



EXTENT OF RESECTION IN TREATMENT OF GLIOMAS

WHAT IS THE EVIDENCE ??

EXTENT OF RESECTION OF GLIOMAS THE DEBATE



- GTR vs. biopsy?
- Debulking vs. biopsy?
- GTR vs. near TR?
- GTR vs. GTR plus margin of “normal” tissue (lobectomy)?
- Only observation.



Hart MG, Grant R, Metcalfe SE .

Cochrane Database of Systematic Reviews.

Review content assessed as up-to-date: 4 January 2007. John Wiley & Sons, Ltd.

- The electronic database search yielded “**2100 citations.**”
- Ten articles identified for possible inclusion however all failed to meet selection criteria and were excluded.
 - 2- not RCTs but literature reviews, 3- prospective but assessed symptoms only, 1- RCT different CT regimens & subsequently analyzed according to the EOR, 4- RCTs but did not specifically compare biopsy v/s resection.
- One RCT of biopsy v/s resection in presumed malignant glioma was identified & discussed (Vuorinen V et al. Debulking or biopsy of malignant glioma in elderly people - a randomized study. *Acta neurochirurgica* 2003;145:5–10).
 - Contained methodological shortcomings.
 - Errors in trial design and under-powering,
 - Findings tainted by high likelihood of being affected by bias and chance.
 - **Conclusion : it is of insufficient reliability to be used to influence treatment decisions.**

Martin A. Proescholdt, Christine Macher, Chris Woertgen, Alexander Brawanski.

Level of evidence in the literature concerning brain tumor resection.

Clinical Neurology and Neurosurgery. 2005; 107, 95-98.

- The level of evidence (LOE) classification was
 - I: 0%
 - II: 6.8%
 - III: 65.7%
 - IV: 27.5%
- 72.5% - observed positive effect of total tumor removal.
- 84.2% - did not report the criteria for treatment assignment.
- 62.5% did not define the terms gross total; radical; partial; or subtotal resection.
- *“To date, no studies with high LOE are available addressing the benefit of gross total brain tumor removal. Although the majority of the reports found a positive effect of radical resection, the reviewed articles contain methodological limitations which may significantly influence the results.”*



LOW GRADE GLIOMAS

- “...the diffuse, infiltrating variety of tumors classified as WHO grade II lesions—specifically, low-grade astrocytomas, oligodendrogliomas, or mixed oligoastrocytomas.”*1
- Low-grade astrocytomas, the most common histological subtypes are the fibrillary, protoplasmic, and gemistocytic variants.
- 15% & 25% of brain tumors in adults & children respectively.*2
- 1500 new cases /yr dx in North America. *3
- Median age : adults 35 years & childhood 6 -12 years.
- Typically arise in frontal, temporal & parietal lobes.*4

*1. Kleihues P, : Pathology and Genetics of Tumours of the Nervous System. Lyon, IARC Press, 2000.

*2. Guthrie BL, Laws Jr ER: Supratentorial low-grade gliomas. Neurosurg Clin N Am 1990; 1:37-48.

*3. Davis FG, Malinski N, Haenszel W, et al: Primary brain tumor incidence rates in four United States regions, 1985-1989: a pilot study. Neuroepidemiology 1996; 15:103-112.

*4. McCormack BM, Miller DC, Budzilovich GN, et al: Treatment and survival of low-grade astrocytoma in adults—1977-1988. Neurosurgery 1992; 31:636-642.

LGG : THE CONTROVERSY

- Median survival : 6.5 - 8 years.*¹
- Published survival estimates : from 3 to > 20 years.
- 5- and 10-year survival rates : 70% and 50%, respectively. *²
- Clinical course of individual LGGs - heterogeneous, with certain lesions tending to behave more aggressively.

➤ THUS THE CONTROVERSY:

What is the most appropriate strategy for treating patients with LGG.????

- Observation
- Surgical intervention
 - Biopsy : open / stereotactic
 - Tumor resection : Extent
- Radiotherapy
- Chemotherapy

*1. Johannesen TB et al: Progress in long-term survival in adult patients with supratentorial low-grade gliomas. J Neurosurg 2003; 99:854-862.

*2. Leighton C et al: Supratentorial low-grade glioma in adults: an analysis of prognostic factors and timing of radiation. J Clin Oncol 1997; 15:1294-1301.

