

Translational Discovery Forum on *Neuro-Oncology*

Case Report

CH

- 40 year old white male presented in 2004 with a CVA near the internal capsule on the left. He had residual right sided hemiplegia and facial weakness.
- Serial imaging done until 6/2008 when increased cellularity noted and biopsy done.

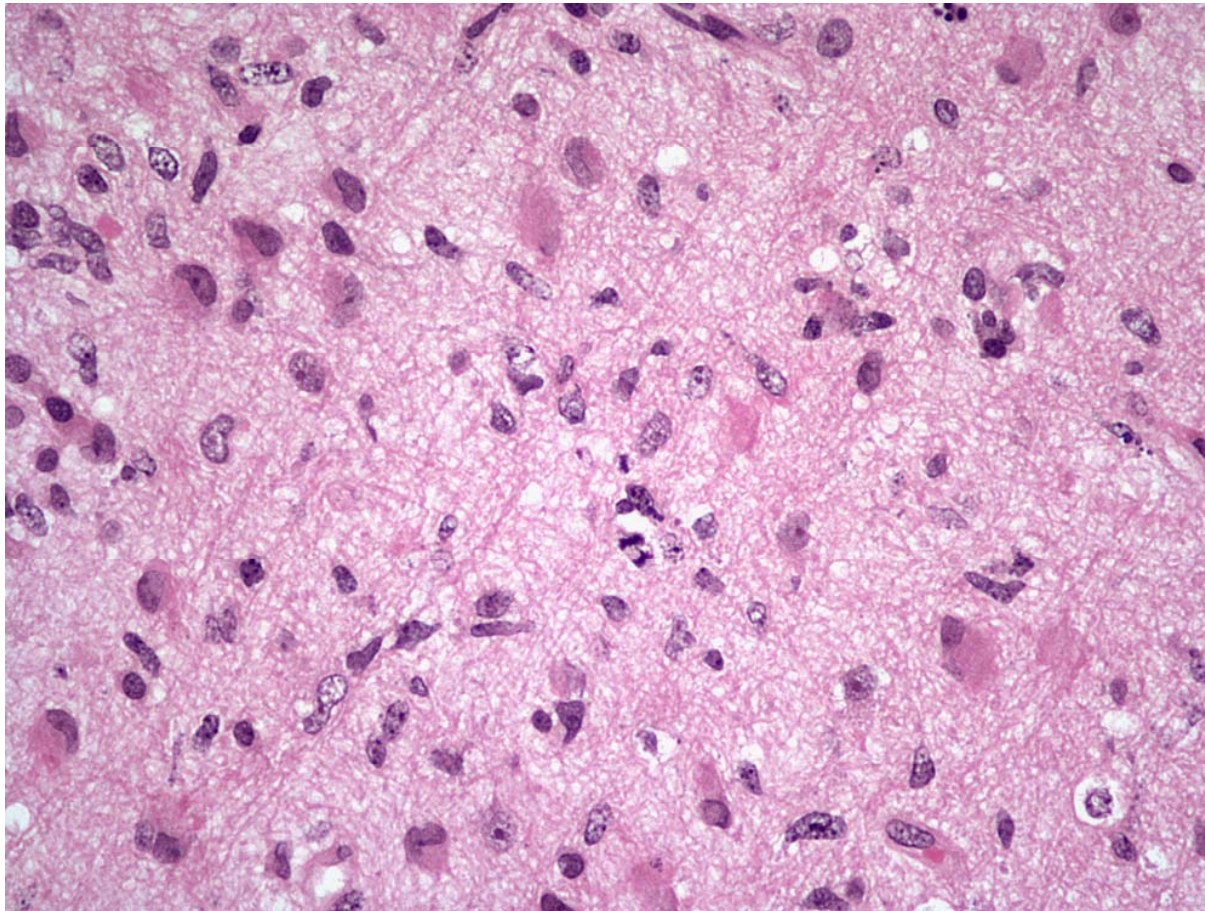
CH

- PMH: Neurofibromatosis Type I, lumbar schwannoma status post resection X 2, GIST tumor of jejunum, hypertension, hyperlipidemia, capillary hemangioma
- FH: 2 children with NF1
- SH: works as shipping supervisor

