

# LOW GRADE GLIOMAS: MANAGEMENT AND CONTROVERSIES

- ▣ Large proportion of primary brain tumors.
- ▣ 15 to 35% in most reported series.  
(Piepmeier J, Christopher S, Spencer D, et al: Variations in the natural history and survival of patients with supratentorial low grade astrocytomas. *Neurosurgery* 38:872.879, 1996 )
- ▣ Include a remarkable diversity of lesions.
- ▣ Virtually every tumor of glial origin that is not overtly malignant.
- ▣ WHO grade 1 and 2 are considered low grade.

- ▣ 5-year survival percentages range from 42 to 92% in the literature.

Laws ER Jr, Taylor WF, Clifton MB, Okazaki H: Neurosurgical management of low-grade astrocytoma of the cerebral hemispheres. **J Neurosurg** 61:665– 673, 1984.

Nakamura M, Konishi N, Tsunoda S, Nakase H, Tsuzuki T, Aoki H, Sakitani H, Inui T, Sakaki T: Analysis of prognostic and survival factors related to treatment of low-grade astrocytomas in adults. **Oncology** 58:108–116, 2000

- ▣ 50 to 75% of patients with low-grade gliomas eventually die as a result of either progression of low-grade tumor or degeneration to a malignant glioma.

Keles GE, Lamborn KR, Berger MS: Low-grade hemispheric gliomas in adults: A critical review of extent of resection as a factor influencing outcome. *J Neurosurg* 95:735-745, 2001



- ▣ Among several perioperative risk factors, only
  - 1) age and
  - 2) histologyhave generally been accepted as prognostic factors for patients with low grade gliomas

Janny P, Cure H, Mohr M, Heldt N, Kwiatkowski F, Lemaire JJ, Plagne R, Rozan R: Low grade supratentorial astrocytomas: Management and prognostic factors. **Cancer 73:1937-1945, 1994.**

Johannesen TB, Langmark F, Lote K: Progress in long-term survival in adult patients with supratentorial low-grade gliomas: A population-based study of 993 patients in whom tumors were diagnosed between 1970 and 1993. **J Neurosurg 99:854-862, 2003.**

# Management Controversies

? To intervene or not

? How to intervene

Surgery ; Radical Vs Partial

Radiotherapy: Timing,

Low Vs High Dose

Role of Chemotherapy

# Conservative Management

- ▣ Significant proportion of the patients may be appropriate candidates.
- ▣ Anticonvulsant medication
- ▣ Repeated neurodiagnostic imaging studies.
- ▣ Withholding intervention until there has been a change either clinically or radiologically.

# Rationale for wait and watch policy

- ▣ Characteristic imaging features with long history.
- ▣ Increased life span by surgery never proven.
- ▣ Increasingly patients are diagnosed neurologically intact.

- ▣ Postpones surgical morbidity and mortality if any.
- ▣ Alternate treatment strategy are available
  - Stereotactic biopsy and radiotherapy
- ▣ Technical reasons
  - Distinction between tumor-brain difficult and early radical surgery seldom serves purpose.



- Wait and watch policy can lead to-
  - Underestimating degree of malignancy
  - Diagnosis by imaging is inadequate and may be incorrect (Error rate of diagnosis 15-50%)

( Douglas Kondziolka, M.D., M.Sr F.R.C.S.(C), L. Dade Lunsford, M.D., And A. Julio Martinez, M.D. *University of Pittsburgh, and the Specialized Neurosurgical Center, Presbyterian- University Hospital, Pittsburgh, Pennsylvania; Unreliability of contemporary neurodiagnostic imaging in evaluating suspected adult supratentorial (low-grade) astrocytoma. J Neurosurg 79:533-536, 1993 )*

- *The results of this study indicate that modern high resolution neuroimaging alone cannot be used as a reliable tool to predict the histological diagnosis of astrocytoma (50% false-positive rate).*

- ▣ Grading gliomas based on imaging characteristics alone underestimated the degree of malignancy in 1/3 cases
- ▣ Tissue diagnosis should be attained whenever deemed safe and possible

Scott JN, Brasher PM, Sevick Ru, Rewcastle NB, Forsyth PA. How often are nonenhancing supratentorial gliomas malignant? A population study. *Neurology* 2002;59:947-9.

- ▣ Recent studies have showed that contrast enhancement may occur in upto 40% of low grade gliomas.

Scott CB, Scarantino C, Urtasun R, Moysas B, Jones CU, Simpson JR, et al. validation and predictive power of Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis classes for malignant glioma patients: A report using RTOG 90-06. *Int J Radiat Oncol Biol Phys* 1998;40:51-5.

