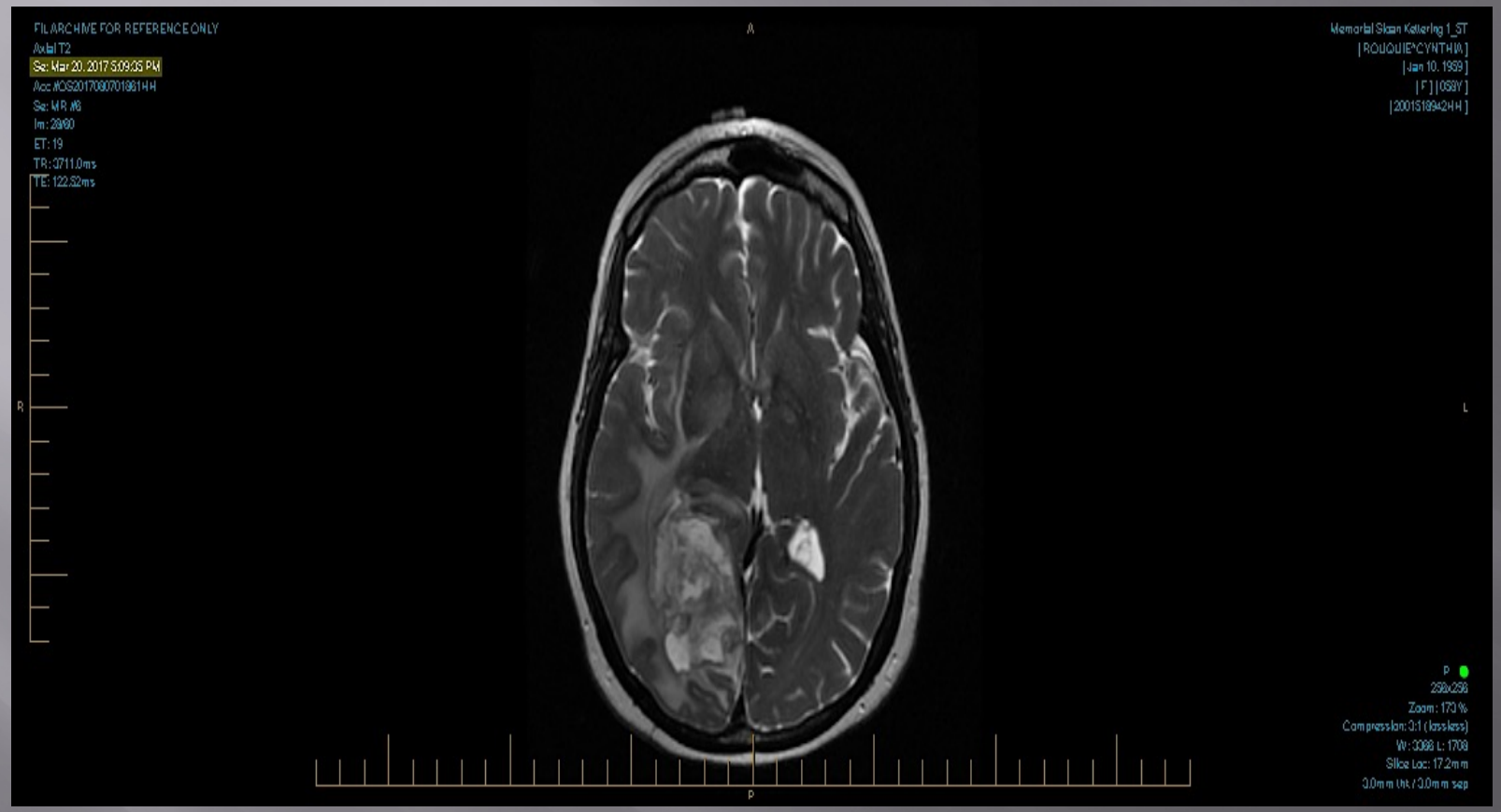
Case Presentation 1

- Started on Chemoradiation-TMZ 10/3/16-11/11/16. (total 4 cycles)
- After 2 cycles; MRI 1/17 demonstrated questionable progression.
- March 2017 developed generalized weakness, HA.
- Repeat MRI –progression
- Resection March 2017
- Final pathology: AA with necrosis, treatment effect. IDH 1 wild type, MGMT unmethylated. EGFR gene amplification detected in 92% of cells.
- Decision to start CCNU 5/3/17 & 6/27/17.
- MRI July 2017 demonstrated progression of tumor with new areas of enhancement.