CH

- Physical Exam: Slight facial droop on right, grade 2-3, strength 4+ / 5 on right, tandem walk leans to right.
- Laboratory: WNL

Anaplastic Astrocytoma



CH: Course

- XRT plus temozolomide 75mg/m²/ day for 6 weeks completed fall 2008.
- Maintenance temozolomide
- CNS hemorrhage 6/29/2009 with residual flaccid right upper extremity, 3/5 in lower, moderate aphasia

CH: Course

- With physical therapy strength improved and in ambulating around deck he fell off and fractured is right hip, 9/2009.
- Off temodar, tumor progressed. T has been restarted and decadron increased.
- Off temodar for CVA, tumor progressed and when restarted tumor remitted.



Primary Brain Cancer: Incidence in 2008

- 21,810 new cases predicted¹
- 13,070 deaths/year¹
- 1.4% of all cancers and 2.4% of all cancer deaths²
- 20%–25% of pediatric cancers^{2,3}
- 60% are malignant glioma³

1. Thun, Michael J et al. *CA Cancer J Clin.* 2008;58:71-96.

2. <http://www.cancer.org/>. Accessed June 2000.

3. Chamberlain MC, Kormanik PA. *West J Med.* 1998;168:114-120.

Neurofibromatosis I

- Autosomal dominant: 1/3000 people
- Vascular abnormalities increased.
- Neurological events in 55% including headache, epilepsy, stroke, neurofibroma, white matter disease, hydrocephalus, tumors, AVM.
- Majority of tumors are not malignant or high grade.



Prognostic Features

- Age
- Grade of Tumor
- Performance Status
- Extent of Resection
- MGMT status



Treatment of Gliomas

- Dependent upon histology, location, symptoms, age and performance status of the patient.
- Main stay for all patients: Surgery
- Tissue is important in determining treatment and prognosis

Glioblastoma Multiforme: Overall Characteristics

- Grade IV malignant glioma
- Most malignant, invasive, difficult-to-treat primary brain tumor
- Frequency: most common in older adults (peak age, 55–65 years)
- Recurrence: rapid growth; size may double every 10 days
- Median survival: ~ 1 year

Anaplastic Astrocytoma: Overall Characteristics

- Grade III malignant glioma
- Less aggressive than GBM, malignant with somewhat better prognosis
- Frequency: highest in young adults (30–40 years)
- Recurrence: often as a higher-grade glioma
- Challenge: difficult to remove completely with surgery
- Median survival: 3–4 years

High Grade Gliomas

- Due to infiltrative nature all high grade gliomas require adjuvant therapy after surgery
- For unresectable tumors the major treatment will be radiation and/ or chemotherapy



Malignant Gliomas

BTCG

- Supportive 14 weeks
- Radiation 36 weeks

Radiation Therapy: Survival

- Anaplastic Astrocytoma 36 mos (55%)
- GBM 10 mos (6%)

Malignant Glioma: Primary Treatment

- Glucocorticoids control edema
- Surgery:
 - 10%–15% of patients have complete resection
 - Remaining majority of patients have residual and measurable disease after surgery

