Preuss Resident Research Award: Maximal Resection of Low-grade Intrinsic Brain Tumors using "Awake" Craniotomy and Multiple Marginal Smear Biopsies: Neurological Deficit Rate and Long-term Survival Data

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INTRODUCTION

"Awake" craniotomy with multiple marginal biopsies was used to resect 154 presumed low-grade brain tumors. Intraoperative neurological deficits were more likely to be permanent (47.1%) than those detected postoperatively (12.5%). The permanent, significant neurological deficit rate was 6.5%. The survival rate for Grade 2 lesions was 65.1% (43 patients) at 10 years and 85.9% (71 patients) at 5 years. Survival was better after total resection.

OBJECTIVE

Consensus as to the best management of low-grade intrinsic brain tumors is lacking. Options include limited or radical resection, radiotherapy, a combination of surgery and radiotherapy or regular surveillance scanning and clinical review with or without a biopsy.[1,6,9–11,14,21,22] The published literature provides no clear evidence of benefit to any particular management strategy.[15,19] The three central neurosurgical questions are whether, firstly, some low-grade gliomas can be cured by surgery, and, secondly, whether maximal, but subtotal, surgical resection prolongs life, and, thirdly, the extent to which radical surgery has a damaging effect on patients' quality of life (in terms of seizure frequency or new postoperative deficits). There have been no randomized controlled trials examining the role of surgery, and it must be unlikely that any will ever be successfully conducted.

This population of 125 patients had 154 maximal resections of low-grade intrinsic brain tumors between 1989 and 2004, using the technique of "awake" craniotomy with multiple marginal biopsies. We report temporary and permanent postoperative neurological deficit rates. We also report 5- and 10-year survival rates. Seventy one patients with histologically proven World Health Organization Grade 2 lesions were available for 5-year follow-up and 43 were available for 10-year follow-up.

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METHODS

Each patient in this series underwent radical resection of a supratentorial intrinsic brain tumor, using multiple marginal smear biopsies. Each lesion was located adjacent to eloquent cortex. Seventy six of the patients were male and 49 were female. The average age at the time of surgery was 37.5 years (range, 14–66 yr). Histopathological examination revealed 93 Grade 2 lesions (52 astrocytomas, 10 oligoastrocytomas, 29 oligodendrogliomas, 2 ependymomas). Fifteen lesions were of intermediate grade (i.e., between Grades 2 and 3). The remaining 17 patients had lesions that were Grade 3 or greater.

The aim of the "awake" craniotomy with multiple marginal biopsies is to maximize tumor resection while minimizing significant postoperative neurological deficit rate. The anaesthetic technique used is an "awake, asleep, awake" technique, using an infusion of remifentanil and propofol while the patient is "asleep" and a small background dose of remifentanil only when the patient is "awake".[2–5,7,12,13,16,18,20] Before "waking" the patient, cortical mapping is performed. An Ojemann cortical stimulator OCS-1 is used over all of the exposed gyri at 6 mAmperes with 1 millisecond pulses at 20 Hertz. Cortical mapping is not uniformly successful. When it does work, it is very useful for defining the primary motor cortex and anterior speech area (when the patient is awake), but is less useful for the supplementary motor cortex.

During the "awake" period, the neuroanaesthetist continuously monitors the appropriate functions such as speech, visual field, or limb power. Any deficits produced during the resection are fastidiously recorded and reported to the surgeon. The surgeon tempers the resection based on the degree of neurological disability produced. At the end of the resection, the patient is resedated and the closure completed. In the

TABLE 39.1. Permanent postoperative deficits impacting on leisure/work

Deficit	No. of patients
Increased hemiparesis	1
New hemiparesis	4
Dysphasia + hemiparesis	1
Dysphasia	3
Parietal lobe dysfunction	1
Total	10

6 hours immediately postoperatively, the patient is intensively monitored for neurological deficits. Maximal tumor resection is facilitated by the ready availability of a neuropathologist who examines serial biopsies from the tumor resection cavity. The usual pattern for marginal biopsies is to take one deep central biopsy, four deep marginal biopsies (at 3, 6, 9 and 12 o'clock), four middle marginal biopsies (at 3, 6, 9 and 12 o'clock), and four superficial marginal biopsies (at 3, 6, 9 and 12 o'clock). A minimum of 13 biopsies are routinely taken. If there is any other suspicious area, this is also biopsied. The resection may be continued if any of the marginal biopsy smears are positive for tumor, assuming this is not producing significant deficit, and marginal biopsies are repeated thereafter. The resection is classified as "complete" or "incomplete" based on the final marginal biopsies.

Postoperatively, the patients are followed closely, initially with twice yearly magnetic resonance imaging scans and clinical reviews. Subsequently, reviews and scans are on an annual basis, or earlier if clinically indicated.

RESULTS

Neurological Deficits

Of 125 patients (154 procedures), 67 experienced new or significantly increased neurological deficit. Fifty-one of these deficits were first detected intraoperatively and 16 were first detected in the immediate postoperative period. Of the 67 new or increased deficits that occurred intra- and postoperatively, 10 became permanent and impacted on work or leisure activities (*Table 39.1*). A permanent deficit was more likely to result when the deficit was first detected in the intraoperative setting (47.1% of these became permanent). Of the deficits first detected postoperatively, 12.5% became permanent (*Table 39.2*), 6.5% of which were significant, impacting on work and leisure activities.