Prognostic factors : assigning LGG patients to low- and high-risk subgroups

Improved survival outcomes

- Age <40 years at diagnosis
- Seizures at diagnosis
- Absence of additional neurological deficits at diagnosis
- KPS score ≥ 70
- MMSE score $> 26/30$.
- MIB-1 index $< 8\%$
- *Histology either low-grade ODG or oligoastrocytoma* (esp. chromosome 1p deletions)

Poor survival outcomes

- Max tm diameter > 5 to 6 cm
- Presence of contrast enhancement.

Shaw E, et al: Prospective randomized trial of low- versus high-dose radiation therapy in adults with supratentorial low-grade glioma: initial report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group study.

J Clin Oncol 2002; 20:2267-2276.

LGG : DEDIFFERENTIATION

- Also known as malignant transformation : well-described phenomenon.
- 13% to 86% of tumors initially dx LG were observed to recur at a higher histological grade.
- Time to malignant differentiation variable- (range 28 to 60 mths).
- Factors resulting in the transformation: unclear, and the effect of treatment on this malignant transformation remains controversial.

Berger MS et al: The effect of extent of resection on recurrence in patients with low grade cerebral hemisphere gliomas. *Cancer* 1994; 74:1784-1791.

Vertosick Jr FT et al: Survival of patients with well-differentiated astrocytomas diagnosed in the era of computed tomography. *Neurosurgery* 1991; 28:496-501.

LGG : OBSERVATION

- Uncommon for a patient with the clinical presentation and imaging characteristics of an LGG to be followed up with regular imaging unless a histological diagnosis is obtained at first presentation.
- Some still advocate this extremely conservative approach – esp. deep-seated lesions or lesions located in eloquent cortex
- Advantage
 - Defers treatment-related risk
 - Defers treatment-related costs for patients who remain asymptomatic
- Disadvantage
 - Increase the risk for tumor progression
 - development of new neurological deficits or intractable seizures,
 - Increases risk for malignant dedifferentiation of the lesion.
 - Initial presumptive diagnosis may be incorrect.

*Recht LD et al. Suspected low-grade glioma:
is deferring treatment safe?.*

Ann Neurol 1992; 31:431-436.

- retrospective case-controlled study
- 58% of cases being observed only eventually required surgery at a median interval of 29 months.
- 50% of the tumors then showed anaplastic features.
- “Although they had a higher incidence of malignant transformation at the time of operation and shorter time to tumor progression relative to patients who were operated on initially....., the study concluded that no difference was observed in overall survival or QOL.”

*van Veelen ML et al: Supratentorial low grade astrocytoma:
prognostic factors, dedifferentiation, and the issue of
early versus late surgery.*

J Neurol Neurosurg Psychiatry 1998; 64:581-587.

- 30 patients
- presenting only with seizure
- **early v/s late surgical resection did not affect overall survival.**
- “If observation is chosen, disease progression may be detected based on the onset of new neurological deficits, a change in seizure pattern or frequency, or simply an increase in lesion size or new contrast enhancement seen on MRI.”
- **However both studies were statistically weak as $n < 50$.**

LGG : OBSERVATION

- Tumor growth rates can be unpredictable and are often nonlinear, leading to
 - sudden changes in tumor size- can drastically change the surgical landscape
 - turning an initially resectable or radio responsive lesion into one that is difficult to remove safely or is more resistant to adjuvant therapies.
- Psychological stress associated with not knowing with certainty :
increased distress and reduced quality of life for both the patient and the caregiver.
- *Little evidence exists to support this treatment strategy, although it has not been refuted, either.*

SURGICAL INTERVENTION

- Choice of procedure depends on
 - patient's clinical status
 - anatomic location
 - surgeon's preference
- Goals of surgical intervention
 - establishing a diagnosis
 - treating neurological symptoms
 - decompressing mass effect
 - tumor cytoreduction.
- “Currently, the only agreed-on surgical standard for adults with suspected or known supratentorial non–optic-pathway LGGs is to **obtain a tissue diagnosis before active treatment commences.**”
 - *Practice parameters in adults with suspected or known supratentorial nonoptic pathway low-grade glioma. Neurosurg Focus 1998;4:e10.*

