

The Role of Surgery in High-grade Glioma – Is Surgical Resection Justified? A Review of the Current Knowledge

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Abstract

Introduction: The aims of this article were to review the role of surgical resection in the management of high-grade gliomas and to determine whether there is any survival benefit from surgical resection. **Methods:** A literature review of the influence of surgical resection on outcome was carried out. Relevant original and review papers were obtained through a PubMed search using the following keywords: glioma, resection, prognosis and outcome. **Results:** Presently, there is a lack of evidence to support a survival benefit with aggressive glioma resection, but this should not detract patients from undergoing surgery as there are many other clinical benefits of glioma excision. In addition, limiting surgical morbidity through the use of adjuvant techniques such as intraoperative magnetic resonance imaging (MRI), functional MRI and awake craniotomy is becoming increasingly important. **Conclusions:** Ideally, a randomised controlled trial would be the best way to resolve the issue of whether (and to what extent) surgical resection leads to improvements in patient outcome and survival, but this would not be ethical. The second best option would be well-controlled retrospective studies with a multivariate analysis of all potential confounding factors.

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Introduction

High-grade glioma (malignant glioma) is the most common primary intra-axial tumour of the central nervous system (CNS). Despite recent therapeutic advances in glioma treatment, the outcome for high-grade glioma has been disappointing. The first reported case of glioma resection was performed by Rickman Godlee in 1884.¹ More than a century later, patient outcome remains poor with marginal improvement since the 1970s.^{2,3} The higher end of current reported mean survival is about 16 to 18 months, which is fairly similar to figures reported more than 20 years ago.⁴⁻⁶ The term glioblastoma, which refers to high-grade glioma, was introduced by Mallory⁷ in 1914 and is still in common use today. The oncologic principle of total tumour resection achieved by complete excision with a clear margin has improved survival drastically in many other solid organ malignant tumours. However, this is harder to achieve in glioma surgery due to potential neurological deficits that may be incurred with wide margin resection, especially when the tumour is situated near the eloquent cortex.^{8,9}

The goals of surgical resection in high-grade glioma are purported to be improved survival outcome, symptomatic control, cytoreduction and histological diagnosis.

Does Surgical Resection Prolong Survival?

The invasive and widely infiltrative nature of high-grade gliomas makes curative resection impossible.¹⁰ This is supported by the fact that even hemispherectomy has been associated with a poor survival rate. Hemispherectomy as a means to achieve total glioma resection was pioneered by Walter Dandy in 1928,¹¹ but despite this procedure, patient survival in the early 1930s was reported to be less than 2 years.¹¹⁻¹⁵ Eight decades later, even when near total excision has been achieved and corroborated with post-resection magnetic resonance imaging (MRI), the median survival rate remains a dismal 13 months.⁵

Tumour recurrence commonly occurs close to the resection margin.¹⁶ This is attributed to the findings of increased tumour cell density along the margin, with a sharp drop being noted as the distance from the resection cavity increases. It forms the basis of the premise that a

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wider resection margin coupled with adjuvant therapy would delay recurrence and prolong survival.

To date, 4 extensive reviews of the available literature have been carried out in an attempt to resolve the controversy of whether surgical resection improves survival in malignant gliomas (Table 1). Two of these reviews evaluated the existing evidence prior to 1990.^{17,18} Another reviewed publications from 1991 to 1999.¹⁹ The most recent update is from the Cochrane database of systematic reviews.²⁰ This review identified only 1 study with adequate scientific rigour. It was a randomised trial, which enrolled 23 patients and compared biopsy to surgical excision. The results showed no difference in outcome between the 2 treatment options; however, these findings may not be conclusive because of the small sample size of the study. All 4 reviews unanimously bemoaned the lack of well-conducted studies and arrived at a similar conclusion: that there is absence of good scientific evidence to support claims of survival benefit from surgical resection of malignant gliomas.