CR Case Presentation 2
2017 prior to resection



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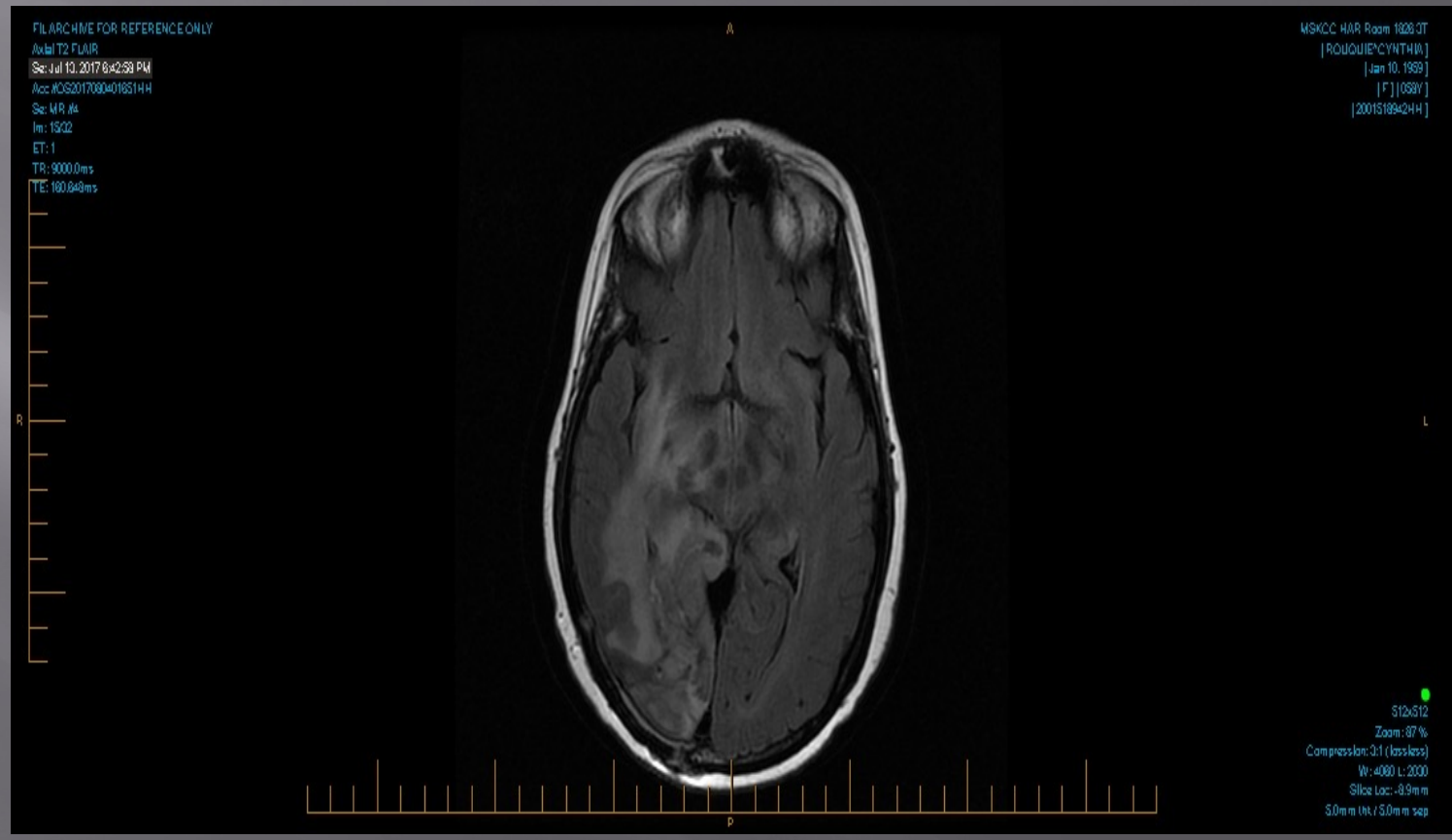
July 2017-Progression

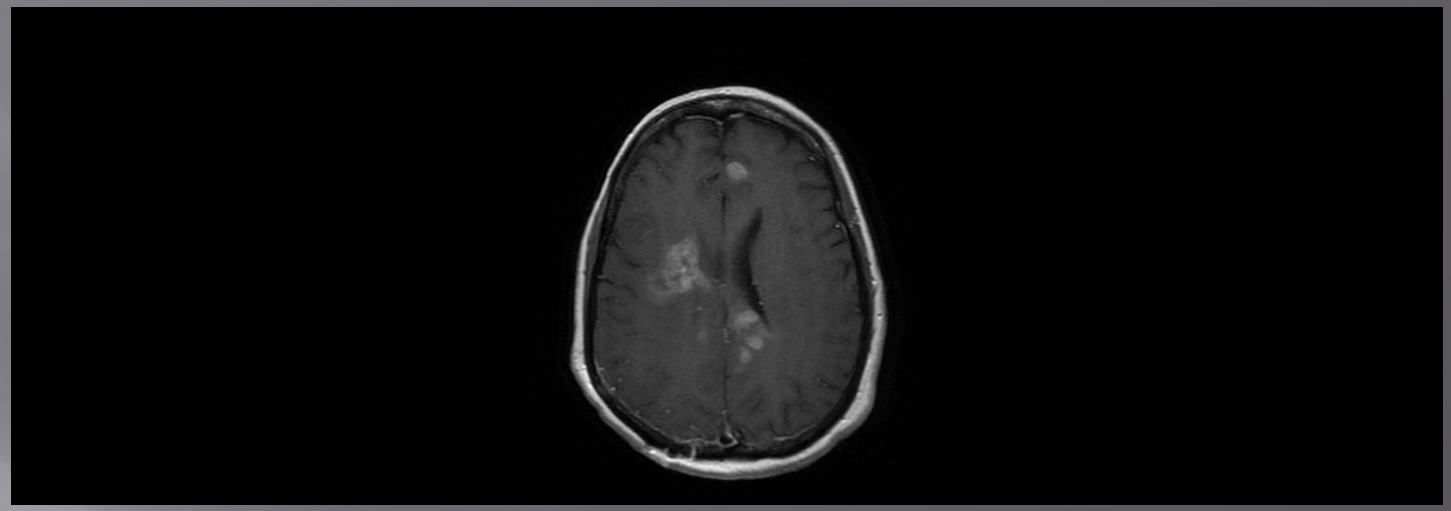
CR

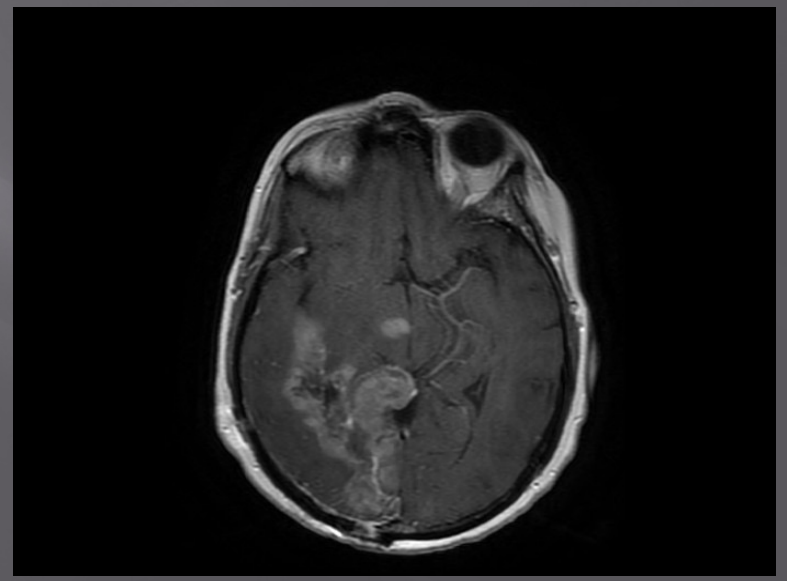
- Continued clinical deterioration
- MRI evidence in July 2017 demonstrating progression