LGG : Biopsy

- Stereotactic or image-guided.
- Minimally invasive : Tissue for histological diagnosis.
- Advantage
 - Suitable if open surgical resection is declined, deferred, or carries unacceptably high risks.
 - Identification of patients harboring more aggressive lesions, for which a course of observation alone may be inappropriate.*¹
 - Tissue can be analyzed for oligodendroglial characteristics, such as chromosome 1p loss.
- Surgical risks
 - Low- morbidity and mortality rates <1%. *²
 - Mortality – ICH, SAH or uncontrollable cerebral edema,
 - Generally observed only among biopsies of high-grade lesions.*³

*1. Lunsford LD et al: Brain astrocytomas: biopsy, then irradiation. Clin Neurosurg 1995; 42:464-479.

*2. Lunsford LD et al: Survival after stereotactic biopsy and irradiation of cerebral nonanaplastic, nonpilocytic astrocytoma. JNS 1995; 82:523-529.

*3. Bernstein M, Parrent AG: Complications of CT-guided stereotactic biopsy of intra-axial brain lesions. J Neurosurg 1994; 81:165-168

LGG : Biopsy

- *Disadvantage:*
 - Possibility of misdiagnosis or inaccurate tumor grading
 - Tumor heterogeneity
 - Diagnosis bias resulting from limited tumor sampling.
- “The concordance between biopsy and open resection specimens is lower in patients with larger tumors, suggesting that multiple biopsies, which can be collected in a single trajectory pass, may be useful in this subpopulation....”*
- *Diagnostic accuracy may be improved by*
 - Specific regional targeting of the biopsy site within the tumor mass.
 - Including the enhancing regions of initial scan in the biopsy.
 - Complicated - HG lesions may not always show contrast enhancement.
 - Preoperative planning of biopsy targets based on physiologic imaging modalities (e.g., PET, SPECT, MRS) may increase the certainty of sampling the most aggressive portion of a particular tumor.

* Woodworth GF, McGirt MJ, Samdani A, et al: Frameless image-guided stereotactic brain biopsy procedure: diagnostic yield, surgical morbidity, and comparison with the frame-based technique. J Neurosurg 2006; 104:233-237.

Douglas Kondziolka, L. Dade Lunsford, A. Julio Martinez.

Unreliability of contemporary neurodiagnostic imaging in evaluating suspected adult supratentorial (low-grade) astrocytoma.

Journal of Neurosurgery 1993; 79:533-536

- N=20 young (mean age 37 years), all lobar lesions: CT/MRI s/o LGG
- Histological diagnosis (Biopsy) : without morbidity. Only 10 (50%) had low-grade astrocytomas, whereas 9 (45%) had anaplastic astrocytomas and 1 (5%) had encephalitis.
- **Conclusion:**
- Modern high-resolution neuroimaging alone cannot be used as a reliable tool to predict the histological diagnosis of astrocytoma (**50% false-positive rate**).
- All patients with supratentorial SOL exhibiting “typical” imaging features of astrocytoma should undergo stereotactic biopsy for confirmation.

Barker et al. (UCSF), Cancer 1997

- Nonenhancing tumors are not always low-grade.
- Chance of anaplasia increases in older patients (50% by mid-40's)

Providing a diagnosis? Bx/ resection

Glantz et al., Influence of the type of surgery on the histological diagnosis in patients with anaplastic gliomas Neurology, 1991 vol. 41 no. 11 1741

“More extensive resections more frequently provide higher grade diagnosis”

Providing a diagnosis ? Bx v/s resection

Identification of oligo component in Gr 3 tumors was more likely as EOR ↑

Perry et al., Cancer 1999

% containing oligo components: ($p = 0.01$)

| | |
|-----|-----|
| Bx | 3% |
| STR | 29% |
| GTR | 43% |

Carter et al., SEER data

% containing oligo components: (more specimens -> more oligo)

| | | |
|-----------|-----|-------------|
| Bx | 32% | |
| Resection | 62% | $p < 0.001$ |

LGG: Surgical Resection

- Role is well established in patients with accessible LGG who have symptoms of
 - local mass effect
 - increased intracranial pressure
 - intractable seizures
- Resection serves several purposes in these circumstances
 - alleviation of mass effect
 - cytoreduction
 - providing tissue for diagnosis
- Cytoreduction: “... can also reduce cerebral edema and potentially improve radio sensitivity and chemo sensitivity. The degree of tumor removal offers the advantage of providing more tissue for histological analysis, increasing the accuracy of pathologic diagnosis.also reduces the number of tumor cells at risk for accumulating additional genetic aberrations, thereby reducing the risk for tumor progression and decreasing the potential for malignant transformation....” *

* Smith JS, Chang EF, Lamborn KR, et al: Role of extent of resection in the long-term outcome of low-grade hemispheric gliomas. J Clin Oncol 2008; 26:1338-1345.