Lacroix et al⁵ retrospectively analysed 416 consecutive cases of glioblastoma multiforme (GBM) treated at the MD Anderson Cancer Centre. However, 44% of the cases were previously treated at other institutions prior to referral (cytoreductive surgery or biopsy only, with or without adjuvant chemotherapy or radiotherapy). No comparison group was available (matched untreated group). The patients' tumour volumes were quantified prospectively based on preoperative and postoperative MR images. Tumour volume was defined based on contrast enhancement on T1-weighted imaging and increased signal intensity on T2-weighted imaging. Volumetric measurement was then performed using a software program. This method of assessing extent of resection is quantitative and reliable

compared to older methods which were based on intraoperative surgeons judgement and/or radiologists assessment of preoperative and postoperative MR imaging without quantification of tumour volume, both of which were prone to subjectivity and variability. The authors reported longer survival in patients with at least 98% tumour resection (median survival 13 versus 8.8 months). In the group without prior treatment (56%), the reported survival was 13 months for patients with a 98% or more resection and 10.1 months for less than 98% resection.

To conclude that the extent of surgical resection unequivocally improves survival outcome, we recommend the following criteria: 1) the presence of a physiological model or explanation; 2) a significant difference in outcome between glioma patients who underwent resection versus those who did not; 3) an increased survival outcome with increased extent of resection. The researchers may have formulated an attractive model of reduction of tumour load, but the Lacroix⁵ study did not satisfy the second and third criteria. They did a statistical search for a resection cut-off that is statistically significant, but a better alternative would have been to pre-assign the extent of resection that they were interested in or to follow it up with a randomised trial comparing 98% or more resection with less than 98% resection. They also found that resection of less than 98% did not show any significant improvement in survival outcome as compared to untreated patients. Because of these limitations, generalising the Lacroix finding—wherein resection of 98% or more is synonymous with improved outcome—in any neurosurgical institution may not be correct. However, this study suggests that even in the presence of bias in patient selection, the survival benefit from radical glioma resection may be as high as 3 months in the best of hands, provided that post-surgical neurological deficit is kept low.

Table 1. Systematic Reviews of the Extent of Resection Influencing Outcome

Authors	Studies included in literature reviewed	Clinical question	Study descriptions	Conclusions
Nazzaro and Neuwelt, ¹⁷ Quigley and Maroon ¹⁸	Prior to 1990 (all reported trials)	Extent of high grade glioma resection versus survival outcome	No RCT. Lack of prospective observational data. Confounding factors not accounted for.	Flawed study designs. Little evidence to support hypothesis that aggressive surgical management significantly prolongs survival.
Hess ¹⁹	1991 to 1999 (all reported trials)		Retrospective data except for 1 prospective study. Only 4 adjusted for confounding factors.	No reliable clinical study. Little scientific evidence to support assertion that aggressive surgical resection prolongs survival.
Grant ²⁰	Up to 2006 (RCTs only)	Effect of surgical resection versus biopsy on survival, time to progression or quality of life.	1 RCT found inequalities among groups. Underpowered. Radiological misdiagnosis (30 randomised, only 23 with high-grade gliomas).	Single, small, underpowered study. Unable to conclude if one form of treatment (surgical excision or biopsy only) is superior to another.

RCT: randomised controlled trial

Table 2 summarises additional studies, which support improved survival following glioma resection. Most are retrospective in nature with no matched control, let alone randomised control; thus, there is no strong evidence that aggressive surgical resection per se significantly improves survival outcome. In contrast, there is evidence to support the benefit of postoperative radiotherapy and chemotherapy in improving outcome following surgical resection.²⁸

Why Surgical Resection Then?

Failure to demonstrate prolonged survival should not stop physicians from considering surgical resection due to the numerous other benefits of tumour removal.

1. Symptomatic Relief and Neurological Improvement

Symptomatic relief from mass effect and obstructed

cerebrospinal fluid (CSF) circulation are obvious benefits of glioma resection. Distortion of brain structure and compression of neural pathways contribute to both general symptoms and focal deficits, which may show some degree of improvement following surgical resection.