CR-Case Presntation 1

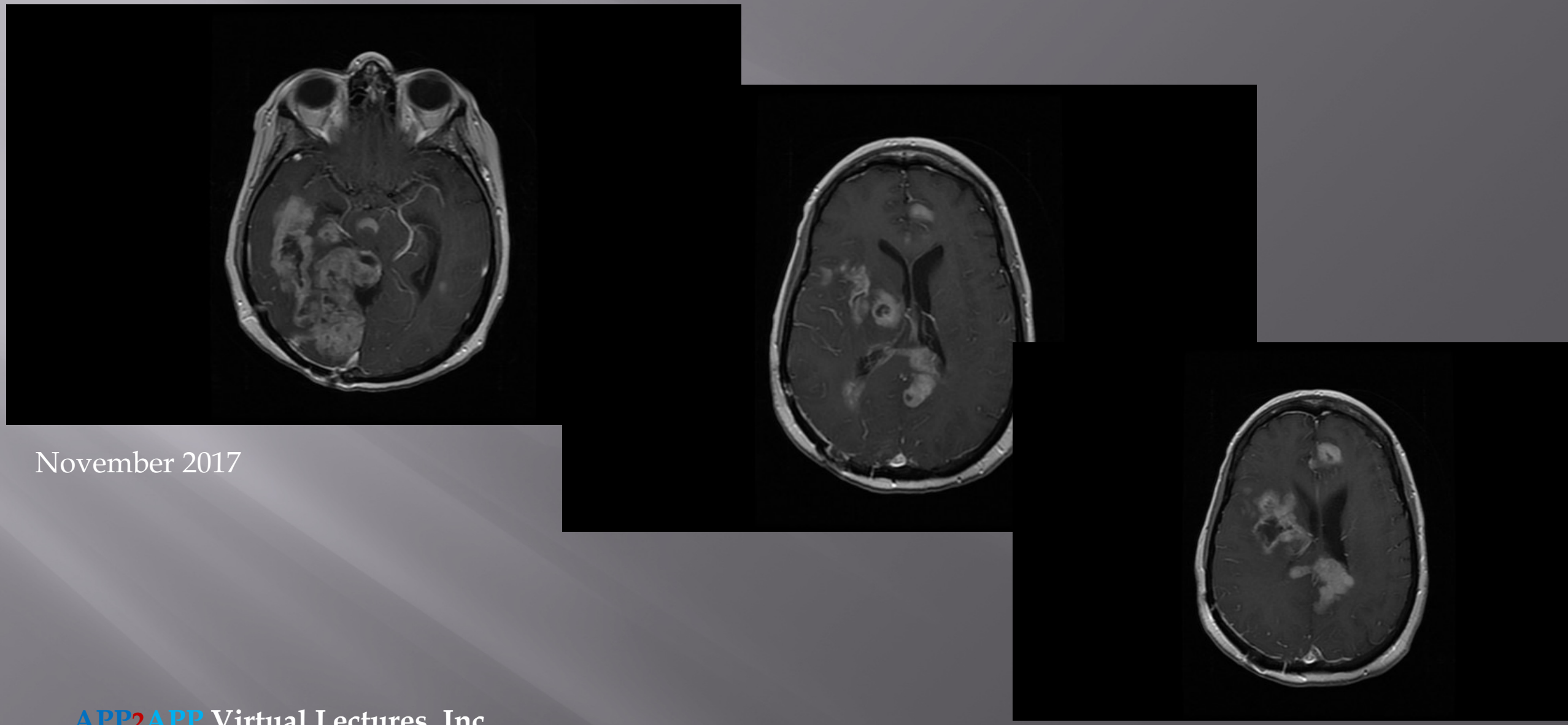
- Patient continues to decline neurologically; increased left field cut, neglect, confusion, poor cognition/short term memory.
- Chemo changed to Bevacizumab 10mg/kg IV q2weeks.
- Some discussion regarding enrollment in trial.
- 10/17: MRI imaging demonstrated continued progression of disease; now extending into left hemisphere- now multifocal
- Decision to add Irinotecan 125 mg/m2 IV every 2 weeks.
- Continued on Decadron





Case Presentation 1

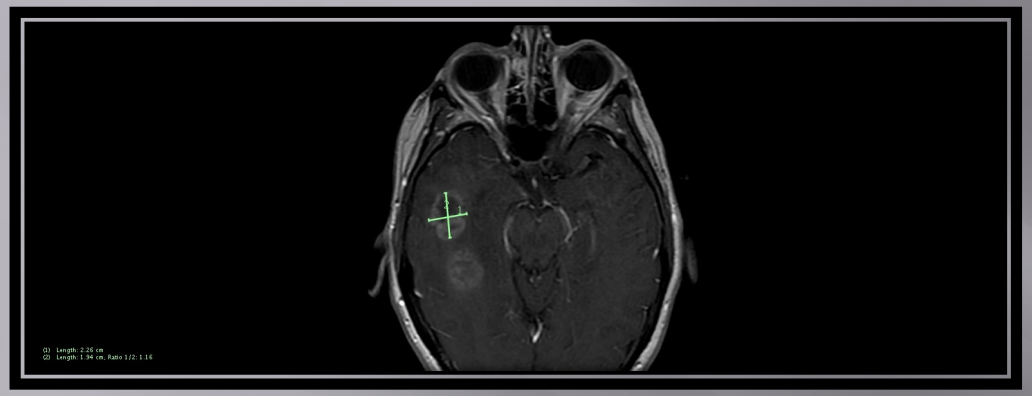
- Rapid neurological deterioration despite treatment with Bevacizumab & Irinotecan.
- Considered chemotherapy failure
- Began discussion of hospice with patient and family.
- Deceased December 23rd, 2018