- ▣ The expectant management of patients with LGGs can bring on other risks, such as,

Malignant degeneration  
Subsequent tumorgrowth, and  
Irreversible neurological deficit.

- ▣ How ever despite these theoretical risks, several retrospective series revealed that the timing of surgical intervention *did not* affect the **rates of** malignant transformation, overall survival, or QOL.

Reijneveld JC, Sitskoorn MM, Klein M, Nuyen J, Taphoorn Mj. Cognitive status and quality of life in patients with suspected versus proven low grade gliomas, *Neurology* 2001;56:618-23

# Surgery

- ▣ Radical or total resection is the surgical procedure of choice.
- ▣ Many patients with these tumors, complete removal of the lesion can result in cure.
- ▣ Partial resection may be appropriate for some low-grade astrocytomas, particularly those that are near important areas of the brain.

# Surgery

Timing

Early Vs Late

Type

Partial Vs Radical



# Rationale for Early Surgery

- ▣ Definitive diagnosis
- ▣ Possibility of gross total resection with potential for cure
- ▣ Control of seizures
- ▣ Neurological improvement
- ▣ Control of ICP
- ▣ Longer disease free interval

Van Veelen ML, Avezaat CJ, Kros JM, van putten W, Vecht C. Supratentorial low grade astrocytoma: Prognostic factors, de-differentiation, and the issue of early versus late surgery. J NeurolNeurosurgery Psychiatry 1998;64:581-7.

- ▣ Enhanced ability of immune cells to wipe out tumor
- ▣ Greater kill by post op RT
- ▣ Chances of killing of cells with increased malignant potential

# Points Against Early surgery

- Longer disease free interval is lead time bias
- Immunological activity against low grade glioma is controversial
- Post op radiotherapy does not kill all cells

# Extent Of Resection

- ❑ Till date no class 1 evidence to support radical resection.
- ❑ There are lot of retrospective data to suggest benefit in survival and in quality of life.
- ❑ Two prospective studies have shown benefit of extensive surgery in overall survival on univariate analysis.
- ❑ On multivariate analysis these showed minimal benefits.

# GLIOMA EXTENT OF RESECTION AND ITS IMPACT ON PATIENT OUTCOME

---

**Nader Sanai, M.D , Mitchel S. Berger, M.D.**

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

- ▣ No general consensus in the literature regarding the role of extent of resection (EOR) in improving patient outcome.
- ▣ A literature search of the PubMed database from January 1990 to December 2007
- ▣ Series of adult hemispheric gliomas.



- ❑ Ten studies since 1990 met The inclusion criteria and have applied statistical analysis to examine the role of EOR in improving survival and delaying tumor progression among patients with low-grade gliomas.
- ❑ In none of these studies were patients randomized with respect to the extent of surgery, and in only three studies did they include a volumetric analysis of EOR
- ❑ Of the nonvolumetric studies, six demonstrated evidence supporting EOR as a statistically significant predictor of either 5-year survival or 5-year progression-free survival.

- ▣ Only one nonvolumetric study did not support EOR as a predictor of patient outcome.
- ▣ Of the three volumetric studies reviewed, all demonstrated statistical significance based on 5-year survival.

- ▣ The effect of a greater EOR in the low-grade glioma studies, the mean survival changed from 61.1 to 90.5 months.
- ▣ This analysis reveals a growing correlation between greater EOR and patient survival.

# Conclusion

- ▣ In addition to providing longer overall survival, more aggressive resections for low-grade gliomas may also affect the risk of malignant transformation among low-grade gliomas.
- ▣ Because no Class I evidence exists to support a particular management paradigm, the optimal combination of surgery and various therapeutic options remains unknown.

**EXTENT OF SURGICAL RESECTION IS INDEPENDENTLY  
ASSOCIATED WITH SURVIVAL IN PATIENTS WITH  
HEMISPHERIC INFILTRATING LOW-GRADE GLIOMAS**

**Matthew J. McGirt, M.D.etal** Department of Neurosurgery,  
The Johns Hopkins School of Medicine, and Neuro-oncology Surgical  
Outcomes Research Laboratory, Baltimore, Maryland.  
*Neurosurgery* 63:700–708, 2008



▣ **METHODS:**

- Retrospective cohort study (n 170)
- 1996 and 2007

**Gross total resection** (GTR) (complete resection of the preoperative fluid-attenuated inversion recovery signal abnormality)

**Near total resection** (NTR) (3-mm thin residual fluid-attenuated inversion recovery signal abnormality around the rim of the resection cavity only),

**Subtotal resection** (STR) (residual nodular fluid-attenuated inversion recovery signal abnormality)

- ▣ Based on magnetic resonance imaging performed less than 48 hours after surgery

- ▣ **Overall survival ( OS )** : the time from surgery to death.
- ▣ **Progression-free survival (PFS)** : the time from surgery to increase in tumor size on follow-up imaging or malignant degeneration.
- ▣ **Malignant degeneration-free survival (MFS)**: the time from surgery to demonstration of gadolinium enhancement on follow-up imaging and/or WHO Grade III or IV tumor on subsequent biopsy.

