Efficacy Of Surgery On Seizure Control In Drug-Resistant, Primary Brain Tumor-Related Epilepsy

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ABSTRACT

Seizures are common in brain tumors. Anti-epileptic drugs (AEDs) constitute the first line of treatment, but unfortunately, refractoriness to current AEDs is common in this population. Surgical resection of the tumor is the next step, but significant time can pass between presentation of seizures and decision to resect, drastically decreasing quality of life. An alternative is to resort to surgery sooner. To see if resection surgery is a viable option, this study was carried out in patients with brain tumors and chronic, intractable epilepsy. We wanted to determine – 1.which cases of tumor-related epilepsy are most amenable to surgery, 2. which types of tumors are most epileptogenic, and 3. whether the location of the tumor affects outcome after resection surgery. We evaluated the effectiveness of surgical intervention on seizure control by studying the Engel score post-operatively in 115 patients with a variety of tumor location, grade and tumor types with intractable epilepsy.

Low-grade gliomas presented with intractable epilepsy more frequently than in patients with high-grade gliomas. Post-surgically, 11 of the 115 patients with the most malignant tumors died. We found better seizure control after surgical resection in patients with benign and/or low-grade tumors. The sample size was too small to answer which tumor type is most epileptogenic, or whether the location of the tumor affects outcome after resection surgery. In view of the safety and efficacy of surgical intervention, it may be appropriate to consider surgical resection earlier in the assessment of treatment options for intractable tumor-induced seizures than is currently practiced.

INTRODUCTION

Neuroectodermal tumors, especially gliomas, are the most common type of primary parenchymal central nervous system tumor, and epilepsy is a common occurrence in people with brain tumors. Seizures may be the presenting symptom, or may develop later during the course of the disease. The incidence of epilepsy in people with brain tumors ranges from 30% to 70% depending on the type and location of the tumor (Villemure and de Tribolet, 1996; Lote et al., 1998; DeAngelis, 2001; van Breemen et al., 2009; Maschio, 2012; Weller et al., 2012; Blumcke et al., 2014). Tumors of lower biological grade activity are associated with a higher incidence of seizures than are high-grade tumors (Hildebrand et al., 2005; Chang et al., 2008; Kahlenberg et al., 2012).

Brain tumor-related epilepsy (BTRE) can be a significant burden (Maschio et al., 2014), and prognosis depends on seizure frequency, location of tumor and treatments used to treat the tumor (Taphoorn, 2003). Typically, longer histories of seizures predispose patients to poor post-operative prognoses (Kim et al., 2004). The location of tumor can also affect seizures – subjects with frontal or temporal tumors are more likely to present with seizures (Sirven et al., 2004; van Breman et al., 2007; de Groot et al., 2012; Wang et al., 2014) and insular tumors (Lee et al., 2010) as compared to tumors in deeper areas of the brain such as the occipital lobe. The presence of seizures as a presenting symptom often predicts not only further seizures, but also increased morbidity and mortality (Moots et al., 1995).

In patients that present with brain tumors, prophylaxis with anti-epileptic drug (AED) therapy is not recommended because of their inefficacy in stopping seizures, and substantial side effects (Glantz et al., 2000; de Oliveira et al., 2014). On the other hand, the first line of treatment for BTRE is AED therapy (Perry and Sawka, 1996; Vecht et al. 2003; van Breeman and Vecht, 2005; Fonkem et al., 2013; Perucca, 2013), most often for several years. Even without the complication of a brain tumor, epilepsy is associated with significant refractoriness to currently used AEDs - two-thirds of people with epilepsy fail to respond to standard AED therapy (Kwan and Brodie, 2002; French et al., 2004; Laxer et al., 2014); but refractoriness is much greater in patients with BTRE (Cascino, 1990; Kerkhof

and Vecht, 2013; Iuchi et al., 2014). Indeed, numerous studies have reported the inability of AEDs to effectively reduce seizures in this population (Pace et al., 1998; van Breemen et al., 2007; Walia et al., 2004; Eddy et al., 2012). The current practice for management of BTRE is to first declare intractability with respect to seizure control after the failure of two main-line AEDs (Kwan and Brodie, 2004). Once drug resistance has been established, the decision to surgically resect the tumor is made. The process of establishing a treatment plan for management of BTRE is time consuming, costly, and carries with it a significant risk of mortality and morbidity (Brodie & Kwan, 2005).