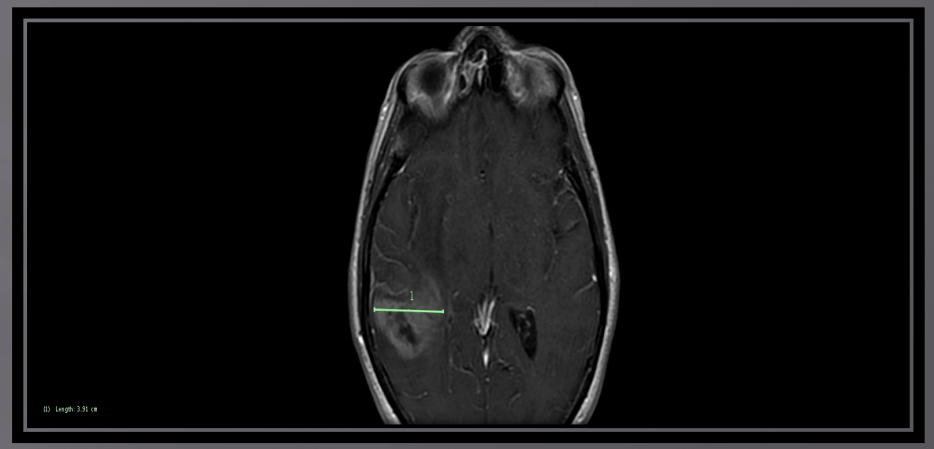


November 2017

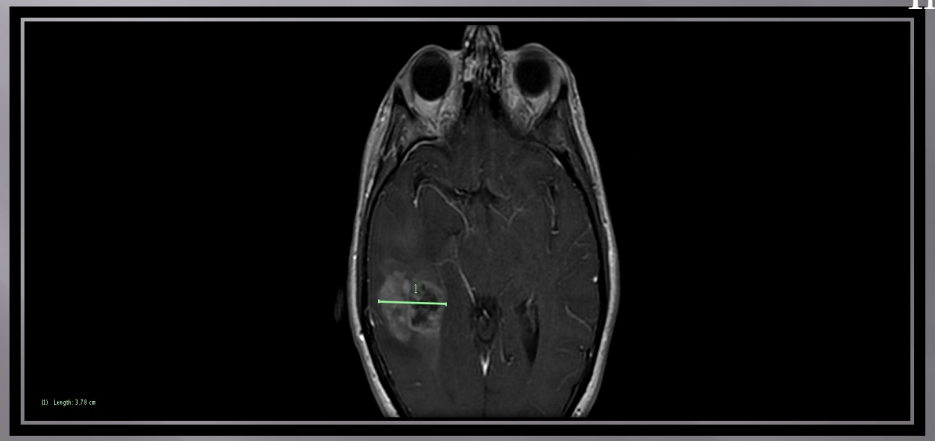
CC- Case Presentation 2

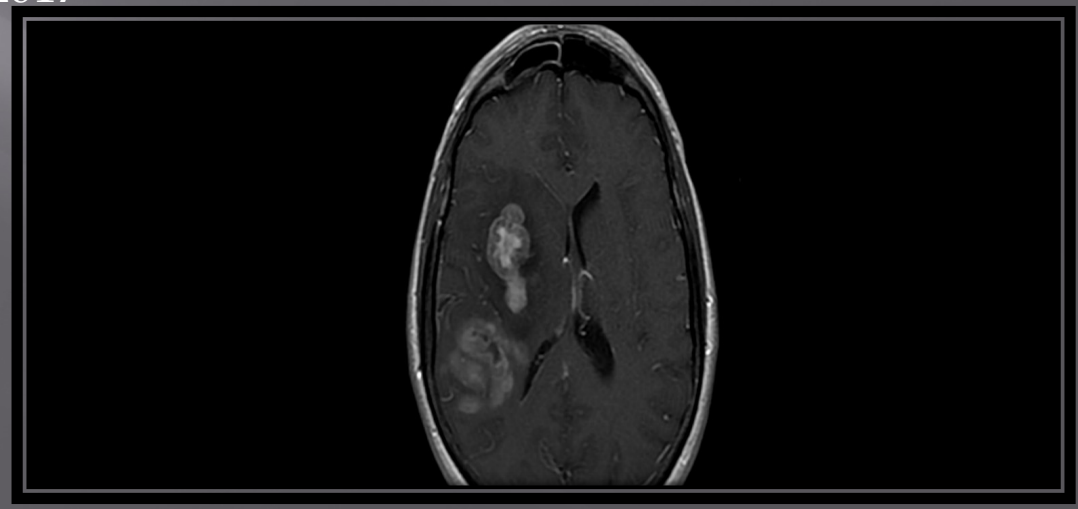
- CC 62 year-old right handed woman 6/1/2017 while riding her pony, jumped off when pony starting speeding out of control.
- Patient fell, hit her head sustaining closed head injury & fractured left ankle.
- No signs of concussion including LOC.
- Brought to ED, CT scan performed, demonstrating 2 tumors in the right frontal lobe.
- MRI imaging: demonstrated extensive tumor involving right temporal & frontal lobes with enhancing masses.
- Denies any seizure activity
- 2 1/2 years ago fell of horse sustaining neck fracture & concussion. Developed one episode of transient confusion.
- Presenting with persisting headache.





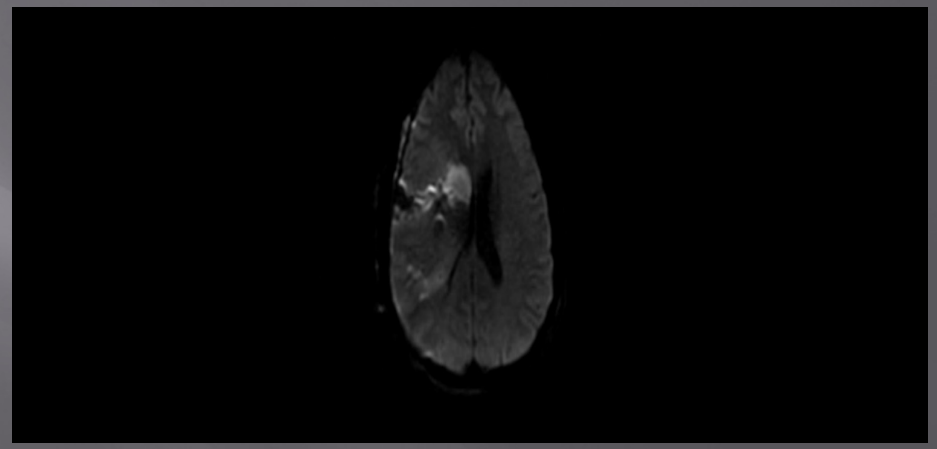
Initial MRI Imaging 6/2/2017





Case Presentation 2

- 6/13/17-Subtotal resection both lesions.
- Post-op imaging revealed acute infarct R caudate/frontal corona radiata.
- Pathology: GBM w MIB 15-20% right frontal tumor. MIB right temporal tumor 40%. IDH-1 WT by IHC. MGMT promoter methylated.