# Results

- ▣ Median time from symptom onset to surgery was 0.26 years (range, 0.1–8.3 years ).
- ▣ GTR 65 (38%)
- ▣ NTR 39 (23%)
- ▣ STR 66 (39%)
- ▣ Progression and malignant degeneration were identified in 70 (42%) and 40 (24%) cases, respectively.
- ▣ For all patients, median time to progression was 4.6 years and median time to malignant degeneration was 8.8 years.
- ▣ Median OS was 12 years

# CONCLUSION

- ▣ GTR was associated with a delay in tumor progression and malignant degeneration as well as improved OS independent of age, degree of disability, histological subtype, or revision versus primary resection.
- ▣ GTR should be safely attempted when not limited by eloquent cortex.

# IMPACT OF INTRAOPERATIVE HIGH-FIELD MAGNETIC RESONANCE IMAGING GUIDANCE ON GLIOMA SURGERY: A PROSPECTIVE VOLUMETRIC ANALYSIS

---

Forty- six patients underwent resection using iMRI guidance.

Surgery was terminated after iMRI in 23 patients (52%)

Twenty- one patients (47%) underwent additional resection of residual tumor after iMRI.

For enhancing gliomas, the median EOR increased significantly from 84% (range, 59%–97%) to 99% (range, 85%–100%) with additional tumor removal after iMRI (P 0.001).

Mustafa Aziz Hatiboglu, M.D., Jeffrey S. Weinberg, M.D., DimaSuki, Ph.D., GaneshRao, M.D.etal ,Department of Neurosurgery, The University of Texas,M. D. Anderson Cancer Center, Houston, Texas.



- For non-enhancing gliomas, the median EOR increased (from 63% to 80%) with additional tumor removal after iMRI, but not significantly, owing to the small sample size (7 patients).
- Overall, the EOR increased from 76% (range, 35%–97%) to 96% (range, 48%–100%)(P 0.001).
- Gross total resection was achieved after additional tumor removal after iMRI in 15 of 21 patients (71%).
- Overall, 29 patients (65%) experienced gross total resection, and in 15 (52%), this was achieved with the contribution of iMRI.

**CONCLUSION: High- field iMRI is a safe and reliable technique, and its use optimizes the extent of glioma resection.**

# USEFULNESS OF INTRAOPERATIVE ULTRA LOW-FIELD MAGNETIC RESONANCE IMAGING IN GLIOMA SURGERY

---

- ▣ Intraoperative resection control led to further tumor resection in 12 (28.6%) of 42 patients with contrast-enhancing tumors and in 10 (47.6%) of 21 patients with noncontrast-enhancing tumors. In contrast-enhancing tumors, further resection led to an increased rate of complete tumor resection (71.2 versus 52.4%).

Christian Senft, M.D., Volker Seifert, M.D., Ph.D., Elvis Hermann, M.D.etal  
Department of Neurosurgery, Johann Wolfgang Goethe University, Frankfurt,  
Germany

# Radiotherapy

? Optimum time

Straight after surgery Vs at progression

? Optimum dosage

High dose Vs low dose

? Will disease-free and overall survival (OS) be improved by adding chemotherapy to RT

- ▣ In the Mayo Clinic study, Shaw et al compared the outcome of 126 patients with supratentorial astrocytoma or mixed oligo-astrocytoma treated with surgery alone or surgery plus either low-dose (53 Gy) or high-dose (53 Gy) RT.
- ▣ The 5-year OS was 32% with surgery alone, 47% with low-dose RT, and 68% with high-dose RT, suggesting that surgery without postoperative RT was inadequate treatment and high-dose RT was better than lower dose.

Shaw EG, Daumas-Duport C, Scheithauer BW, et al: Radiation therapy in the management of low-grade supratentorial astrocytomas. J Neurosurg 70:853-61, 1989

- ▣ In the Canadian study of 167 patients reported by Leighton et al, the median survival time was 10.5 years with a 5-year OS of 72%, without any difference for patients who had surgery alone (i.e. RT deferred to the time of recurrence) versus immediate RT.

