



June Parker. *The Coming of November*. Pastel, 24" × 40". Courtesy of Gallery on the Green, S. Egremont, Mass.

*Advances in surgical and perioperative approaches have allowed more complete resection of malignant intrinsic glial neoplasms, even in functionally critical areas, without increased morbidity.*

# Optimizing Outcomes With Maximal Surgical Resection of Malignant Gliomas

*Stephen J. Hentschel, MD, and Raymond Sawaya, MD*

**Background:** *Aggressive surgical resection of malignant gliomas is a controversial issue in neurosurgery. Studies with rigorous methodology that fully address this issue have only recently become available.*

**Methods:** *The controversy regarding the role of maximal surgical resection of malignant gliomas is reviewed. The authors discuss surgical techniques and adjunctive technologies that can be utilized to assist in resection of these lesions.*

**Results:** *Using current microneurosurgical techniques, it is possible to resect malignant gliomas in gross total fashion. An aggressive approach in which 98% or more of the tumor mass is resected results in a statistically significant survival advantage.*

**Conclusions:** *An aggressive surgical procedure for malignant gliomas can result in increased survival duration for selected groups of patients.*

## Introduction

A long-standing controversy in the neurosurgical literature involves the efficacy of maximally resecting malignant gliomas. In other fields of oncologic surgery, complete resection of the lesion, hopefully with wide margins, is key to controlling the disease, but malignant

gliomas are invasive into the surrounding brain tissue, and thus wide resections are not possible due to nearby functionally critical areas. Properly designed, prospective studies have only recently become available that have shown a beneficial relationship between the extent of resection of malignant gliomas and survival. With continued refinements in microsurgical techniques and the use of adjunctive surgical technologies, major neurologic morbidity has been reduced to 8.5% and mortality to 1.7% for patients undergoing craniotomies for tumor.<sup>1</sup> This article summarizes the controversy regarding maximal resection for malignant gliomas, clarifies the relationship between increased survival and the extent of resection, and discusses some of the techniques that can be employed to optimize the extent of resection of these tumors.

---

*From the Department of Neurosurgery, The University of Texas M. D. Anderson Cancer Center, Houston, Texas.*

*Submitted October 14, 2002; accepted January 22, 2003.*

*Address reprint requests to Raymond Sawaya, MD, Department of Neurosurgery, M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Box 442, Houston, TX 77030.*

*No significant relationship exists between the authors and the companies/organizations whose products or services may be referenced in this article.*

Table 1. — Relationship Between Survival and Extent of Resection in Glioma Patients at the M. D. Anderson Cancer Center

Extent of Resection	Median Survival (95% CI)	Rate Ratio (95% CI)	P Value
≥85%	10.90 mos (9.7-12.2)	1.11 (0.8-1.5)	.5
≥90%	11.43 mos (10.1-12.7)	1.27 (1.0-1.7)	.08
≥94%	11.90 mos (10.3-13.4)	1.31 (1.0-1.7)	.03
≥96%	13.10 mos (11.3-14.9)	1.56 (1.2-2.0)	.0004
≥98%	13.40 mos (12.0-14.9)	1.74 (1.4-2.2)	<.0001
100%	13.60 mos (12.2-15.0)	1.78 (1.4-2.3)	<.0001

CI = confidence interval.  
From Sawaya R. Radical resection of glioblastoma: techniques and benefits. *Contemp Neurosurg.* 2002;24(5):1-5.

Table 2. — M. D. Anderson Cancer Center Clinical Outcome Scale for Patients With Glioblastoma Multiforme

Characteristic	Score
Tumor necrosis on MRI:	
Yes	2
No	0
Age (yrs):	
<45	0
45-64	1
≥65	2
Karnofsky score:	
<80	1
≥80	0

From Lacroix M, Abi-Said D, Fournay DR, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. *J Neurosurg.* 2001;95:190-198.