Although removal of the tumor has been shown to be beneficial (Tribolet and Villemore, 1996), response to resection surgery depends on the neuropathological characteristics of the tumor (Thom et al., 2012). In the present study, we wanted to determine whether in individuals with brain tumor and intractable epilepsy, the tumor type, grade and location impacts the incidence of refractory epilepsy and/or surgical outcome. For this, we reviewed data of all such patients who presented to the Medical College of Georgia from 1981 to 2002.

METHODS

This was a retrospective study of 115 patients with brain tumors and intractable epilepsy who underwent resection surgery at the Medical College of Georgia from 1981 and 2002. Patients had a minimum of two years post-operative follow up and were all administered AEDs for one year after resection surgery. Original pathologic diagnoses were re-evaluated. Tumor grade was based on the WHO classification (Louis et al., 2007). Surgical outcome was graded based on Engel's system of classification (Engel, 1993). Tumor locations were subdivided into anterior temporal lobe (Ant TL), lateral temporal lobe (Lat TL), frontal lobe (FL), extra frontal (parietal or occipital) and diffuse, or multi-focal locations (Table 1a). Tumor types were subdivided into astrocytoma, glioblastoma multiforme, oligodendroglioma, oligoastrocytoma and benign (including ganglioglioma, gangliocytoma, dysembryoplastic neuroepithelial tumor and pleomorphic xanthroastrocytoma; Table 1b). To compare the effect of tumor location, grade and type on Engel score post-surgery, we

compared patients with favorable outcome (Engel score I) with those of combined Engel score II, III and IV. Since data were non-parametric, results were analyzed by a Chi-square and Fisher's Exact test.

Table 1a – Classification of patients according to <u>tumor location</u>

Tumor location		**# / (total)**
Temporal lobe (TL)		71 / (115)
	Anterior TL	49 / (71)
	Lateral TL	22 / (71)
Extra-temporal lobe		44 / (115)
	Frontal lobe	19 /(44)
	Extra-frontal (parietal or occipital)	13 / (44)
	Diffuse or multi-focal	12 / (44)

Table 1b – Classification of patients according to <u>tumor type</u>

Tumor Type (WHO classification)	**# / (total)**
AC (Astrocytoma)	44 / (115)
OG (oligodendroglioma)	19 / (115)
Benign*	49 / (115)
Other or unknown	3 / (115)

*Benign includes ganglioglioma, gangliocytoma, dysembryoplastic neuroepithelial tumor and pleomorphic xanthroastrocytoma

RESULTS

A. Patient demographics

Classification of all patients included in this study according to tumor location (Table 1a), tumor type (Table 1b) and tumor grade (Table 1c) is shown in Table 1. The average age of patients in this study was 29.97 ± 1.33 years. Out of the 115 patients, 43 were female and 72 were male. Astrocytomas (44/115) and benign tumors (49/115) were the most prevalent tumors in this population. Out of the 115 patients, 14 patients with the most malignant tumors died post-surgically. With respect to brain regions, survival rates were as follows - temporal lobe: 61/71; extra-temporal lobe: 40/44 (14/115 deceased in total). With respect to tumor grade, survival rates were Grade I: 50/51; Grade II: 45/45; Grade III: 3/9 and Grade IV: 0/7 (14/115 deceased in total). The average age of patients who were deceased was 41.35 ± 3.27 years.

Table 1c – Classification of patients according to tumor grade

Tumor Type (WHO classification)	**# / (total)**
Grade I	51 / (115)
Grade II	45 / (115)
Grade III	9 / (115)
Grade IV	7 / (115)
Unknown	3 / (115)

B. Classification of Engel scores

Out of the surviving 101 patients, the following Engel scores were observed: Score I: n=54; Score II: n=23; Score III: n=19 and Score IV: n=5 (Table 2). The distribution of all patients with their Engel scores after surgery is shown in Table 3.