Chang EF, Potts MB, Keles GE, et al: Seizure characteristics and control following resection in 332 patients with low-grade gliomas. J Neurosurg 2008; 108:227-235.

Department of Neurological Surgery & Brain Tumor Research Center, University of California,
San Francisco, California

- Retrospective study - Seizures in 81% cases
- 50% had uncontrolled seizures at the time of resection despite antiepileptic Rx.
- Postoperative : 90% were seizure free or had meaningful improvement.
- Surgical resection : effective means of reducing seizure burden.
- **Factors associated with post-op freedom from seizures:**
 - *Gross total tumor resection*
 - Preoperative seizure history of < 1 year
 - Non-simple partial seizure type.

LGG: Surgical Resection

- Contemporary neurosurgical methods: USG, functional mapping, frameless navigational, and intraoperative imaging - more extensive resections with less morbidity.
- Intraoperative USG:
 - real-time intraoperative data, helpful in detecting the tumor, delineating its margins, and differentiating tumor from peritumoral edema, cyst, necrosis, and adjacent normal brain tissue.
 - use is limited by artifact from blood and surgical trauma at the margin of resection, post resection tumor volumes based on intraoperative ultrasonography significantly correlate with those determined by postoperative MRI.*¹
- Intraoperative MRI: may allow for greater extent of resection, particularly when tumor-infiltrated tissue cannot be grossly distinguished from normal tissue.*²

*1. Hammoud MA et al: Use of intraoperative ultrasound for localizing tumors and determining the extent of resection: a comparative study with magnetic resonance imaging. JNS 1996; 84:737-741.

*2. Claus EB et al: Survival rates in patients with low-grade glioma after intraoperative MRI guidance. Cancer 2005; 103:1227-1233.

LGG: Surgical Resection

Sanai N, Mirzadeh Z, Berger MS: Functional outcome after language mapping for glioma resection. **N Engl J Med** 2008; 358:18-27.

- Stimulation mapping techniques:
 - minimize morbidity
 - allows radical resections of tumors located in or around cortical and subcortical functionally eloquent sites
- *“For lesions in and around language pathways, awake mapping remains the gold standard for minimizing morbidity and maximizing extent of resection.”*
- Intraoperative corticography - useful adjunct, but it is primarily reserved for patients with intractable epilepsy.

LGG: Surgical Resection

- Role for surgery in minimally symptomatic or asymptomatic lesions remains controversial.
- Historical debate: “whether the extent of resection actually confers any survival advantage for these patients ??”
- Recent body of evidence suggests that more extensive resection at the time of initial diagnosis is a favorable prognostic factor.
- *“...Although most reports are retrospective, it is unlikely that the necessary prospective randomized studies will be conducted to address the role of extent of resection on outcome in LGG patients owing to the relatively limited numbers of patients, the typically long survival times, and a general lack of equipoise with regard to treatment options among care providers...”*

Smith JS, Chang EF, Lamborn KR, et al: Role of extent of resection in the long-term outcome of low-grade hemispheric gliomas. J Clin Oncol 2008; 26:1338-1345.

Smith JS et al: Role of extent of resection in the long-term outcome of low-grade hemispheric gliomas.

Department of Neurosurgery, Brain Tumor Research Center, University of California, San Francisco, CA.

J Clin Oncol 2008; 26:1338-1345.

- N= 216, retrospective study

VOLUMETRIC EXTENT OF RESECTION ANALYSIS

| Extent of resection | 8-yr overall survival | Progression free survival |
|---------------------|-----------------------|---------------------------|
| ≥ 90% | 91 % | 43 % |
| < 90 % | 60 % | 21 % |

“EOR was a significant predictor of overall survival and showed a trend toward predicting progression-free survival.”

Smith JS et al: Role of extent of resection in the long-term outcome of low-grade hemispheric gliomas. *J Clin Oncol* 2008; 26:1338-1345.