## Benefits of Maximal Resection

### Prolonged Survival

A recent study at The University of Texas M. D. Anderson Cancer Center found that a resection of 98% or more of the tumor volume was an independent variable associated with longer survival in patients with glioblastoma multiforme (GBM) (Table 1).<sup>2</sup> The median survival for these patients was 13.4 months compared with 8.8 months for patients who had lesser resections ( $P<.0001$ ). The pre- and post-operative magnetic resonance imaging (MRI) scans of these 416 patients with GBM were analyzed prospectively and volumetric data were collected to determine the extent of resection as accurately as possible.<sup>3</sup> This eliminated a drawback encountered in many studies in which nonquantitative and subjective descriptions, such as “gross total,” “subtotal,” and “partial,” were used to describe the extent of surgical resection.<sup>4,6</sup> A multivariate analysis identified five independent predictors of survival, three of which were chosen for the outcome scale: tumor necrosis, patient age, and Karnofsky score (Table 2). Using this

analysis, groups were created to allow survival estimation based on the scale according to the extent of resection (Table 3). For patients under 45 years of age with a Karnofsky score above 80 and no necrosis on their MRI scan, it is likely that these three factors outweigh the influence of the extent of resection; thus, a statistical difference was not found between the group with 98% or greater resection and the group with lesser resection. Also, the numbers for this younger group were too small to allow meaningful statistical analyses. The median survival in this group was nearly 3 years (35.3 months). A similar argument can also be applied to patients ≥65 years of age with a Karnofsky score of less than 80 and with necrosis on their MRI. Unfortunately, the median survival in this group of patients was less than 1 year (8.6 months).

This was not a randomized, controlled study, and thus the patients may have been partially “preselected” for better survival. That is, patients may have been selected for surgery if the treating surgeon believed that a maximal resection of the tumor was possible, whereas patients who were believed to have tumors

Table 3. — Clinical Outcome Groups and Length of Survival in 416 Patients With Glioblastoma Multiforme

Score	Group	No. of Patients	Median Survival (mos)*	Median Survival (No. of Patients)		P Value
				≥98% Resection	<98% Resection	
0	A	15	35.3 mos (N/A)	35.3 (8)	32.8 (7)	.85
1-2	B	89	14.9 mos (11.7-18.0)	19.0 (49)	10.9 (40)	.001
3	C	184	10.7 mos (9.2-12.2)	13.1 (79)	8.3 (105)	.005
4-5	D	128	8.2 mos (6.6-9.8)	8.6 (61)	7.8 (67)	.13

\* 95% confidence interval.  
From Lacroix M, Abi-Said D, Fournay DR, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. *J Neurosurg.* 2001;95:190-198.

that were not maximally resectable may not have been selected for surgery. Therefore, it is difficult to determine from a retrospective study whether the characteristics of the tumor or the extent of resection imparts a better prognosis in these patients. However, these two variables are closely related, and differentiating between them may be irrelevant from a practical perspective.

### *Relief of Mass Effect*

Malignant gliomas are rapidly growing tumors that can reach large sizes prior to detection. In the M. D. Anderson series,<sup>2</sup> the median preoperative tumor volume at presentation was 34 cm<sup>3</sup>. Compared with patients with lesser resections, those undergoing gross total resections have been shown to have better neurologic outcomes on follow-up without added perioperative morbidity or mortality.<sup>1,7,8</sup> In addition, with the significant reduction in mass effect, it is our experience that patients with maximal resections tolerate radiotherapy better and experience fewer side effects.

### *Oncologic Advantage*

Fewer cells remaining after resection of a tumor should improve prognosis because fewer cells will need to be eliminated by either adjuvant therapies or the body's own defenses.<sup>9</sup> Despite the fact that a 99% resection of a tumor mass consisting of 10<sup>9</sup> cells leaves 10<sup>7</sup> cells alive, a reduction in the number of cells that may be resistant to therapy, that may undergo further malignant transformation, or that may release growth factors and immune inhibiting agents is potentially advantageous. The limits of adjuvant therapies in terms of cellular thresholds of effectiveness are not known. Also, an important consideration is the ability to provide tissue from tumor samples for research purposes. Samples from human brain tumor tissue are needed to develop new therapies since it is unlikely that significant advances toward a cure for glioblastoma will be achieved using animal models alone.