Table 2 – Classification of patients according to Engel criteria

Engel score	**# / (total)**
Engel score I	54 / (101)
Engel score II	23 / (101)
Engel score III	19 / (101)
Engel score IV	5 / (101)

Table 3- Surgical outcome depending on tumor location, type and grade (see legend)

Tumor Type/ Grade (WHO)	**Surgical Outcome (Engel Criteria) /Location**				**Deceased Lost to F/U**	**Totals**
	I T/ET	**II T/ET**	**III T/ET**	**IV T/ET**	**T/ET**	**T/ET**
ACI	2/0	1/0	2/0	0/0	0/0	5/0
ACII	6/3	7/2	4/3	0/0	0/1	17/9
ACIII	1/0	0/0	1/0	2/1	1/0	5/1
ACIV/GBM	0/0	0/0	0/0	0/0	5/2	5/2
OGII	5/4	0/1	0/1	0/0	0/1	5/7
OAII	0/0	1/1	0/2	1/1	0/0	1/3
Mixed OA/OG(III)	0/1	0/0	0/0	1/1	0/0	1/2
GG or GC(I)	14/10	4/3	4/0	0/0	1/0	23/13
GG/GC/PXA(II)	0/1	1/0	0/0	0/0	0/0	1/1
DNT	4/3	1/1	1/1	0/0	0/0	6/5

Other or Unknown	2/0	0/0	0/1	0/0	0/0	2/1
Total	34/22	15/8	12/8	3/2	7/4	71/44

Legends

F/U	Follow up
T/ET	Temporal / extra-temporal
AC	Astrocytoma
GBM	Glioblastoma multiforme
OG	Oligodendroglioma
OA	Oligoastrocytoma
GG	Ganglioglioma
GC	Gangliocytoma
PXA	Pleomorphic xanthroastrocytoma
DNT	Dysembryoplastic neuroepithelial tumor

C. Effect of tumor location on Engel score post-surgery

With respect to tumor location (Table 4a), we compared subjects with a favorable Engel score (I) to those with Engel scores of II, III and IV combined. All cases combined, the proportion of patients with a favorable Engel score was (56 out of 104 = 53.85%) as compared to Engel scores II-IV (48 out of 104 = 46.15%). Between tumor sites, we did not observe differences in the effect of resection surgery when tumor was in the temporal lobe as compared to extra-temporal lobe (Fisher's Exact test; p=1.000). Within the temporal lobe, no difference in efficacy of surgery on Engel score was observed when anterior temporal lobe tumors were compared to lateral temporal lobe tumors (Fisher's Exact

test; p= 0.5928). In extra-temporal lobe tumor sites, no differences were observed when effect of resection surgery on Engel score for frontal tumors were compared with extra-frontal tumors (Fisher's Exact test; p= 0.1159). A Fisher's Exact test did not reveal any difference in outcome after tumor resection when temporal lobe (TL) tumor site was compared to frontal lobe tumor site (p=0.2727) either.

D. Effect of tumor type on Engel score post-surgery

As shown (Table 4b), cerebral tumors were divided into astrocytoma (AC), oligodendroglioma (OG), benign (including ganglioglioma, gangliocytoma, dysembryoplastic neuroepithelial tumor and pleomorphic xanthroastrocytoma) and unknown types. A chi squared analysis revealed significant differences between the groups ($\chi 2$ (1, N = 7) = 59.231; p = 0.0001). On examining differences further using the Fisher's Exact test, we found significant differences in outcome in patients with astrocytomas: 12/44 had favorable outcome vs. 23/44 that didn't (p=0.0287) and benign tumors (32/49 vs. 16/49; p=0.0023), but not in those with oligodendroglioma 10/19 vs. 8/19; p=0.5254). Hence, benign neuroglial neoplasms were associated with a better surgical outcome.