- A. Larger preop tumor volumes have significantly shorter progression-free survival times ($P < .001$).
- **B. Complete resection of FLAIR imaging abnormality (75 patients, 2 events) had a significantly longer overall survival time v/s having any residual (141 patients, 32 events) ($P = .001$).**
- **C. Even small volumes of residual FLAIR abnormality demonstrated shorter overall survival times v/s no residual FLAIR abnormality . ($P = .001$).**
- **D. Patients with a greater percentage of tumor resection had a significantly longer overall survival interval ($P < .001$).**

Evidence in literature

- In the modern neurosurgical era many studies have applied statistical analysis to examine the efficacy of EOR in improving survival and delaying tumor progression among LGG patients.
- Five - included volumetric analysis of extent of resection
- Those not employing volumetric methods: 12 demonstrated *evidence supporting EOR as a statistically significant predictor of either 5-yr survival or 5-yr progression free survival.*
- Published from 1990 to 2005
- Employed combination of multivariate and univariate analyses.
- Recent volumetric LGG EOR analysis, Smith et al 2008
 - *more aggressive resection does predict significant improvement in overall survival compared with a simple debulking procedure.*
 - *predicted overall survival affected by residual tumor volumes as small as 10 cm³*

Sanai et al. *Neurosurgery* 2008. Non-volumetric LGG EOR studies in modern literature

| STUDY | NO. of cases | EOR (n) | 5-year prog-free survival rate | | | 5-year survival rate | | |
|------------------------|--------------|------------------------------------|--------------------------------|----------------|----------------|----------------------|----------------|----------------|
| | | | 5-Yr Prog free survival % | Univar F value | Multivar F val | 5 Yr survival % | Univar F value | Multivar F val |
| Phillipon et al , 1993 | 179 | GTR 45 STR 95 BX 39 | NA | NA | NA | 80 50 45 | .0002 | <.01 |
| Rajan et al | 82 | GTR 45 STR 95 PR 22 BX 39 | NA | NA | NA | 90 52 50 42 | <.05 | NS |
| Leighton et al, 1997 | 167 | GTR 85 STR 23 | NA | NA | NA | 82 64 | .008 | .006 |
| Nakamura et al, 2000 | 88 | Rad 43 N Rad 45 | NA | NA | NA | NA | <.001 | <.001 |
| Shaw et al, 2002 | 203 | GTR 45 STR 95 BX 39 | NA | 0.0137 | NS | 88 56 71 | .0116 | .0349 |
| Johannesen et al, 2003 | 993 | GTR 173 STR 689 BX 131 | NA | NA | NA | NA | NS | NS |

Sanai et al. *Neurosurgery* 2008. Volumetric LGG EOR studies in modern literature

| STUDY | NO. of cases | EOR % (n) | 5-year prog-free survival rate | | | 5-year survival rate | | |
|-------------------------|--------------|------------|--------------------------------|---------------|----------------|----------------------|---------------|----------------|
| | | | 5-Yr Prog free survival % | Univar Fvalue | Multivar F val | 5Yr survival % | Univar Fvalue | Multivar F val |
| Van Veelen et al , 1998 | 90 | > 75 (13) | NA | NA | NA | 62 | .0002 | .04 |
| | | < 75 (59) | | | | 18 | | |
| Claus et al, 2005 | 156 | 100 (56) | NA | NA | NA | 98.2 | .05 | <.05 |
| | | <100 (100) | | | | 92.0 | | |
| Smith et al, 2008 | 216 | 0-40 (21) | NA | NA | .005 | NA | NA | <.001 |
| | | 41-69 (39) | NA | | | NA | | |
| | | 70-89 (55) | NA | | | NA | | |
| | | 90-99 (26) | 75.5 | | | 97.0 | | |
| | | 100 (75) | 78.0 | | | 98.0 | | |

- “... mounting evidence in the modern neurosurgical literature suggests that a more extensive surgical resection may be associated with a more favorable life expectancy for LGG patients.”
 - Sanai N, Berger MS.: Glioma extent of resection and its impact on patient outcome. *Neurosurgery* 2008; 62:753-764.
- “ More aggressive resections for low-grade gliomas also affect the risk for malignant transformation, they take advantage of an opportunity to treat the disease when the neoplasm is at its earliest stage of evolution.”
 - Smith JS, Chang EF, Lamborn KR, et al: Role of extent of resection in the long-term outcome of low-grade hemispheric gliomas. *J Clin Oncol* 2008; 26:1338-1345.