### *Improved Diagnosis*

Although some authors contend that stereotactic biopsy can be used to guide the management of gliomas,<sup>10,11</sup> the discrepancy rate between the biopsy and the resected specimens is 38%, even with expert neuropathologic review.<sup>12</sup> These results are from a study of 81 consecutive patients at the M. D. Anderson Cancer Center, which found that the resulting discrepancy would have affected therapeutic regimens in 26% of cases and had prognostic implications in 38% of cases. Particularly in cases where a surgical resection of the lesion is possible, little is gained by performing

a stereotactic biopsy prior to the open craniotomy unless an abscess, lymphoma, or other nonneoplastic lesion is likely.

## **Reasons for the Controversy**

Extensive reviews have failed to find a statistical correlation between extent of surgical resection and survival in malignant gliomas.<sup>13-15</sup> Why is the concept of aggressive resection for glioblastoma still controversial, given the above arguments and the more recent studies? Several factors that surround the controversy have been identified:

### *Poor Prognosis of Malignant Gliomas*

Despite recent surgical and technological advances, the prognosis for GBM has changed little over the last 20 years. The best average survival for all patients with GBM is still 16 to 18 months, which is similar to the survival average reported 20 years ago.<sup>2,16,17</sup> However, average survival as long as 3 years may occur in some patients who are younger, have a good Karnofsky performance status, and have lesions in favorable locations.<sup>2</sup> Bucy and colleagues<sup>18</sup> reported a case of a patient who underwent surgery in 1958 for a GBM who was alive 26 years later.

### *Invasiveness of Malignant Gliomas*

Studies have shown that tumor cells may invade far beyond the main tumor mass into the brain due to the infiltrating nature of malignant gliomas and to the impossibility of removing all of the tumor cells.<sup>19</sup> Early studies have shown that even hemispherectomy is inadequate for the control of malignant gliomas. In the 1980s, Kelly et al<sup>20</sup> reported no survival advantage using volumetric laser resection but showed that patients with deep tumors could have the same survival as those with more superficial and more easily resectable tumors. While still controversial, this was the beginning of the concept that maximal resection could improve prognosis for malignant gliomas, an idea that has taken 15 more years to statistically demonstrate in a select group of patients.

### *Risk of Surgical Deficits*

It is a falsely held belief by some that radical resection of malignant gliomas is associated with an increased incidence of neurologic morbidity compared with lesser resections, even when considering lesions in eloquent areas.<sup>1,7</sup> Fadul et al<sup>8</sup> showed that patients undergoing radical resections were at no greater risk of being neurologically impaired at 1 week following

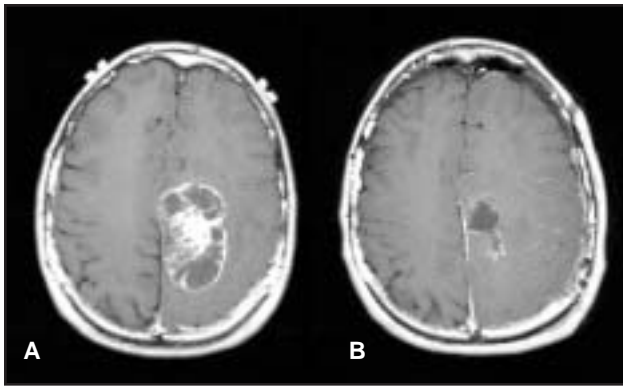


Fig 1. — (A) Preoperative and (B) postoperative contrast-enhanced MRI images demonstrating complete resection of a glioblastoma.

surgery and had fewer acute neurologic complications than patients undergoing lesser resections. When examining the Karnofsky performance status in these two groups of patients, Ammirati and colleagues<sup>7</sup> found that the scores improved by a mean of 6.8 ( $P < .006$ ) compared to preoperative scores in the completely resected group, while there was no improvement in the scores in the subtotaly resected group ( $P < .002$ ).