E. Effect of tumor grade on Engel score

Next, we observed whether the tumor grade had an effect on the Engel score after tumor resection surgery (Table 4c). A chi squared analysis revealed significant differences between the groups when favorable Engel score (I) was compared to Engel scores II, III and IV ($\chi 2$ (1, N = 7) = 84.584; p = 0.0001). We then examined differences in outcome as a result of tumor resection in each of the different tumor grades using the Fisher's Exact test, and found significant differences in Grade I tumors: 33/52 vs. 19/52 (p=0.0104); Grade IV tumors (0/7 vs. 7/7; p=0.0006), but not for Grade II (19/44 vs. 24/44; p=0.5174) or Grade III tumors (2/9 vs. 7/9; p=0.0567). Hence, lower biologic grade tumors were characterized by a better surgical outcome, and higher biologic grade tumors were associated with a worse outcome.

Table 4a- Surgical outcome depending on tumor location

Tumor Grade (WHO)	Surgical Outcome (Engel Criteria)				Deceased Lost to F/U	Totals
	I	II	III	IV		
Anterior temporal lobe (TL)	25	9	8	3	4	49
Lateral TL	9	6	4	0	3	22
Frontal Lobe	12	2	3	0	2	19
Extra-Frontal (Parietal or Occipital)	7	3	2	1	0	13
Diffuse or Multi-focal	3	3	3	1	2	12
Total	56	23	20	5	11	115

Table 4b- Surgical outcome depending on <u>tumor type</u>

Tumor Type (WHO)	Surgical Outcome (Engel Criteria)				Deceased Lost to F/U	Totals
	I	II	III	IV		
AC (astrocytomas)	12	10	10	3	9 (GBM = 7)	44
OG (oligodendroglioma)	10	3	3	2	1	19
Benign*	32	10	6	0	1	49
Other or Unknown	2	0	1	0	0	3
Total	56	23	20	5	11	115

*Benign includes ganglioglioma, gangliocytoma, dysembryoplastic neuroepithelial tumor and pleomorphic xanthroastrocytoma

Table 4c- Surgical outcome depending on tumor grade

Tumor Grade (WHO)	Surgical Outcome (Engel Criteria)				Deceased Lost to F/U	Totals
	I	II	III	IV		
I	33	10	8	0	1	52
II	19	13	10	0	1	44
III	2	0	1	5	1	9
IV	0	0	0	0	7	7
Other or Unknown	2	0	1	0	0	3
Total	56	23	20	5	11	115

DISCUSSION

In this retrospective study, we found that benign neuroglial neoplasms and astrocytomas were the tumor types most frequently evaluated. In addition, benign tumors and lower biologic grade tumors were characterized by a better outcome after surgery. The questions of which tumor grade is most epileptogenic, and whether the location of the tumor affects outcome after resection surgery remain unresolved because of the small sample size. A prospective, randomized controlled trial

designed to evaluate and answer these questions would be a worthwhile endeavor. Although it is not known why low-grade gliomas present more frequently with seizures as compared to high-grade gliomas, one reason could be that slow-growing tumors cause extensive functional reorganization of neuronal circuits.

It has been shown that although AEDs constitute the first line of treatment in BTRE, their use is suboptimal because of refractoriness and side effects. The second line of therapy is to resect the tumor, but a significant amount of time may pass between presentation of seizures and the decision to resect, causing a significant decrease in quality of life. If resection surgery is indeed safe and effective, it may be worthwhile to make the resection decision sooner. This would prevent extensive, time-consuming delays in evaluating AEDs. The present study demonstrates that surgery is an effective approach in reducing the incidence of seizures in patients with tumor-induced epilepsy; the best Engel outcomes were found in patients with benign tumors and/or less aggressive tumors.

We found a most striking reduction in seizure frequency post-operatively in patients with benign, low-grade tumors. Other studies have also found efficiency of surgery in low-grade gliomas (Chang et al., 2008; Brahimaj et al., 2014; Kemerdere, 2014; Pallud et al., 2014), and have even suggested that surgery could actually be the therapy of choice in patients with low-grade gliomas (Riva and Bello, 2014). Low-grade tumors can undergo anaplastic transformation (Mandonnet et al., 2003; Mandonnet et al., 2010; Pallud et al., 2012), forming malignant tumors and ultimately leading to neurological disability and even death. Hence, epilepsy surgery sooner can help to not just halt seizures but prevent malignant transformation of the tumor as well.