LGG : CONCLUSIONS

- Although more indolent than their high-grade counterparts, their associated clinical course is by no means benign.
- To delay the inevitable progression toward malignancy, aggressive LGG resection is supported by a growing body of literature and can improve patient outcome, but it should not be pursued at the expense of a patient's quality of life.
- Such a strategy minimizes the chances of misdiagnosis from sampling error and can immediately relieve symptomatic mass effect, obstructive hydrocephalus, and neurological deficit.
- Greater extent of resection is also correlated with improved survival time and reduces the risk for malignant transformation.
- This necessitates precise delineation of the structural and functional tumor margins using a combination of preoperative imaging modalities, intraoperative mapping techniques, and functional mapping.
- Conservative therapy or observation is not recommended at this time.
- RT should be withheld until progression occurs, although CT agents such as TMZ may be useful as an upfront treatment.

Malignant Astrocytomas

- The most common malignant primary CNS tumors in adults.*1
- Include
 - Anaplastic astrocytoma (AA, WHO grade III)
 - Glioblastoma multiforme (GBM, WHO grade IV)
 - Gliosarcoma
- Even with optimal treatment, median survival . *2,*3
 - < 2 years for GBM
 - 2 to 5 years for AA

● *1. DeAngelis LM: Brain tumors. N Engl J Med 2001; 344:114-123.

● *2. Souhami L, Seiferheld W, Brachman D, et al: report of Radiation Therapy Oncology Group 93-05 protocol. Int J Radiat Oncol Biol Phys 2004; 60:853-860.

● *3. Wen PY, Kesari S: Malignant gliomas in adults. N Engl J Med 2008; 359:492-507.

Malignant Astrocytomas

- Characterized by - invasive and infiltrative nature, making curative resection unlikely.¹
- 1930s- Walter Dandy reported recurrence of contralateral gliomas even after hemispherectomy of the tumor-bearing hemisphere.²
 - 1. Claes A, Idema AJ, Wesseling P: Diffuse glioma growth: a guerilla war. Acta Neuropathol (Berl) 2007; 114:443-458.
 - 2. Dandy WE: Removal of right cerebral hemispheres for certain tumors with hemiplegia: preliminary report. JAMA 1928; 90:823-825.
- Often occur in the cerebral hemispheres *
- Can arise from low-grade astrocytoma (WHO grade II)
- Can also be dx de novo at first biopsy: without signs of a malignant precursor.
- AA has an innate tendency to progress to GBM.
- Both recur locally, often at the margins & even after GTR**

*Keihus P et al: Anaplastic Astrocytoma. Pathology and Genetics of Tumors of the Nervous System, WHO Classification of Tumours, Lyon: IARC Press; 2000.

**Wrench M et al: Neuro Oncol 2002; 4:278-299.

MALIGNANT GLIOMAS: PROBLEM OF INVASION

- Lethal ? grow by invasion, limiting the efficacy of surgery and other Rx. *1
- Malignant glioma cells - great motility in both in vitro and in vivo rodent models. *2
- Autopsy studies - HGG *3
 - extend beyond a single carotid or vertebral artery distribution
 - often spread through the CSF pathways
 - may extend past the 2-cm margins demonstrated by CT or MRI.
- Frequently microsatellites - scattered throughout normal brain tissue *4
- Infiltration of eloquent areas : may limit the extent of tumor resection.
- Stereotactic biopsy samples – distant from enhancing tumor
- contain tumor cells grossly / vitro culture techniques *5
- ***“Thus, imaging techniques and histology have limited resolution in estimating the true extent of tumor cell invasion and thus inevitably underestimate the true extent of these tumors”***

*1. Burger PC et al: J Neurosurg 1988; 68:698-704. *2 . Bernstein JJ. J Neurosci Res 1989; 22:134-143.

*3. Kelly PJ. J Neurosurg 1987; 66:865-874. *4 Salazar OM. Int J Radiat Oncol Biol Phys 1976; 1:627-637.

*5 Silbergeld DL. J Neurosurg 1997; 86:525-531.