### *Lack of Statistically Sound Evidence*

Other than the recent report from the M. D. Anderson Cancer Center,<sup>2</sup> no other studies have examined the relationship between the extent of surgical resection and survival using rigorous preoperative and postoperative imaging analysis in a prospective fashion. In most studies, the extent of resection was not confirmed with postoperative imaging<sup>5,6</sup> or patients had undergone relatively few true maximal resections,<sup>7,21</sup> and only one study was prospective.<sup>21</sup> The opinion of the surgeon at the time of surgery may be remarkably inaccurate, with only a 30% correlation with MRI.<sup>21</sup> Therefore, postoperative imaging is key in determining the extent of resection. In addition to not confirming the extent of resection on imaging, investigators for many of the studies considered a 90% resection to be gross total. This “dilutes” the category of complete resections and thus renders the study unable to identify the group with a better prognosis — that being the  $\geq 98\%$  resection group. Because of these drawbacks, two review studies of the literature prior to 1990<sup>13,14</sup> and another after 1990<sup>15</sup> determined that “...little scientifically credible evidence is available to support the assertion that aggressive surgical resection prolongs survival.”<sup>15</sup> Many authors have called for a prospective, randomized trial to clarify this issue,<sup>9,13-15</sup> but it is unlikely that such a study will be conducted because a significant number of patients are required to determine a difference statistically and because many surgeons would not allow their patients to be randomized to such a trial.

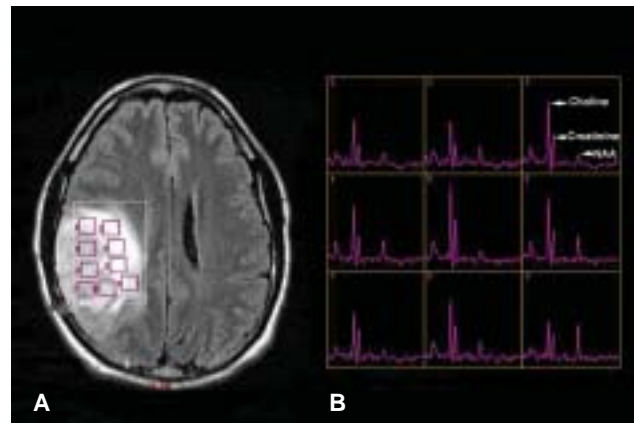


Fig 2. — MR spectroscopy with (A) the tumor and superimposed grid, and (B) the resulting spectrographic profile. The first large peak best initially seen in box 3 represents choline, which is elevated in brain tumors but not in other processes such as edema or infarction. The ratio between choline and creatinine is more sensitive for neoplasia than the absolute height of the choline peak. *N*-acetyl aspartate (NAA) is decreased in tumors and elevated in neurodegenerative processes.

## **Surgical Techniques and Adjunctive Technologies**

The stages of a craniotomy to resect a malignant glioma should include appropriate preoperative and postoperative imaging, preoperative planning including location and size of the craniotomy, and intraoperative decision making. Intraoperative ultrasound and neuro-navigation systems are also available to identify anatomical structures and dissection planes, as well as aid in the determination of the extent of resection.