10-year Follow-up

Forty-three patients (20 astrocytomas, 16 oligodendrogliomas, one ependymoma, three gemistiocytic astrocytomas, and three oligoastrocytomas) were available for 10-year follow-up evaluations. The group comprised 25 men and 18 women with an average age of 36.8 years. Recurrent tumor was managed by repeat resection (n = 15), chemotherapy/radiotherapy (n = 9), radiotherapy (n = 9), and chemotherapy (n = 6). Nineteen patients had no adjuvant treatment.

TABLE 39.2. Perioperative neurological deficits

Onset of deficit	Temporary deficits	Permanent deficits	Total
Intraoperative	27	24	51
Postoperative	14	2	16
Total	41	26	67

Twenty-eight patients (65%) were living in their 10th postoperative year. Of these, 20 (46.5%) were disease-free on imaging (*Table 39.3*). The disease-free 10-year survivors comprised nine astrocytomas, six oligodendrogliomas, two gemistiocytic astrocytomas, and three oligoastrocytomas.

Extent of Resection and Survival

Sixteen patients had clear final marginal biopsies (complete resection) at the time of surgery. Of these, 10 were alive with no imaging evidence of tumor in their 10th postoperative year and one was alive with magnetic resonance imaging evidence of tumor. Three died 5 to 10 years postoperatively and 2 died fewer than 5 years postoperatively. Comparison with those who had positive marginal biopsies (incomplete resection) shows that a greater proportion of those who had complete resection were alive and disease free at 10 years (62.5 versus 33.3%). Additionally, a greater proportion of those who had incomplete resections had evidence of tumor on magnetic resonance imaging (6.25 versus 29.6%). Four of the 14 patients who originally had complete resections underwent further surgery (*Table 39.4*).

DISCUSSION

It is unlikely that randomized controlled data comparing maximal resection of low-grade intrinsic brain tumors to expectant management will ever be available. The accurate, long-term follow-up data of a group that is homogenous in terms of neuropathological diagnosis and management strategy is, therefore, very valuable. Studying this patient group

TABLE 39.3. Survival data

Category	No. of patients
Alive, tumour-free at 10 years	20
Alive, with tumour at 10 years	8
Alive at 5 years, dead by 10 years	10
Died before 10 years	5
Total	43

TABLE 39.4. Survival data and completeness of resection

	Negative marginal biopies (%)	Positive marginal biopsies (%)
Alive, tumour-free on MRI in or beyond 10th postoperative year	10 (62.5)	9 (33.3)
Alive, tumour on MRI in or beyond 10th postoperative year	1 (6.25)	8 (29.6)
Alive in or beyond 5th postoperative year, but dead by 10th postoperative year	3 (18.8)	7 (25.9)
Died before 5th postoperative year	2 (12.5)	3 (11.1)
Total	16	27

has yielded two important findings. Neurological deficits that are first apparent in the intraoperative period are more likely to be permanent than those first detected postoperatively. This means that performing radical surgery on eloquently-located intrinsic brain tumors should only be performed in the "awake" environment in which the surgeon is aware when a deficit is being produced and is in the best position to strike the optimum balance between the extent of tumor resection and the deficit produced. Previous authors have found the technique efficacious, safe and well tolerated by patients,[2,8,17] and this is our experience. We have observed that mild intraoperative deficits, and even severe ones produced when operating in the supplementary motor area, can often resolve completely over a period of weeks, or even months, after surgery. This means that resection of the tumor margins does not necessarily have to be terminated as soon as the patient begins developing a deficit. Deciding when to stop the resection, if the tumor marginal biopsies are still positive and the patient is developing a mild deficit, such as slight dysphasia or limb weakness, can, therefore, be very difficult and very much a question of surgical experience. Most of the severe deficits in this series of patients were produced within the first few years of attempting radical resection. The risk of serious disability is now probably less than 6%, but it is difficult for us to know whether this is a product of better surgical selection (i.e., not operating radically on very large tumors) or better surgical technique.

The second important finding of this study is the 10-year and 10-year disease-free survival data. It is not possible, for reasons enumerated above, to conclude that the survival data after radical resection is better than that for any other management strategy. However, 65% 10-year survival and 46.5% survival without magnetic resonance imaging evidence of disease are good survival odds for lesions traditionally thought to be fatal in 80% of patients at 10 years.[6,9] The cost of these results is a permanent disability risk of 6.5%. When advising patients with newly-diagnosed low-grade gliomas about the different treatment options and the uncertainties about what should be done, surgical results such as these need to be discussed.

CONCLUSIONS

Low-grade intrinsic brain tumors represent one of the most challenging propositions in modern neurosurgery. Management strategies vary widely and it is unclear how best to proceed. A randomized controlled trial of radical resection versus conservative management or primary radiotherapy is not likely to be successfully conducted. However, series such as this one in which a single management strategy (i.e., primary radical resection) is applied to a population of patients with this condition can produce meaningful results.

This series confirms the need for eloquently located intrinsic tumors to be resected "awake," as the majority of new operative deficits occurred intraoperatively (51 versus 16) and deficits first detected intraoperatively were more likely to become permanent (47.1 versus 12.5%).

This series also demonstrates the value of a policy of early radical resection in terms of patient survival. This is clear because of improved survival rates demonstrated in this series compared with historical ones, and also because patients in whom "total" resection was achieved survived longer than those with residual tumor in their marginal biopsies at the end of the resection (62.5 versus 33% alive without tumor on imaging at 10 years).

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