SURGERY FOR MALIGNANT GLIOMAS

- Goals of surgery
- (1) obtain a tissue diagnosis – Rx recommendations can be made and prognosis can be assessed.
- (2) decrease the mass effect
 - improve the patient's signs and symptoms
 - *lessen steroid dependence*
 - *even prevent early death from progressive mass effect.*
- (3) reduce the tumor burden.

SURGERY FOR MALIGNANT GLIOMAS

- “GTR for many solid organ malignant tumors with clear surgical margins is associated with extended survival but for malignant astrocytoma is less clear”. *1
- At best, 99% resection (a 2-log kill) can be achieved.*2
- Remaining 1% is sufficient for these tumors to recur.
- Extensive resection of malignant astrocytomas is difficult
 - Invasive, widely infiltrative and often involve eloquent areas.

*1. Barker 2nd FG. J Neurosurg 1996; 84:442-448

*2. Claes A. Acta Neuropathol (Berl) 2007; 114:443-458.

HGG : EXTENT OF RESECTION (EOR)

- Unclear whether the EOR of HGG is associated with improved survival. ^{*1}
- Recurrence of malignant astrocytomas commonly occurs close to the tumor margin. ^{*2}
- Extensive resection - theoretically decreases the number of remaining cells, renders the decreased tumor burden more responsive to adjuvant therapy, and potentially prolongs survival. ^{*3,4}

*1. Hess KR. J Neurooncol 1999; 42:227-231.

*2. Sneed PK. Int J Radiat Oncol Biol Phys 1994; 29:719-727

*3. Chang SM et al. JAMA 2005; 293:557-564.

*4. Keles GE et al. J Neurosurg 2006; 105:34-40.

Influence of Extent of Resection of HGG on Clinical Outcomes

- **Four systematic reviews of the literature**

- Hess KR: Extent of resection as a prognostic variable in the treatment of gliomas. *J Neurooncol* 1999; 42:227-231.
- Nazzaro JM, Neuwelt EA: The role of surgery in the management of supratentorial intermediate and high-grade astrocytomas in adults. *J Neurosurg* 1990; 73:331-344.
- Grant R, Metcalfe SE: Biopsy versus resection for malignant glioma. *Cochrane Database Syst Rev* 2005; 2:CD002034
- Quigley MR, Maroon JC: The relationship between survival and the extent of the resection in patients with supratentorial malignant gliomas. *Neurosurgery* 1991; 29:385-388.

Systematic reviews of the literature

- LIMITED

- Did not control for confounding variables
- Were often underpowered
- Included biopsies in their analyses
- Frequently included studies conducted before 1990
- Did not adjust for resectability and post-op treatment

- CONCLUDED

- *“the lack of good scientific evidence precludes any definitive statement on the effect of extensive resection on survival of patients with malignant astrocytoma.”*

Lacroix M et al: JNS 2001; 95:190-198.

- A multivariate analysis of 416 patients with GBM : prognosis, extent of resection, and survival.
- Resections > 98% - significantly associated with improved survival.
- Limitations
 - 44% of the patients were previously Rx at other institutions.
 - Adjuvant therapy was not included in the survival analysis.

McGirt MJ, et al: Independent association of extent of resection with survival in pts with malignant astrocytoma.
JNS 2009; 110:156-162.

- Retrospectively reviewed the cases of 1215 patients
- Single institution from 1996 to 2006.
- Deep-seated or unresectable lesions were excluded.
- Mean age & KPS : 51 ± 16 years and 80 ± 10 respectively.
- Surgery: 1⁰ resection in 549 patients (58%) and revision for recurrence in 400 patients (42%).
- WHO Grade IV in 700 patients (74%) and Grade III in 249 (26%).
- 167 astrocytomas and 82 mixed oligoastrocytoma.
- GTR, NTR, and STR - achieved in 330 (35%), 388 (41%), and 231 cases (24%), respectively

MRI < 48 HOURS OF RESECTION:

GTR- no residual enhancement on MRI

NTR - rim enhancement of resection cavity

STR- residual nodular enhancement

Estimated Kaplan-Meier plot of survival (mixed oligoastrocytoma excluded).

➤ **Both GTR & NTR a/w survival benefit v/s STR.**

➤ ***GTR versus NTR was not associated with improved survival.***

➤ Median survival : After GTR, NTR, or STR, was 58, 46, and 34 months, respectively.