High-quality imaging is necessary and should include MRI. The detail obtained with MRI is far superior to computed tomography (CT) in determining the exact anatomic location of the lesion, particularly the relationship with eloquent structures. Also, the high definition provided by MRI allows the surgeon to identify cystic or necrotic portions of the tumor that may not be visible on enhanced CT. This high definition can assist in the tumor dissection by allowing correlation of such structures on imaging with what is seen at open surgery. As well, MRI can identify residual tumor postoperatively more accurately than CT (Fig 1).<sup>21</sup> Adjunctive imaging techniques such as functional MRI, spectroscopy, and positron emission tomography can aid in identifying the relationship of the tumor to eloquent areas and in the separation of tumor from edema from normal brain (Fig 2). The use of these adjuncts varies depending on their availability and the location of the tumor mass.

Standard operative exposures are performed with or without utilizing neuronavigation for the location of the bone flap. Linear or curvilinear incisions as well as flaps are acceptable with regard to blood supply,

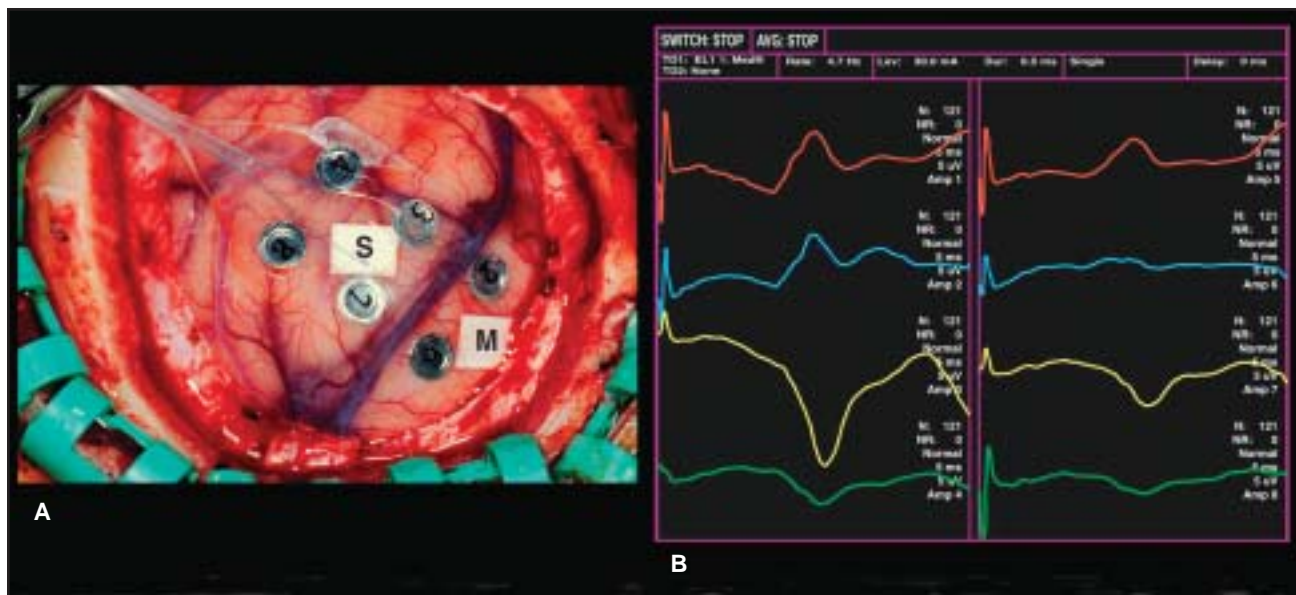


Fig 3. — Somatosensory-evoked potential (SSEP) mapping demonstrating (A) the grid over the motor (M) and sensory (S) cortex, and (B) the resulting potentials. There is a clear reversal of phase between the second and third lines, indicating that one corresponding electrode is over the sensory cortex while the other is over the motor cortex.