Leighton C, Fisher B, Bauman G, et al: Supratentorial low-grade glioma in adults: An analysis of prognostic factors and timing of radiation. J Clin Oncol 15:1295-1301, 1997



# EORTC TRIAL

(European Organisation for Research and Treatment of  
Cancer TRIAL)

*MJ van den Bent, D Afra, O de Witte, et al the EORTC 22845 randomised trial. Lancet  
366:985-990.2005)*

## EORTC 22845

- ▣ **Objective** : To compare the long-term efficacy of early, postoperative radiotherapy for low-grade glioma with that of delayed treatment, including radiotherapy, when tumour progression occurs.
- ▣ **Design and intervention:**
  - Age : 16–65 years
  - Supratentorial and histologically proven low-grade astrocytoma, or low-grade oligoastrocytoma or oligodendroglioma,
  - WHO performance status of 0–2 or Karnofsky performance status (KPS)  $\geq 60$ , and no other systemic diseases or malignancies.

- ▣ Participants were randomised to receive early radiotherapy (within 8 weeks of resective surgery), or treatment, including radiotherapy, when tumor progression occurred (control).
- ▣ Clinical and CT examination were carried out at baseline, every 4 months for 2 years, and then every year until tumor recurrence.
- ▣ The total radiotherapy dose was 54 Gy (in 5 fractions of 1.8 Gy/week for 6 weeks)

## ▣ **Outcome measures :**

Progression-free survival and overall survival time, both calculated from the date of randomisation to the date of progression.

# Results

- ▣ Radiotherapy was interrupted owing to acute reactions in six patients.
- ▣ Other toxic effects were moderate, including skin reactions, otitis and mild headache
- ▣ No malignant transformation of low-grade gliomas in this study.

# Results

	Control	treatment	P value
Median progression-free survival	3.4 Yrs	5.3Yrs	< 0.0001
5-year progression-free survival	37%	44%	0.02
Median overall survival	7.4 yrs	7.2 yrs	0.893
5-year overall survival	66 %	63%	0.49
After progression survival time	3.4	1yr	<0.0001
Number of progression-free patients with seizures	26/102 (25%)	29/71 (41%)	0.0329



## ▣ **Conclusions:**

Compared with treatment at the time of tumor progression, immediate postoperative radiotherapy lengthens progression-free survival by 2 years, but overall survival is unchanged.

# EORTC 22844 Trial

- ▣ Randomized patients to low- versus high-dose RT.
- ▣ Eligibility criteria and stratification factors were the same as EORTC 22845.
- ▣ Patients randomized to low-dose RT received 45 Gy to localized treatment fields encompassing the tumor with a 2-cm margin.
- ▣ Those randomized to high-dose RT received a 14.4-Gy “boost” to the tumor with a 1-cm margin, for a total dose of 59.4 Gy.

- ▣ The 5-year OS rate was 58% with low-dose and 59% with high dose RT ( $P = .73$ ).
- ▣ *The 5-year PFS rate was 47% with low-dose and 50% with high-dose RT ( $P = .94$ ).*
- ▣ Multiple prognostic factors analyzed for their effect on OS, the extent of surgical resection had the greatest impact .
- ▣ Quality of life was lower for the patients receiving high dose RT.

# Radiation Therapy Oncology Group (RTOG) Trial

- ▣ Eligibility criteria:
  - Age 18 years
  - Supratentorial LGG  
(astrocytoma, oligodendroglioma, or mixed oligo-astrocytoma).
- ▣ Patients randomized to low-dose RT received 50.4 Gy to localized treatment fields encompassing the tumor with a 2-cm margin.
- ▣ Those randomized to high-dose RT received a 14.4-Gy “boost” to the tumor with a 1-cm margin, for a total dose of 64.8 Gy.

- ▣ Two hundred eleven patients were randomized between 1986 and 1994, of which 203 were eligible/analyzable.
- ▣ The 5-year OS rate was 72% with low-dose and 65% with high-dose RT ( $P$  .48) .
- ▣ The 5-year PFS rate was 55% with low-dose and 52% with high-dose RT ( $P$  .65).



- ▣ The 5-year actuarial incidence of severe, life-threatening, or fatal neurotoxicity (ie, radionecrosis) was 2% with low-dose RT (50.4 Gy in 28 fractions of 1.8 Gy each) and 10% with high-dose RT (64.8 Gy in 36 fractions of 1.8 Gy each).
- ▣ Neurocognitive function : no difference in outcome between patients who received low- and high-dose RT.

# Chemotherapy Plus Radiation Therapy

- ▣ The Southwest Oncology Group (SWOG) study.