➤ Five-year survival rates : GTR, NTR, and STR were 42%, 41%, and 12%, respectively.

McGirt MJ, Chaichana KL, Gathinji M, et al. Independent association of extent of resection with survival in patients with malignant brain astrocytoma. JNS. 2009;110:156-162.

EOR FOR GBM

- For both 1⁰ & 2⁰ resection:
 - NTR - independent survival benefit compared with STR. ($P < .002$)
 - *GTR - independent survival benefit compared with NTR. ($P < .05$)*
- After 1⁰ GBM resection, median survival after GTR, NTR, or STR was 13, 11, and 8 months.
- For revision of recurrent GBM, median survival after GTR, NTR, and STR was 11, 9, and 5 months from the time of revision surgery.

Variables a/w overall survival after 1⁰ resection of GBM

- Independently associated with improved overall survival.
 - Decreasing age
 - Increasing KPS
 - increasing extent of resection
 - Gliadel wafer
 - temozolomide
 - subsequent resection of late recurrence
- GTR / NTR - independent survival benefit compared with STR independent of disability or subsequent treatment modalities.

Variables a/w overall survival after revision resection of GBM

- Independently associated with improved overall survival.
 - Decreasing age
 - Increasing KPS
 - increasing extent of resection
 - temozolomide
 - subsequent resection of late recurrence
- GTR / NTR - independent survival benefit compared with STR independent of disability or subsequent treatment modalities.

Benefits of extensive resection

- Lower tumor load : increase the efficacy of adjuvant CT/ RT in killing the remaining cancer cells and increasing survival. *1,2
- Secondary benefits.
 - Increased relief of symptoms and neurological improvement.*3

*1. Pelloski CE. J Clin Oncol 2007; 25:2288-2294.

*2. Friedman HS. J Clin Oncol 2000; 18:3522-3528.

*3. Nakamizo A. Cancer Res 2005; 65:3307-3318.

Barker et al. *Neurosurgery* 49:1288, 2001

Is response to postoperative adjuvant radiation in newly-diagnosed glioblastoma improved by prior resection?

- N = 301 (GBM) prospective study.
- More extensive surgical resection predicted better imaging-assessed response to postop adjuvant radiation in both univariate and multivariate analyses (adjusted for age, KPS)

Martin J. van den Benta et al . *EUROPEAN JOURNAL OF CANCER*. 42 (2006) 582–8

Resection and TMZ – EORTC 26981 (Stupp)

| | 2-year survival | | median survival | |
|-----|-----------------|------|-----------------|------|
| | +TMZ | -TMZ | +TMZ | -TMZ |
| GTR | 37% | 14% | 18m | 14m |
| STR | 23% | 9% | 14m | 12m |
| Bx | 10% | 5% | 9m | 8m |

McGirt MJ et al. Gliadel (BCNU) wafer plus concomitant temozolomide therapy after primary resection of GBM
J Neurosurg 2009; 110:583-588.

- n=147
- multimodality treatment involving radiation therapy, temozolomide, and intraoperative placement of Gliadel resulted in the longest mean survival time of 20 months

Conclusions : HGG

- Prognosis for HGG is poor.
- Management typically consists of surgery followed by RT + CT.
- Even after extensive treatment, residual tumor is inevitable and patients eventually succumb to this disease.
- Age and KPS score are the most significant prognostic factors.*1
- “Individual patient survival is heterogeneous, with some long-term survivors. Hence all out sincere efforts to be made” *2

*1 McGirt et al. *JNS*. 2009;110:156-162

*2 Dehdashti AR et al: *Can J Neurol Sci* 2007; 34:339-342.

Conclusions : HGG

- “No evidence based recommendations as to the best surgical management of patients with malignant glioma can be made.”
- “Until there is concrete evidence one way or the other, it is important to consider each case individually and for the surgeon to carry out the procedure which he deems to be the most appropriate for that particular patient, taking into account the risks and benefits.”
- “Such decisions are best made at a multi-disciplinary team meeting (NICE guidance)”.
- *“Given the lack of trial-based evidence, individual clinicians should be encouraged to enter their patients into a controlled clinical trial, if such a trial were to be established in the future.”*



- How will you manage a case of low grade glioma (Grade II) whose post-operative MRI on day 1 or 2 shows a small residual tumor ??



THANK YOU