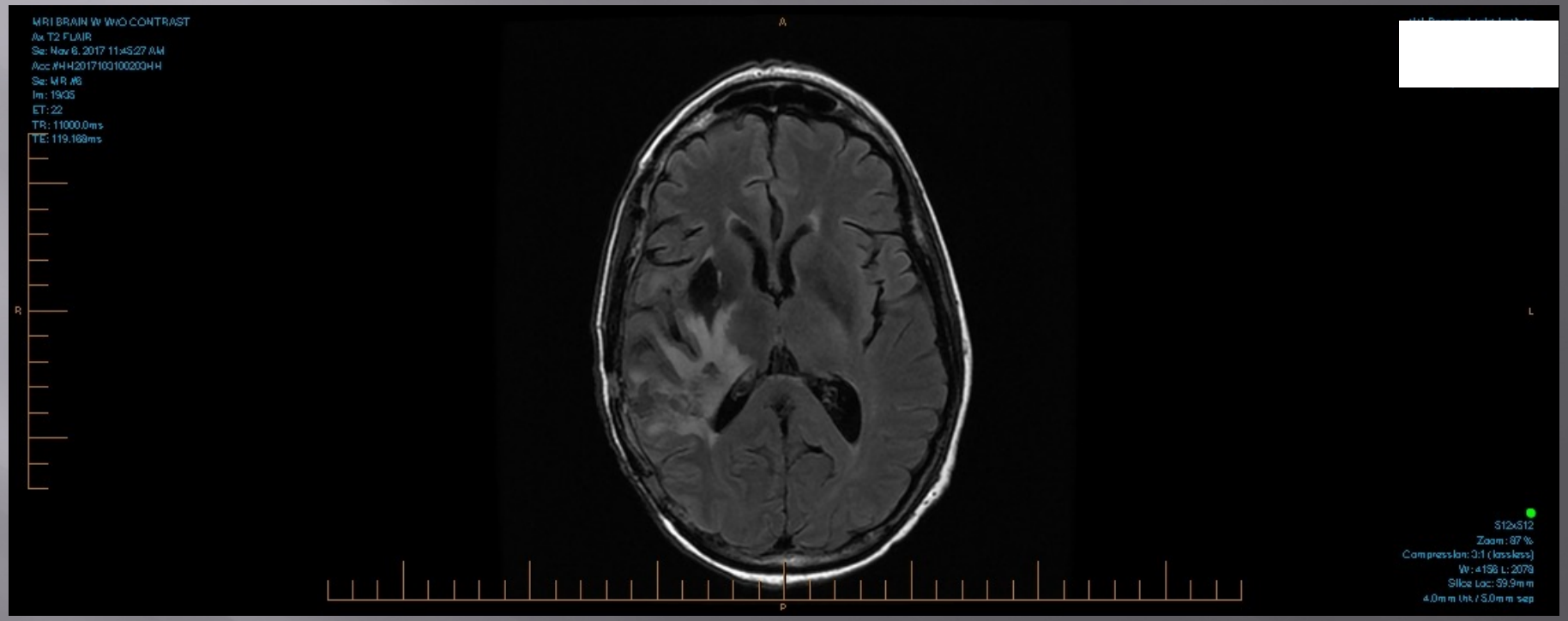
Case Presentation 2

- Neurological examination: Delayed recall, left homonymous hemianopia, mild left hemiparesis, ataxic gait secondary to LLE weakness.
- Overall tolerating chemotherapy well. Complains of nausea with vomiting.

Case Presentation 2
Treatment

- Chemoradiation: 60 Gy/33 fractions with concurrent TMZ @75mg/m2
- Completed 6 cycles of adjuvant TMZ 110mg/m2 q28 days, x5 days
- Surveillance MRI every 2 months essentially stable
- Refused steroids; believed steroids would enhance tumor progression
- Started Ketogenic diet