Global symptoms such as headache, nausea, vomiting and general malaise often show dramatic improvement after surgery.²⁹ Relief of local compression may contribute to the partial reversal of neurological deficit.³⁰ An often used indicator of potential neurological improvement following glioma resection is a trial course of dexamethasone (16 mg per day). Patients with improved functional status after steroid use are usually the ones who will also show improvement in their quality of life after aggressive surgical resection, provided that there is low postoperative morbidity.³¹

Table 2. Studies (1999-2006) Excluded by the Cochrane Review

Paper	Study type	Results reported
Lacroix 2001 ⁵	Retrospective. n = 416 44% had prior treatment elsewhere. Multivariate analyses.	Improved survival associated with 98% or more total resection (median survival 13 versus 8.8 months). Adjusted rate ratio 1.6 (95% CI, 1.3-2; <i>P</i> <0.0001)
Buckner 2003 ²¹	3 large cooperative trials: BTSG, NCCTG, RTSG. Retrospective data, multivariate analysis including recursive partitioning analysis (RPA).	Survival advantage for patients who underwent resection.
Laws 2003 ²²	Retrospective outcome data of 788 patients over 4 years (1997-2001), multivariate analysis of resection versus biopsy.	<i>P</i> <0.0001 Increased survival time even after eliminating “poor” risk patients who may have been over-represented in biopsy group.
Proescholdt 2003 ²³	120 articles up to 2003.	No studies with high LOE (52.5% of studies had Level IIIb evidence which formed the majority). 72.5% of studies observed a positive effect of total resection but they contain methodological limitations which may significantly influence results.
Bucci 2004 ²⁴	Retrospective. Pediatric population. MRI-validated total resection (defined as more than 90% resection). Small group (n = 39). Median follow-up of 47.6 months.	Median survival of patients with total resection versus residual disease, 122.2 versus 21.3 months (<i>P</i> <0.005).
Brown 2005 ²⁵	Phase II trial. No matched control cohort. Gross total resection group had better initial quality of life assessment.	After multivariable analyses, patients with gross total resection were less likely to be depressed and had improved quality of life at 2 months follow-up.
Schneider 2005 ²⁶	Prospective (n = 31). Resection extent measured by postoperative MRI. Unadjusted for known prognostication factors.	Median survival for complete versus incomplete resection, 537 versus 237 days (<i>P</i> = 0.0037).
Stark 2005 ²⁷	Retrospective (n = 267). Univariate analysis of survival time (not adjusted). Resection extent measured by postoperative CT with contrast.	Gross total resection associated with prolonged survival. <i>P</i> = 0.014.

CT: computed tomography; EOR: extent of resection; LOE: level of evidence; RCT: randomised controlled trial

BTSG: Brain Tumour Study Group; NCCTG: North Central Cancer Treatment Group; RTOG: Radiation Therapy Oncology Group

Brown et al²⁵ evaluated the quality of life following 3 separate treatment regimens for high-grade gliomas. In this trial, patients with gross total glioma resection and adjuvant therapy had improved overall quality of life at 2- and 4-month follow-up. There was no survival benefit.

Ammirati et al⁸ and Sawaya et al⁹ found that gross total resection is associated with better patient neurological performance scores compared to those observed after more limited resections. Furthermore, partial excision, with significant residual tumour, may lead to an increased risk of postoperative bleeding and oedema exacerbation.

2. Oncologic Reduction to Augment Adjuvant Therapy

Oncologic reduction is another benefit of aggressive surgical resection. A 99% excision would reduce the amount of neoplastic cells by a factor of two, from 10^9 to 10^7 cells. A lower tumour load increases the efficacy of adjuvant therapy, and vice versa. This was demonstrated in an in vivo study, which showed increased chemotherapy resistance with a higher glioblastoma (GBM) load. A 4-fold increase in the GBM tumour load requires a 2-fold increase in the BCNU concentration in order to achieve the same effect.³² This effect has also been suggested in clinical studies. Stewart et al³³ performed a systematic review and meta-analysis of the effect of systemic chemotherapy on high-grade gliomas. They showed improved survival with a combined modality of surgical resection, radiotherapy and chemotherapy, as compared to surgery and radiotherapy. Surgical treatment included biopsy only, incomplete resection or complete resection. Subgroup analysis did not show evidence of a differential effect of chemotherapy on extent of resection; however, there was a trend towards improved survival in the patients who underwent complete and incomplete resection, compared to those in the biopsy group, although the improvement was not statistically significant.