Eyre HJ, Crowley JJ, Townsend JJ, et al: A randomized trial of radiotherapy versus radiotherapy plus CCNU for incompletely resected low grade gliomas: A Southwest Oncology Group study. J Neurosurg 78:909-914, 1993.

- ▣ Randomized patients to postoperative RT alone or with chemotherapy.
- ▣ Median survival time was 4.45 years for RT alone compared to 7.4 years for RT plus CCNU.
- ▣ However, the 10-year survival rate was 40% for RT alone versus 20 % for RT plus CCNU ( $P = .7$ )

# Radiation Therapy Oncology Group (RTOG) protocol 9802 study

- ▣ Stratified pts to high and low risk.
- ▣ High risk patients randomized to RT alone Vs RT with CT (PCV).
- ▣ Total 251 pts randomized.

	RT	RT +CT	P value
Mean overall survival	7.5	Not reached	
5yr survival	63 %	72%	0.33
Median PFST	4.4	Not reached	
5 yr PFS	46%	63%	0.06
OS for 3 addl yrs among 2 yr survivors	72%	84%	0.03
PFS for 3 addl yrs among 2 yr survivors	52%	74%	0.002

- ▣ **Conclusions:** PFS but not OS were improved for adult WHO grade II LGG pts receiving RT +PCV versus RT alone. However, beyond 2 years, the addition of PCV to RT conferred both a significant OS and PFS advantage, and reduced the risk of death by 48% and progression by 55%, suggesting a delayed benefit for chemotherapy. Additional studies including 1p19q analysis are planned.



# Role of temozolamide

- ▣ Quinn JA, Reardon DA, Friedman AH, et al: Phase II trial of temozolomide in patients with progressive low-grade glioma. J ClinOncol 21: 646-651, 2003.
- ▣ Forty-six patients with low-grade glioma have been treated.
- ▣ The objective response rate was 61% (24% complete response and 37% partial response), with an additional 35% of patients having stable disease. Median progression-free survival (PFS) was 22 months, with a 6-month PFS of 98% and a 12-month PFS of 76% .Toxicity observed during the study was limited to only six patients.

- ▣ Various trials are underway.
- ▣ RT (54 Gy) followed by temozolomide chemotherapy, or temozolomide both during and following RT.( Both RTOG and EORTC )
- ▣ Randomizing the pts to monotherapy with either RT (50.4 Gy) or temozolomide.
- ▣ Stratifying patients by chromosome 1p deletion (present *v* absent), age (<40 *v* >40), and contrast enhancement (present *v* absent)

- **RTOG Trial (0424) is using concurrent radiation with temozolomide, followed by adjuvant temozolomide or 12 cycles, for patients with three or more high-risk features.**
  
- **The high-risk features per the RTOG 0424 study include**
  1. **Astrocytoma dominant histology,**
  2. **Age >40,**
  3. **Tumor that crosses midline,**
  4. **Size >6 cm,**
  5. **Neurological function greater than 1.**
  
- **Results of these ongoing trials are awaited and will help determine the role of temozolomide with or without radiation in LGGs.**
  
- **Additional trials comparing PCV to temozolomide will be needed in future for LGGs.**

- ▣ In adults with LGG, there is no difference in OS whether RT is given postoperatively or delayed to the time of recurrence.
- ▣ However, about two thirds of adults with LGG will develop tumor progression by 5 years following surgery alone.
- ▣ When RT is administered, lower doses produce a survival outcome similar to higher doses with less neurotoxicity.
- ▣ Data on whether chemotherapy (PCV or temozolomide) either alone or with RT improves outcome will be forthcoming from ongoing trials.

# Gamma knife radiosurgery for low-grade astrocytomas

The study was about the effect of GKRS in LGG around Optic Apparatus

	Grade 1	Grade 2
	12	39
Mean age	9.8	30.9
Mean diameter	25.4 mm	23.7 mm
Dose	12.5 Gy	15.7Gy
Response rate	50	46.2
Control rate	91.7 %	87.2 %

**YOSHIHISA KIDA, M.D., TATSUYA KOBAYASHI, M.D., AND YOSHIMASA MORI, M.D.**  
*Department of Neurosurgery, Komaki City Hospital, Komaki City, Japan J Neurosurg (Suppl 3) 93:42-46, 2000*



# Take Home Message

- ▣ One should perform radical surgery wherever possible.
- ▣ Radical surgery should not come at the cost of quality of life.
- ▣ Radiotherapy to be given in cases of **Age >40, Residual tumor.**
- ▣ Chemotherapy should be added in cases of high risk cases and in those having 1p,19q deletion.

- ▣ Neurosurgeons must consider both the median survival and the quality of life while managing low grade gliomas.

***Thank***

***You***