November 2017



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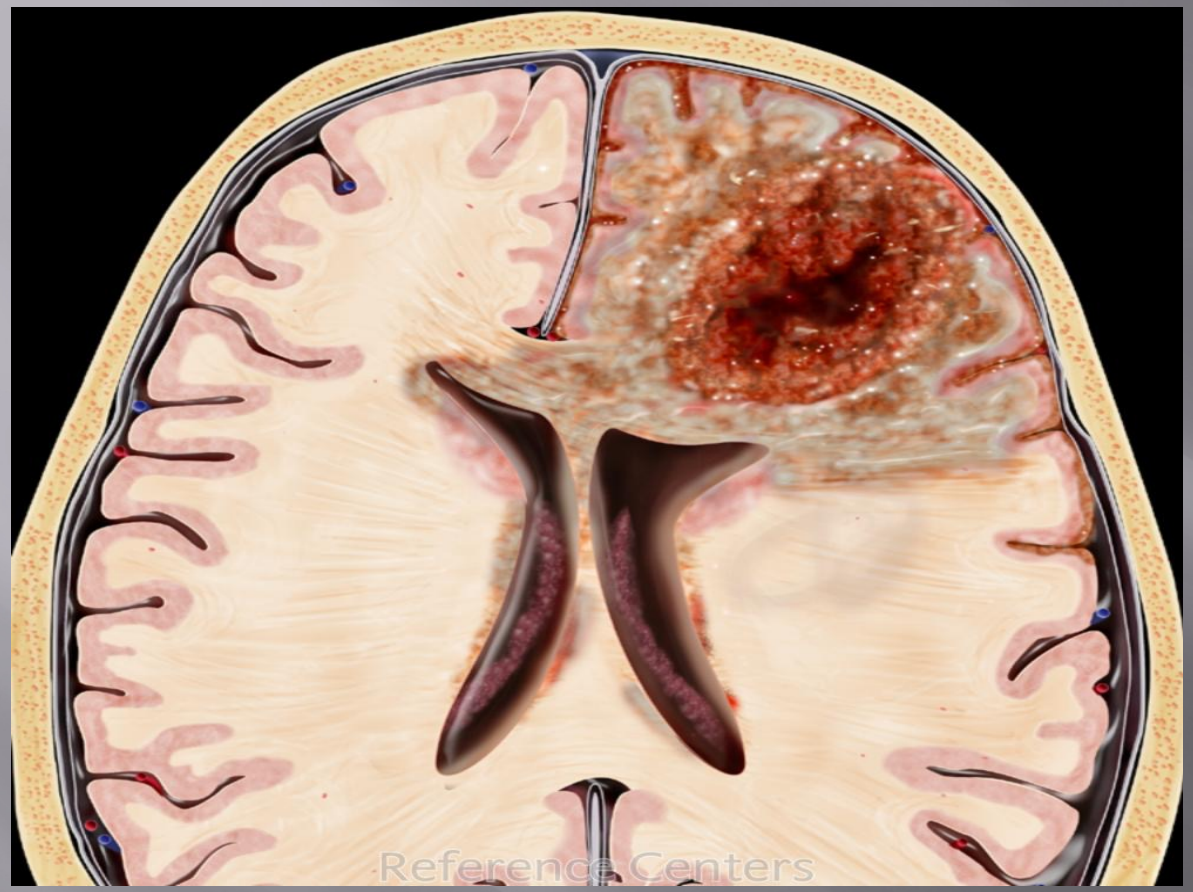
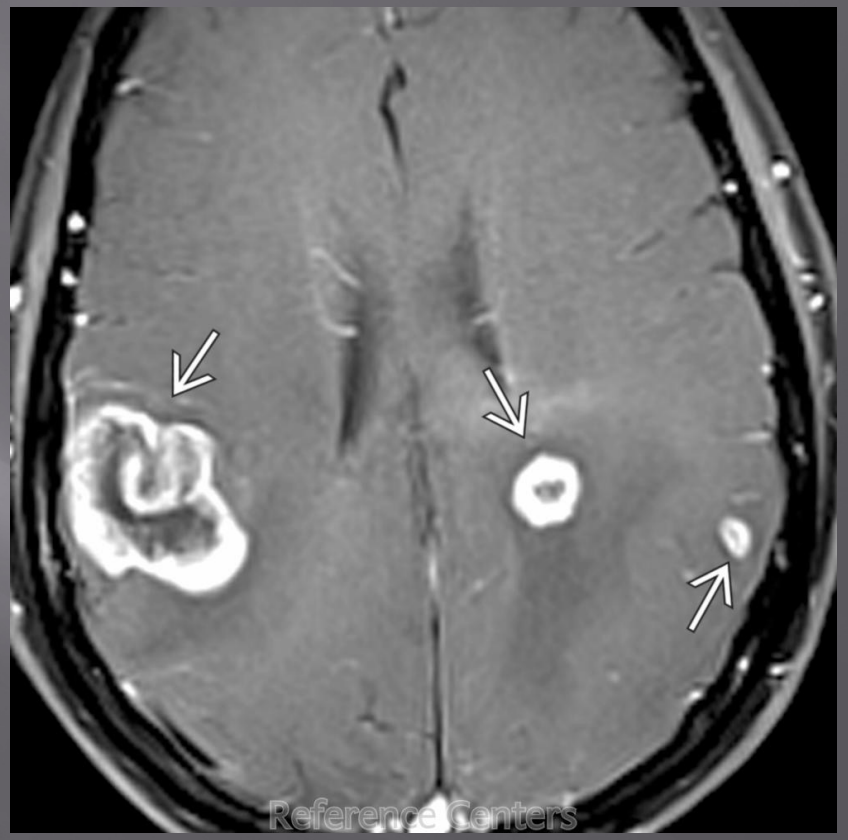
CC-Case Presentation 2

- Continued to do well clinically until 7/2018
- Started on CCNU/Bevacizumab IV at reduced dose
- November 2018 concern for disease progression and now with left hemiparesis
- Surgical options discussed
- Continued with surveillance MRI q 6 weeks-2 months
- Returned to hospital 1/1/19 after being found unresponsive
- Deceased 1/4/2019

Diagnosis of GBM/Presentation

- GBM presentation can vary & will depend on location.
- May present with seizures, headache, focal neurological deficits.
- Majority of patients may mimic acute stroke.
- Diagnosis essentially made through imaging, surgical biopsy/resection/pathology
- Majority of gliomas located in supratentorial region
- Brainstem gliomas
- Rarely occur in cerebellum





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Axial graphic shows a centrally necrotic infiltrating mass with extension across the corpus callosum; a peripheral rind of tumor is seen surrounding the necrotic core, typical of GBM.

What has changed?

Imaging Advances

- Advanced diffusion weighted imaging
  - ❖ Can assist in discriminating GBM from CNS lymphoma
- Perfusion weighted imaging
  - ❖ Can be used to monitor clinical effectiveness of antiangiogenic drugs such as bevacizumab
  - ❖ Measure relative rCBV-decreased in patients with drug response to bevacizumab
  - ❖ Increased rCBV values correlates with EGFR amplification-may have prognostic & treatment monitoring applications
    applications.
- PET Scan
  - ❖ Assists in differentiating GBM from CNS lymphoma

Classification of Tumors
Revised WHO Classification

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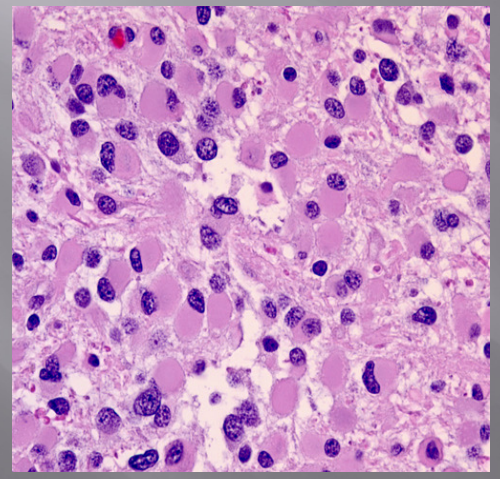
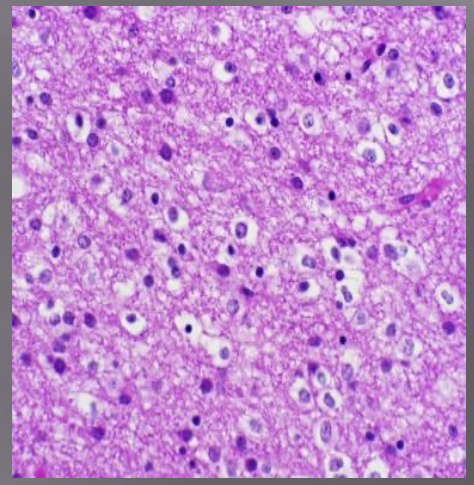
WHO Classification

- 2016 revised WHO classification of tumors of the CNS.
- Last revision 2007.
- Classification in past based on concepts of histogenesis or phenotype and microscopic similarities.