3. More Accurate Diagnosis

The accuracy of histological diagnosis is dependent on the size of the tissue sample. This is especially true in the setting of false negatives associated with stereotactic biopsy as a result of limited tissue samples, which is estimated to be around 10%.³⁴ Jackson et al³⁵ reported a discrepancy rate of 38% between biopsy and subsequently resected specimens in 81 patients. This discrepancy was found to affect treatment in 26% of cases. The prognosis was altered in 38% of the cases.

4. Aid in Research

The collection of large human tumour samples allows for comprehensive molecular analysis and fingerprinting of each tumour, which in turn may lead to the development of individually-tailored molecular therapies. Only through

further understanding of the biology of gliomas can we hope to find a cure in the future.

Controversy Unravelled

There is inconclusive evidence to support aggressive resection in prolonging the survival of patients with high-grade glioma. All of the studies to date have not been able to provide definitive evidence on this issue.

With radical excision, the reported outcome is, at best, a mean survival benefit of about 13 months.⁵ In the elderly (>65 years old), this is further reduced to 3 months.³⁶ However, such data suffer from selection bias, as patients with poor expected outcome would not have undergone surgery. Even when there is a possibility of survival benefit, this is only seen with radical excision in excess of 98%.⁵

As such, we advocate the following guidelines for the resection of high-grade gliomas:

1. Tumour resection should be considered for histological confirmation, cytoreduction and to alleviate mass effect.
2. Aggressiveness of tumour resection is limited by the risk of incurring further or new neurological deficits, particularly deficits, which delay postoperative radiotherapy and chemotherapy.
3. Adjuvant intraoperative procedures to facilitate safe tumour resection should be encouraged.

What are the Surgical Adjuncts that Exist to Limit Surgical Morbidity?

Because of the limited lifespan of high-grade glioma patients, it is crucial that surgical debulking does not compound any existing neurological deficit. Otherwise, any potential gain from the surgical resection would be offset by the morbidity. Many techniques have been developed to identify eloquent cortex, especially language, motor and sensory cortex. These adjuncts aid in defining the resection limit, and further debulking beyond this limit will likely increase the risk of surgical morbidity.

Functional MRI (fMRI) helps to identify language and motor centres. Mueller et al³⁷ compared the location of the fMRI activation with positive responses to intraoperative cortical stimulation and showed that in patients with more than 2 cm between the margin of the tumour and the activation, no decline in motor function occurred from surgical resection. fMRI of tactile, motor and language tasks is feasible in patients with tumours that are near the eloquent cortex, and shows promise as a means of determining postoperative motor deficit risk following surgical resection of frontal or parietal lobe tumors.

Intraoperative MRI potentially permits greater safety during aggressive resection of tumours by providing real-time images of residual tumour and the surrounding brain. It also leads to greater surgical accuracy by minimising

neuronavigation errors due to intraoperative brain shift. In a study of 137 patients with WHO Grade III-IV gliomas, Nimsy et al³⁸ found that 66% of patients with Grade III tumours and 28% of patients with Grade IV tumours underwent extended resection with the guidance of intraoperative MRI, thereby increasing the percentage of complete resections by 15% in Grade III gliomas and by 12% in Grade IV gliomas. Unfortunately, this increase is only marginal because in many cases, the tumour extends into the eloquent brain areas and could not be excised safely.

The integrated application of functional navigation on top of intraoperative MRI resulted in a lower postoperative morbidity rate, e.g., a transient new neurological deficit of 10.2% and a permanent neurological deficit of 2.9%. Oh et al³⁹ went on to suggest that this may become the standard of care in due time owing to the fact that patients with less residual tumour may respond more favourably to adjuvant chemotherapy with temozolomide.

Awake craniotomy with local cortical electrical stimulation helps identify the eloquent motor cortex, which cannot be reliably mapped out by anatomical landmarks. Employing identification techniques developed by doing awake craniotomy in 65 patients at the Mayo Clinic, Meyer et al⁴⁰ found that resecting tumour until the onset of neurological deficits resulted in slightly more than half (52%) of the patients having a greater than 90% reduction in T2 signal postoperatively. At the same time, these techniques allow for good functional recovery. Ninety-four per cent of the 48 patients who developed intraoperative deficits achieved a modified Rankin grade of 2 or less at 3-month follow up. Combining awake craniotomy with intraoperative cortical stimulation could reduce early neurological deterioration.