Although studies have shown that the anatomic location of the tumor determines outcome after resection surgery (Wang et al., 2014), we failed to find a significant effect of tumor location (temporal vs. extra-temporal) on reduction of seizure frequency. However, our sample size was too small to say anything definitive. Although tumor location affects presentation of seizures (Sirven et al., 2004; van Breman et al., 2007; Lee et al., 2010; de Groot et al., 2012; Wang et al., 2014), the

peritumoral tissue can also affect the presence and severity of seizures (Gerin et al., 2013; Pallud et al., 2014).

Current treatment modalities for brain tumor related epilepsy are more beneficial for benign tumors (Shields and Choucair, 2014; Black, 1991); but the same cannot be said for malignant tumors that are still fatal, despite the advances in our understanding of the processes underlying malignancy (Kornblith and Walker, 1988; Owonikoko et al., 2014). This study, and others (McLendon and Halperin, 2003; Carlsson et al., 2014), have noted the high rate of mortality in patients with glioblastoma multiforme (GBM).

The reasons why some brain tumors are associated with seizures are numerous – structural distortion, edema, vascular compression, intracerebral hemorrhages, excitotoxicity, alterations in ion channels, inflammation and alterations in functional connectivity have been considered (Sontheimer, 2004; Bartolomei et al., 2006; Shamji et al., 2009; You et al., 2012), but not confirmed. An underexplored area in this field is genomics. Genes related to immune response, inflammation, cell cycle repair, neurotrophins and neurotransmitter receptors have been proposed to be involved (Berntsson et al., 2009). However, not every aspect of BTRE can be explained by just one mechanism, and it is likely that tumor-related factors interact with genetic and environmental factors to create a complex entity.

Brain tumor and epilepsy are both disorders that are very complicated and evolve over time, and understanding just one is daunting enough. Current practice involves treating the tumor as the primary issue, and the accompanying seizures as an afterthought. Hence, the tumor may be addressed but seizures may remain or worsen, leading to a substantial decrease in quality of life for the patient (Maschio et al., 2014; Klein et al., 2003). Hence, BTRE should be treated as a single entity that is related to, but separate from either of the diseases (de Groot et al., 2012). Care and management of BTRE currently is done by a large, multidisciplinary group of neurologists, oncologists, radiologists and surgeons. Even if these professionals are in the same institution, there is rarely any crosstalk among them so as to come up with a strategy to treat BTRE as one entity, leading to suboptimal care

(Maschio and Paladin, 2014). Another issue is the presence of cognitive deficits in individuals with BTRE which could be due to the tumor itself, seizures or a combination of the two (Hilverda et al., 2010). There are no guidelines in place to address this.

The issue of drug-drug interactions also needs to be addressed. Patients with BTRE are exposed to both - AEDs and chemotherapeutic agents increasing possibilities of drug-drug interactions. Administration of valproic acid (an enzyme- inhibiting AED) is more beneficial in glioblastoma multiforme (GBM) than an enzyme-inducing AED (Oberndorfer et al., 2005). However, opposite results have also been reported (Jaeckle et al., 2009), warranting more investigation into this topic. Although surgery afforded a decrease in seizure frequency in this study and others, surgery can be associated with risks (Langfitt et al., 2007; Teixidor et al., 2007; Sanai and Berger, 2008); and sophisticated resection techniques are crucial for complete freedom from seizures and other effects of BTRE.

Although more studies are needed to understand the effect of tumor location and grade on epileptogenesis, we found that surgery is a safe and effective approach in reducing the incidence of seizures in patients with tumor-induced epilepsy, and could be considered as a viable treatment option- especially in low-grade tumors- earlier than is currently practiced.

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DISCLOSURE

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