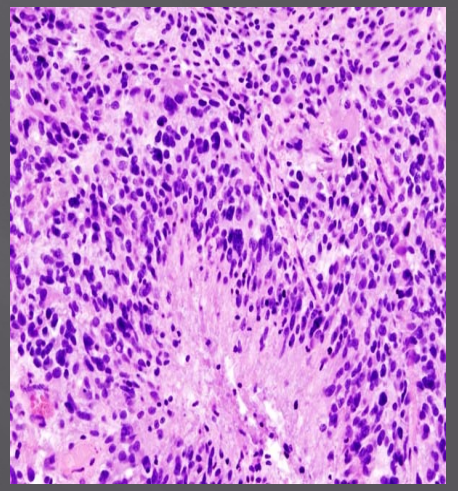
Astrocytoma



Oligodrendroglioma



Glioblastoma



WHO 2016 Classification Tumors of the CNS

- Use of phenotypic and genotypic parameters now used along with histogenesis.
- Goal: yield more biologically homogeneous and narrowly defined diagnostic entities → greater diagnostic accuracy.
- Improved patient management.
- More accurate determination of prognosis and treatment response.

World Health Organization (WHO 2016) Grading of CNS System Tumors

- Grade I: low proliferative potential, usually discrete. Possibility of cure with surgical resection.
- Grade II: Infiltrative, low mitotic index, but often recurs, my dedifferentiate to a higher grade lesion.
- Grade III: Increased cellularity, higher proliferative index; polymorhpic.
- Grade IV: Hypercellular higher proliferative index, highly pleomorphic. Bizarre appearance with endothelial proliferation; necrosis definitive finding.

Adapted from: https://braintumor.org/wp-content/assets/WHO-Central-Nervous-System-Tumor-Classification.p

Glioblastoma-Subgroups

- IDH-WT GBM: includes Giant-Cell, Gliosarcoma and Epithelioid GBM
- IDH-mutant GBM
- GBM-NOS (not otherwise specified)

WHO Classification-CNS Tumor Diagnosis

- Consist of a histopathological name followed by the genetic features.
- Example: Oligodendroglioma, IDH-mutant and *1p/19q-co-deleted*.
- For a tumor lacking a genetic mutation-term "wildtype"; e.g. Glioblastoma, IDH-wildtype

"GENOTYPE TRUMPS PHENOTYPE"

GBM Molecular Pathophysiology

- IDH
- MGMT
- EGFR

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Epidermal Growth Factor Receptor

- EGFR amplification may correlate with survival & prognosis.
- Tumors with EGFR amplification tend to be resistant to drugs & RT.
- Makes the environment more hospitable to tumor growth.
- EGFR amplification is a common driver of GBM progression.
- EGFR is found in nearly 40% of all cases of GBM.
- EGFR is associated with cell survival, angiogenesis & decreased time to progression.
- EGFR receptor-EGFRvIII

Carlsson SK, Brothers SP, Wahlestedt C. Emerging treatment strategies for glioblastoma multiforme. *EMBO Molecular Medicine*; 2014.

Epidermal Growth Factor Receptor

- Monotherapy and combination EGFR targeted therapies initially promising on initial trials; later studies failed to demonstrate improvement in survival rates.
- Other pathways PI3-K/mTOR, PDGFR, VEGF/angiogensis, Hedgehog-GLI1; also thought to be therapy promising.

Lo HW. EGFR-Targeted Therapy in Malignant Glioma: Novel Aspects and Mechanisms of Drug Resistance. 2010, *Curr Mol Pharmacol, 3(1): 37-52.*

EGFR TARGETED THERAPIES
Epidermal Growth Factor Receptor

- Gefitinib (Iressa): used in locally advanced & metastatic NSCLC
- Erlotinib (Tarceva): used in metastatic NSCLC
- Cetuximab (Erbitux): used in squamous cell CA Head & Neck (recurrent or metastatic
- Lapatinib (Tykerb/Tyverb): used in advanced & metastatic breast CA; HER-2 + who have failed other drugs
- Panitummumab (Vectibix): Used in colorectal CA that has failed other therapies with metastatic disease***

**All but Panitummumab has been used in Phase I & II GBM trials.

IDH Mutations (Isocitrate dehydrogenase enzyme 1 & 2)

- Assessing for IDH mutation standard for diagnostics.
- Two types of IDH mutations observed in GLIOMA; IDH1, IDH2.
- Studies have shown IDH mutations are early events in gliomagenesis, & remain present with tumor progression.
- IDH mutated tumors occur in all grades II-IV diffuse glioma-but are absent in other primary brain tumors.
- Occur in 70-80% of all adult grades II & III glioma cases; 5-10% in GBM in particular in patients <50 years of age.
- Clinical significance: IDH mutated tumors have improved outcome compared to non-IDH mutated tumors of similar histopathological grade.
- IDH mutations used to identify patients that will benefit from chemotherapy to radiotherapy.

Molecular Prognostic Factors- MGMT promoter methylation (O-6-methylguanine-DNA methyltransferase)

- DNA repair protein that reverses damage induced by alkylating agents such as TMZ
- Methylation of the MGMT gene promoter results in decreased expression of the enzyme potentially rendering tumor cells more susceptible to alkylating agents.
- Usually present in IDH mutation.
- Best predictive factor in outcome.

de Groot JF. High-grade gliomas. *Continuum*. 2015; 21(2).