Conclusion

Based on the current literature, there is still a lack of evidence on whether surgical resection improves patient survival. However, there are benefits, albeit short-term ones, to be had from surgical resection, and these should be borne in mind. Technological advances in the form of intraoperative and functional MRI along with awake craniotomy techniques may be employed to minimise surgical morbidity and improve the extent of surgical resection. Ideally, randomised controlled trials would best answer the perennial question of whether surgical resection improves patient outcome and survival, but these will not be possible because of inherent ethical concerns. Well-controlled retrospective studies with a multivariate analysis of all potential confounding factors can answer further questions but unfortunately will not provide Class I evidence.

REFERENCES

- Bennett H, Godlee RJ. Excision of a tumour from the brain. *Lancet* 1884;2:1090-1.
- Avgeropoulos NG, Batchelor TT. New treatment strategies for malignant gliomas. *Oncologist* 1999;4:209-24.
- Davis FG, Freels S, Grutsch J, Barlas S, Brem S. Survival rates in patients with primary malignant brain tumors stratified by patient age and tumor histological type: an analysis based on Surveillance, Epidemiology, and End Results (SEER) data, 1973-1991. *J Neurosurg* 1998;88:1-10.
- Curran WJ Jr, Scott CB, Horton J, Nelson JS, Weinstein AS, Nelson DF, et al. Does extent of surgery influence outcome for astrocytoma with atypical or anaplastic foci (AAF)? A report from three Radiation Therapy Oncology Group (RTOG) trials. *J Neurooncol* 1992;12:219-27.
- Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. *J Neurosurg* 2001;95:190-8.
- Stupp R, Dietrich PY, Ostermann Kraljevic S, Pica A, Maillard I, Maeder P, et al. Promising survival for patients with newly diagnosed glioblastoma multiforme treated with concomitant radiation plus temozolomide followed by adjuvant temozolomide. *J Clin Oncol* 2002;20:1375-82.
- Mallory FB. Principles of Pathologic Histology. Philadelphia: WB Saunders, 1925.
- Ammirati M, Vick N, Liao YL, Ciric I, Mikhael M. Effect of the extent of surgical resection on survival and quality of life in patients with supratentorial glioblastomas and anaplastic astrocytomas. *Neurosurgery* 1987;21:201-6.
- Sawaya R, Hammoud M, Schoppa D, Hess KR, Wu SZ, Shi WM, et al. Neurosurgical outcomes in a modern series of 400 craniotomies for treatment of parenchymal tumors. *Neurosurgery* 1998;42:1044-55.
- Kelly PJ, Daumas-Duport C, Scheithauer BW, Kall BA, Kispert DB. Stereotactic histologic correlations of computed tomography- and magnetic resonance imaging-defined abnormalities in patients with glial neoplasms. *Mayo Clin Proc* 1987;62:450-9.
- Dandy WE. Removal of right cerebral hemisphere for certain tumors with hemiplegia. *JAMA* 1928;90:823-5.
- Gardner WE. Removal of the right cerebral hemisphere for infiltrating glioma. *Arch Neurol Psychiatry* 1932;67:787-9.
- Rowe SN. Mental changes following the removal of the right cerebral hemisphere for brain tumor. *Am J Psychiatry* 1937;94:605-14.
- Hillier WF Jr. Total left cerebral hemispherectomy for malignant glioma. *Neurology* 1954;4:718-21.
- Burklund CW, Smith A. Language and the cerebral hemispheres. Observations of verbal and nonverbal responses during 18 months following left ("dominant") hemispherectomy. *Neurology* 1977;27:627-33.
- Sneed PK, Gutin PH, Larson DA, Malec MK, Phillips TL, Prados MD, et al. Patterns of recurrence of glioblastoma multiforme after external irradiation followed by implant boost. *Int J Radiat Oncol Biol Phys* 1994;29:719-27.
- Nazzaro JM, Neuwelt EA. The role of surgery in the management of supratentorial intermediate and high-grade astrocytomas in adults. *J Neurosurg* 1990;73:331-44.
- Quigley MR, Maroon JC. The relationship between survival and the extent of the resection in patients with supratentorial malignant gliomas. *Neurosurgery* 1991;29:385-8.
- Hess KR. Extent of resection as a prognostic variable in the treatment of gliomas. *J Neurooncol* 1999;42:227-31.
- Grant R, Metcalfe SE. Biopsy versus resection for malignant glioma. *Cochrane Database Syst Rev* 2005;2:CD002034.