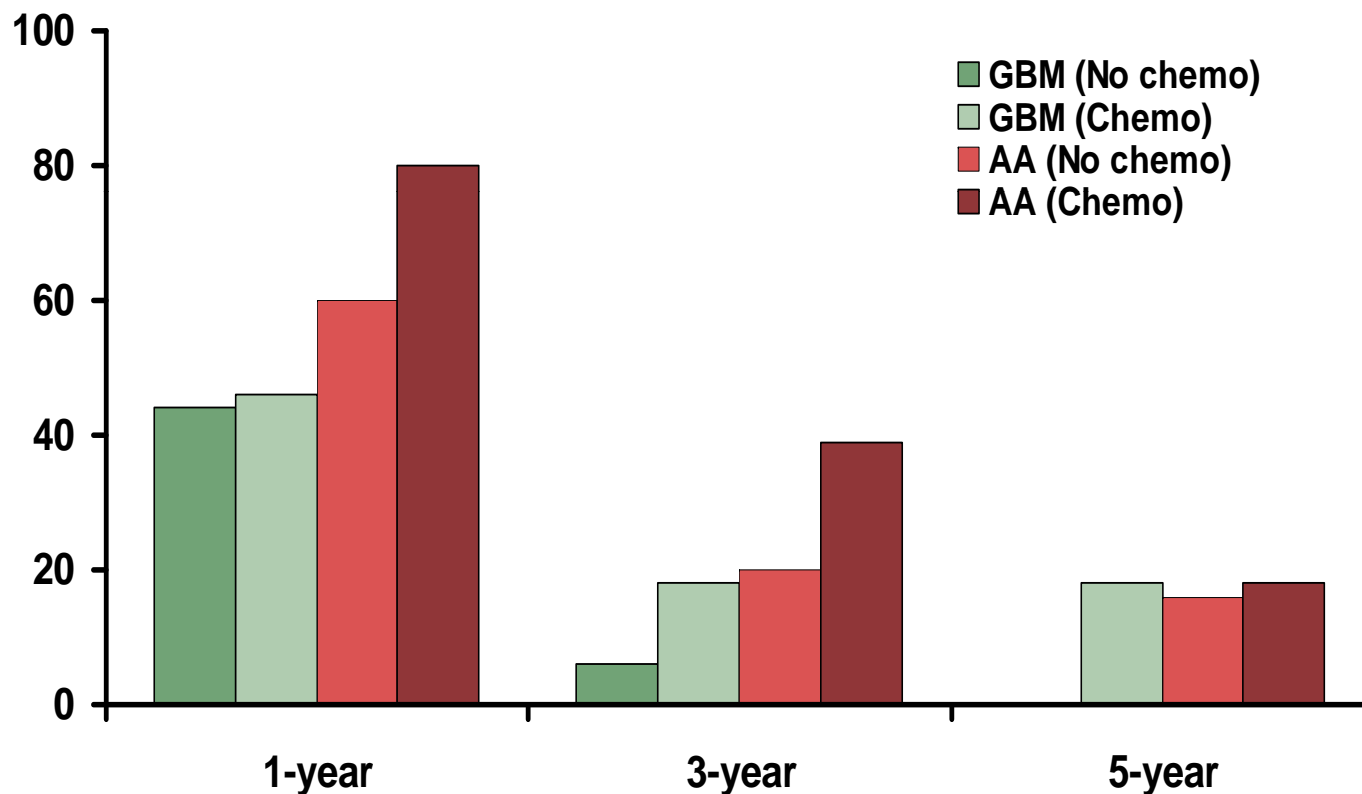
Malignant Glioma: Secondary Treatment

- Radiation therapy
 - Focal brain
 - Stereotactic
 - Brachytherapy
- Adjuvant chemotherapy
 - Single agent: BCNU, CCNU, temozolomide
 - Combination: PCV regimen

BCNU, carmustine; CCNU, lomustine;
PCV, procarbazine + lomustine + vincristine.

Chamberlain MC,
Kormanik PA. *West J
Med.* 1998;168:114-120.

Adjuvant Chemotherapy Improves Survival in Patients With Malignant Glioma



GBM, glioblastoma multiforme;
AA, anaplastic astrocytoma.

Chamberlain MC et al. *West J Med.* 1998;168:114-120.

STUPP Trial

- Randomized trial done in Europe
- XRT vs XRT plus daily temodar then maintenance temodar for 6 months
- Median age 56yrs, 84% debulked
- 2year survival: T+XRT 27%, XRT 11%
- Median survival 14.6/ 12 months
- SEER Median survival 7 months



MGMT silencing and Prognosis

- MGMT gene encodes DNA repair protein
- Protein removes alkyl groups from guanine, important in alkylation
- High levels of MGMT create resistant phenotype by blunting the therapeutic effect of alkylators
- Silencing of gene by methylation reduces DNA repair

STUPP/MGMT

- 45% of patients MGMT was methylated
- Median survival : T+XRT 21.7/ 15 mos
- Methylated vs un methylated 18.2 / 12.2
- Methylated vs Un: 2year 46% vs 22.7 %

Malignant Glioma at Relapse

- Essentially all patients relapse after response to initial treatment
- Most tumors recur within 2 cm of original tumor
- Treatment is palliative
- Responses are not durable
- Few patients with GBM survive more than a few months after relapse



Need New Treatments

- Bevacizumab : antiangiogenesis
- Targeted agents.