cosmesis, and possible reoperation. A cortical incision or a corticectomy, depending on the location and size of the lesion, is made if the lesion is superficial. For deeper or smaller lesions, entrance through a sulcus, if possible, is preferred. Determining the location for such an incision into the brain requires knowledge of the anatomy of the region that may be significantly altered due to the distortion caused by the mass of tumor. Various surgical adjuncts are available to assist the surgeon in determining the pathologic anatomy, including ultrasound,<sup>22</sup> neuronavigation,<sup>23</sup> intraoperative CT<sup>24</sup> or MRI,<sup>25,26</sup> and somatosensory-evoked potential (SSEP) mapping<sup>27</sup> (Fig 3). When the lesion is near speech or motor areas, the procedure can be performed with the patient awake to permit intraoperative stimulation mapping.<sup>28</sup>

Regardless of the depth of the lesion, the dissection should be in the white matter plane outside of the lesion with the goal of circumferential dissection.<sup>29</sup> Subpial dissection is a useful technique around the margins as even malignant gliomas respect pial borders.<sup>30</sup> In some cases, identifying the correct plane can be challenging and requires a combination of the above surgical adjuncts. However, the surgeon's interpretation of the color and consistency of the tissue, together with knowledge of anatomy, is most important in determining where the resection will cease. The main goal of surgery is removal of the enhancing tissue, which should be possible even in functionally critical areas as there should be no neurons within the tumor itself. While this is generally true, approximately 7% of gliomas will have invaded eloquent areas without altering function, thus rendering aggressive resections

potentially threatening to critical functions such as speech and motor areas.<sup>31,32</sup> In most cases, an effective technique of tumor resection utilizes the suction and bipolar cautery since usually these tumors are soft and amenable to resection in this manner.<sup>30</sup> However, when the tumor is firm or fibrous, the ultrasonic aspirator is useful. A potential drawback with the ultrasonic aspirator is that it may aerosolize tumor cells, thus distributing them some distance from the original site, but the clinical significance of this is uncertain.<sup>33</sup>

## Conclusions

With the advances in surgical techniques and perioperative technology, it is now possible to maximally resect malignant intrinsic glial neoplasms, even within functionally critical areas, without increased morbidity. Studies have demonstrated a survival advantage with 98% or greater resection of these lesions, particularly in younger patients with good Karnofsky scores.

*This work was made possible in part by the Bill Doré Fund in Neurosurgical Research.*

## References

1. Sawaya R, Hammoud M, Schoppa D, et al. Neurosurgical outcomes in a modern series of 400 craniotomies for treatment of parenchymal tumors. *Neurosurgery*. 1998;42:1044-1056.
2. Lacroix M, Abi-Said D, Fourney DR, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. *J Neurosurg*. 2001;95:190-198.
3. Shi WM, Wildrick DM, Sawaya R. Volumetric measurement of brain tumors from MR imaging. *J Neurooncol*. 1998;37:87-93.
4. Veitch CJ, Avezaat CJ, van Putten WL, et al. The influence of the

extent of surgery on the neurological function and survival in malignant glioma: a retrospective analysis in 243 patients. *J Neurol Neurosurg Psychiatry*. 1990;53:466-471.

5. Kreth FW, Warnke PC, Scheremet R, et al. Surgical resection and radiation therapy versus biopsy and radiation therapy in the treatment of glioblastoma multiforme. *J Neurosurg*. 1993;78:762-766.

6. Curran WJ Jr, Scott CB, Horton J, 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;12:219-227.

7. Ammirati M, Vick N, Liao YL, et al. Effect of the extent of surgical resection on survival and quality of life in patients with supratentorial glioblastomas and anaplastic astrocytomas. *Neurosurgery*. 1987;21:201-206.

8. Fadul C, Wood J, Thaler H, et al. Morbidity and mortality of craniotomy for excision of supratentorial gliomas. *Neurology*. 1988;38:1374-1379.

9. Laws ER Jr. Radical resection for the treatment of glioma. *Clin Neurosurg*. 1995;42:480-487.

10. Coffey RJ, Lunsford LD, Taylor FH. Survival after stereotactic biopsy of malignant gliomas. *Neurosurgery*. 1988;22:465-473.