21. Buckner JC. Factors influencing survival in high-grade gliomas. *Semin Oncol* 2003;30(6 Suppl 19):10-4.
22. Laws ER, Parney IF, Huang W, Anderson F, Morris AM, Asher A, et al. Survival following surgery and prognostic factors for recently diagnosed malignant glioma: data from the Glioma Outcomes Project. *J Neurosurg* 2003;99:467-73.
23. Proescholdt MA, Macher C, Woertgen C, Brawanski A. Level of evidence in the literature concerning brain tumor resection. *Clin Neurol Neurosurg* 2005;107:95-8.
24. Bucci MK, Maity A, Janss AJ, Belasco JB, Fisher MJ, Tochner ZA, et al. Near complete surgical resection predicts a favorable outcome in pediatric patients with nonbrainstem, malignant gliomas: results from a single center in the magnetic resonance imaging era. *Cancer* 2004;101:817-24.
25. Brown PD, Maurer MJ, Rummans TA, Pollock BE, Ballman KV, Sloan JA, et al. A prospective study of quality of life in adults with newly diagnosed high-grade gliomas: the impact of the extent of resection on quality of life and survival. *Neurosurgery* 2005;57:495-504.
26. Schneider JP, Trantakis C, Rubach M, Schulz T, Dietrich J, Winkler D, et al. Intraoperative MRI to guide the resection of primary supratentorial glioblastoma multiforme – a quantitative radiological analysis. *Neuroradiology* 2005;47:489-500.
27. Stark AM, Nabavi A, Mehdorn HM, Blomer U. Glioblastoma multiforme – report of 267 cases treated at a single institution. *Surg Neurol* 2005;63:162-9.
28. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005;352:987-96.
29. Hentschel SJ, Lang FF. Current surgical management of glioblastoma. *Cancer J* 2003;9:113-25.
30. Whittle IR, Pringle AM, Taylor R. Effects of resective surgery for left-sided intracranial tumours on language function: a prospective study. *Lancet* 1998;351:1014-8.
31. Mitchell P, Ellison DW, Mendelow AD. Surgery for malignant gliomas: mechanistic reasoning and slippery statistics. *Lancet Neurol* 2005;4:413-22.
32. Ng WH, Wan GQ, Too HP. Higher glioblastoma tumour burden confers resistance to chemotherapeutic agent – in vitro evidence. *J Clin Neurosci* 2007;14:261-6.
33. Stewart LA. Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomised trials. *Lancet* 2002;359:1011-8.
34. Sawaya R. Extent of resection in malignant gliomas: a critical summary. *J Neurooncol* 1999;42:303-5.
35. Jackson RJ, Fuller GN, Abi-Said D, Lang FF, Gokaslan ZL, Shi WM, et al. Limitations of stereotactic biopsy in the initial management of gliomas. *Neuro-oncol* 2001;3:193-200.
36. Muacevic A, Kreth FW. Quality-adjusted survival after tumor resection and/or radiation therapy for elderly patients with glioblastoma multiforme. *J Neurol* 2003;250:561-8.
37. Mueller, WM, Yetkin FZ, Hammeke TA, Morris GL III, Swanson SJ, Reichert K, et al. Functional magnetic resonance imaging mapping of the motor cortex in patients with cerebral tumors. *Neurosurgery* 1996;39:515-20.
38. Nimsy C, Ganslandt O, Buchfelder M, Fahlbusch R. Intraoperative visualization for resection of gliomas: the role of functional neuronavigation and intraoperative 1.5 T MRI. *Neurol Res* 2006;28:482-7.
39. Oh DS, Black PM. A low-field intraoperative MRI system for glioma surgery: is it worthwhile? *Neurosurg Clin N Am* 2005;16:135-41.
40. Meyer, FB, Bates LM, Goerss SJ, Friedman JA, Windschitl WL, Duffy JR, et al. Awake craniotomy for aggressive resection of primary gliomas located in eloquent brain. *Mayo Clin Proc* 2001;76:677-87.