Glioblastomas-Wildtype vs IDH mutation

- 2016 CNS WHO divides Glioblastomas into two categories.
- Glioblastoma, IDH-wildtype (90% of all cases) which corresponds most frequently with clinically defining tumor as "primary" glioblastoma or *de novo* glioblastoma and predominates in patients >55 years.
- Glioblastoma, IDH-mutant (about 10% of all cases) corresponds closely to so-called secondary glioblastoma with a history of prior lower grade diffuse glioma-arising in younger patients

Current Treatment Strategies

Some guiding principles

Surgical Resection

- Maximal surgical resection.
- Multiple retrospective studies have confirmed the therapeutic benefits of gross total resection of tumors.
- Overall survival is extended in patients with GTR.
- Use of fluorescent marker 5-aminolevulinic acid while operating under blue light in OR may assist NS with achieving GTR goal.
- If not possible, brain biopsy need for pathology/molecular markers.

Chemotherapy

- Very few chemotherapy options inpatients with GBM due to *"blood brain barrier"* .
- Many available chemotherapy agents cannot pass BBB.
- In those agents identified as having the ability to cross the BBB-challenging as they have not been proven effective in GBM.
- Chemotherapy can be given prior to surgery, concurrent with RT, or as adjuvant therapy.
- Delivery options include oral, IV, IA, intrathecal or intratumoral.

Temozolomide

- 2005 landmark study demonstrating effectiveness against GBM.
- Alkylating agent, works at damaging the DNA of the tumor.
- Major side effects include bone marrow suppression (WBC, platelets), constipation, nausea/vomiting & fatigue.
- Overall well tolerated.

Standard Treatment

- 2005-standard treatment for GBM RT & TMZ → 6 cycles

Average survival-14.5 mos; 2 year survival rate 27%

- 2015-standard treatment for GBM RT & TMZ → 6-12 cycles with addition of tumor treating fields (NovoTTF, Optune)

Average survival-20.9 mos; 2 year survival rate 43%.

- This includes maximal surgical resection prior to commencement of therapy.

Initial Treatment

- Chemoradiation (RT + TMZ) 6 weeks
  - RT with 60Gy 5 days/week
  - TMZ 75mg/m2 7 day/week
  - After 6 weeks; chemo break x2-3 weeks with initial MRI
- Adjuvant TMZ 6-12 cycles
  - TMZ 150mg/m2 and increase as tolerated
- MRI q2-3mos
  - Assess for progression

GBM Progression

- No standard guideline for GBM progression
- Can be rechallenged with TMZ x 6cycles
- Addition of bevacizumab-monoclonal antibody that works against vascular proliferation and therefore starves the tumor of blood supply-directly works against VEGF
- Other agents/combinations
  - ❖ Bevacizumab + CCNU-overall outcome survival increased by 12 months.
  - ❖ Irinotecan- monotherapy or in combination with bevacizumab
  - ❖ PVC (Procarbazine + CCNU + Vincristine
  - ❖ EGFR targeted agents

Emerging Therapies Immunotherapies & Other Targeted Treatments

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What we know.

- GBMs are associated with 3 over-lapping pathways.
- On-going research efforts to inhibit signaling pathways.
- No single molecularly targeted agents have proven to be effective.
- Hypothesis: Molecular heterogeneity of GBM-rendering emerging therapies ineffective.
- Recurrent tumors-molecular profile changes from original compounding treatment-tumor is constantly evolving.
- Recurrent tumors; described as an ever evolving molecular landscape.

Immunotherapy Strategies-GBM

- Cytokines
  - Interferon, high dose IL-2
- Vaccines
  - EGFRvIII Vaccines
  - Several studies examining effectiveness of vaccines targeted at EGFRvIII-
  - benefit not conclusive; further investigation on-going
- Checkpoint Inhibitors
- Adoptive cell transfers (CART cells)
- Multiple trials targeted at identified pathways.

Vaccines

POLIOVIRUS THERAPY FOR GLIOBLASTOMA HAS THREE-YEAR SURVIVAL RATE OF 21 PERCENT

Phase 1 study of Duke therapy shows long-term survival benefit for a lethal cancer

Emerging Treatment Strategies

- Monoclonal antibiodies
  - Prevent receptor signaling by disrupting downstream receptor activation
  - Currently bevacizumab inhibits vascular growth of tumors (VEGF)
  - AMG595 directly effects EGFRvIII receptors-but in only small population of patients with GBM
- Innate immunotherapy
  - Reengineer patient's innate immune system to combat their own GBM tumor
- Oncolytic viruses
  - Replication incompetent except in specific cell populations such as tumors.
  - Selected viruses find their host cell through specific marker identification; virus undergoes lytic expansion leading to cell destruction.
  - Once tumor cell population is eliminated; patients can be treated with anti-viral medication
  - Herpes Simplex 1 currently being explored.

Emerging Treatment Strategies

- Novo-TTF™

- ❖ Antimitotic treatment selectively disrupts division of cells.
- ❖ Tumor treating fields that uses low-intensity, intermediate frequency an electrical field.
- ❖ In clinical trials TTF has shown to cause mitotic arrest and apoptosis.
- ❖ Added to maintenance TMZ clinical trials demonstrated significantly prolonged progression-freedom/ OS.
- ❖ Clinical trials examining the benefits of Novo-TTF + XRT + concurrent TMZ vs standard therapy

Stupp R, Taillibert S, Kanner AA, Kesari S, Steinberg DM, Toms SA et al. Maintenance therapy with tumor-treating fields plus temozolomide vs temzolomide alone for glioblastoma: a randon
JAMA, 2015; 314(23: 2535-2543. doi: 1o.1001/jama.2015.16669.

NovoTTF™

Ketogenic Diet-GBM

- All tumor cells have altered/dysregulated metabolism.
- Have an increased reliance on glucose.
- Evidence demonstrating treatments affecting cellular metabolism may be effective method to improve current therapies.
- Ketogenic diet is a high fat, low carbohydrate & protein diet.
- Clinical trials demonstrate possible effectiveness when used with other adjuvant therapies; bev, temozolomide, RT vs. monotherapy.
- Uses with tolerability and feasibility of diet.

Woolf EC, Scheck AC. The ketogenic diet for the treatment of malignant glioma. *J. of Lipid Res*. 2015. 56 (5-10).

Clinical Trials

- Currently 320 active & recruiting clinical trials GBM internationally.
- Most studies directed at methylated GBM vs unmethylated
- Some studies directed a recurrent GBM
- Investigations on going examining effectiveness of NovoTTF + XRT + concurrent TMZ
- Further investigation on going immunotherapy and other targeted chemotherapies.
- Maximum surgical resection + intraoperative XRT

https://clinicaltrials.gov

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