11. Kondziolka D, Lunsford LD. The role of stereotactic biopsy in the management of gliomas. *J Neurooncol*. 1999;42:205-213.

12. Jackson RJ, Fuller GN, Abi-Said D, et al. Limitations of stereotactic biopsy in the initial management of gliomas. *Neurooncology*. 2001;3:193-200.

13. Quigley MR, Maroon JC. The relationship between survival and the extent of the resection in patients with supratentorial malignant gliomas. *Neurosurgery*. 1991;29:385-389.

14. 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.

15. Hess KR. Extent of resection as a prognostic variable in the treatment of gliomas. *J Neurooncol*. 1999;42:227-231.

16. Walker MD, Green SB, Byar DP, et al. Randomized comparisons of radiotherapy and nitrosoureas for the treatment of malignant glioma after surgery. *N Engl J Med*. 1980;303:1323-1329.

17. Stupp R, Dietrich PY, Ostermann Kraljevic S, 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;20:1375-1382.

18. Bucy PC, Oberhill HR, Siqueira EB, et al. Cerebral glioblastomas can be cured. *Neurosurgery*. 1985;16:714-717.

19. Kelly JP, Dumas-Duport C, Kispert DB, et al. Imaging-based stereotaxic serial biopsies in untreated intracranial glial neoplasms. *J Neurosurg*. 1987;66:865-874.

20. Kelly PJ, Kall BA, Goerss S, et al. Computer-assisted stereotaxic laser resection of intra-axial brain neoplasms. *J Neurosurg*. 1986;64:427-439.

21. Albert FK, Forsting M, Sartor K, et al. Early postoperative magnetic resonance imaging after resection of malignant glioma: objective evaluation of residual tumor and its influence on regrowth and prognosis. *Neurosurgery*. 1994;34:45-61.

22. Hammoud MA, Ligon BL, el Souki R, et al. Use of intraoperative ultrasound for localizing tumors and determining the extent of resection: a comparative study with magnetic resonance imaging. *J Neurosurg*. 1996;84:737-741.

23. Barnett GH. The role of image-guided technology in the surgical planning and resection of gliomas. *J Neurooncol*. 1999;42:247-258.

24. Engle DJ, Lunsford LD. Brain tumor resection guided by intraoperative computed tomography. *J Neurooncol*. 1987;4:361-370.

25. Black PM, Alexander E 3rd, Martin C, et al. Craniotomy for tumor treatment in an intraoperative magnetic resonance imaging unit. *Neurosurgery*. 1999;45:423-433.

26. Sutherland GR, Kaibara T, Louw D, et al. A mobile high-field magnetic resonance system for neurosurgery. *J Neurosurg*. 1999;91:804-813.

27. Woolsey CN, Erickson TC, Gilson WE. Localization in somatic sensory and motor areas of human cerebral cortex as determined by direct recording of evoked potentials and electrical stimulation. *J Neurosurg*. 1979;51:476-506.

28. Matz PG, Cobbs C, Berger MS. Intraoperative cortical mapping as a guide to the surgical resection of gliomas. *J Neurooncol*. 1999;42:233-245.

29. Sawaya R. Radical resection of glioblastoma: techniques and benefits. *Contemp Neurosurg*. 2002;24(5):1-5.

30. Toms SA, Ferson DZ, Sawaya R. Basic surgical techniques in the resection of malignant gliomas. *J Neurooncol*. 1999;42:215-226.

31. Ojemann JG, Miller JW, Silbergeld DL. Preserved function in brain invaded by tumor. *Neurosurgery*. 1996;39:253-259.

32. Skirboll SS, Ojemann GA, Berger MS, et al. Functional cortex and subcortical white matter located within gliomas. *Neurosurgery*. 1996;38:678-685.

33. Preston JK, Masciopinto J, Salamat MS, et al. Tumour cell dispersion by the ultrasonic aspirator during brain tumour resection. *Br J Neurosurg*. 1999;13:486-489.