Association of magnetic resonance imaging–based preoperative tumor volume with postsurgical survival time in dogs with primary intracranial glioma

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OBJECTIVE
To assess the relationship between preoperative volume of primary intracranial gliomas in dogs as determined via MRI and survival time after surgical debulking and adjunctive immunotherapy.

DESIGN
Retrospective cohort study.

ANIMALS
47 client-owned dogs enrolled in clinical trials regarding glioma treatments.

PROCEDURES
Medical records of all dogs undergoing craniotomy at the University of Minnesota Veterinary Medicine Center with histologically confirmed glioma between 2008 and 2015 were retrospectively reviewed, and outcome data were collected. Preoperative T2-weighted or post–gadolinium administration T1-weighted MRI scans, performed at several referral institutions with scanners of magnet strengths ranging from 0.5 to 3.0 T, were used to measure tumor volumes as a percentage of total calvarial volume. Data were analyzed to assess the effect of each 2% fraction of tumor volume on median survival time (MST) after surgery and adjuvant treatment.

RESULTS
Tumor volumes ranged from 0.5% to 12.2% of total intracranial volume. Overall MST was 185 days (range, 2 to 802 days). No association was identified between preoperative tumor volume and MST. Only 3 (6%) dogs had low-grade tumors that had relatively small volumes, measuring 1.4%, 2.1%, and 4.3% of total calvarial volume. The MST for these 3 dogs (727 days) was longer than that for high-grade tumors (174 days); however, owing to the low number of dogs with low-grade tumors, no statistical comparison was performed.

CONCLUSIONS AND CLINICAL RELEVANCE
Preoperative tumor volume determined via MRI was neither associated with nor predictive of outcome following surgery and adjunctive treatment for dogs with glioma. Tumor grade was predictive of outcome, but unlike tumor volume that was measured with MRI, invasive biopsy was necessary to definitively diagnose tumor grade. (*J Am Vet Med Assoc* 2018;252:98–102)

As advanced imaging modalities such as MRI have become more readily available, diagnosis of primary brain tumors in veterinary patients has become more routine.[1] Primary brain tumors can arise from various cell types. Of the primary intracranial tumors in dogs, glial cell tumors have a prevalence of up to 1.0% on the basis of literature review and necropsy findings.[2]

Glioma includes several types of primary tumors, such as astrocytoma, oligodendroglioma, ependymoma, and glioblastoma. These tumors are also categorized by grade on the basis of histologic assessment and biological characteristics. In a recent study,[3] high

ABBREVIATIONS

MST   Median survival time

accuracy and interobserver agreement in tumor volume measurements on MRI scans were achieved with a planimetry method. Those findings suggest that, after a brief training period, clinicians should be able to accurately perform similar measurements with certain free-source software.[4] Good agreement was also achieved in that study[3] when performing volume measurements on MRI scans in different planes (coronal, sagittal, and axial).

Standard treatment options for all types of primary brain tumors in dogs have been investigated.[5-10] A systematic review[11] of these options revealed that radiotherapy or surgery provides a better outcome than treatments based on clinical signs. Although extra-axial (presumed meningioma), intra-axial (presumed glioma), and pituitary tumors were included in that review,[11] the findings suggest that meticulous

surgical resection of meningiomas leads to longer MSTs. Limited access to qualified surgeons as well as the lack of reliable data regarding outcome may influence the decision to treat a dog with a primary brain tumor, particularly an intra-axial tumor.

As more veterinary clinicians use advanced imaging of the brain, data regarding imaging characteristics of different tumors will aid in informed clinical decision-making. In most situations involving intracranial tumors, tumor type and grade are unknown before surgery. Clinicians must therefore make decisions and educate clients with the limited information available to them, including that obtained via MRI. Tumor size has been shown to influence prognosis and MST for several canine tumor types, such as thyroid carcinoma and mammary gland tumors.[12,13] However, for canine splenic tumors, an increase in tumor mass relative to body weight provides a better prognosis and larger tumors are more likely to be benign than smaller tumors.[14]

The aim of the study reported here was to determine whether the size of primary intracranial glioma was associated with MST in dogs treated by curative-intent surgical debulking and autologous vaccine-based immunotherapy. Our hypothesis was that overall survival time would be inversely proportional to the volume of the primary tumor prior to surgery.

Materials and Methods

Animals

All medical records of dogs undergoing craniotomy at the University of Minnesota Veterinary Medicine Center with histologically confirmed glial cell tumors between 2008 and 2015 were reviewed. All of these dogs had been enrolled in clinical trials involving immunotherapeutic treatment for primary high-grade glioma. To be included in the trials, dogs were required to have had a solitary intracranial mass with MRI characteristics most consistent with a glioma that was deemed by 2 investigators (GEP and MAH) to be suitable for surgical resection and be judged as able to survive the anesthetic episode for surgical resection and postoperative MRI. The definition of surgical suitability was surgeon dependent, given that many of the treated dogs had tumors that had been deemed inoperable by the referring neurologists, but only dogs with tumors of brainstem structures were excluded from the trials. Other exclusion criteria for the trials included the presence of severe neurologic dysfunction, such as severe herniation or level of consciousness at or below stupor, brain tumors other than high-grade glioma, tumors of brainstem structures, and severe concomitant illness such as other malignant neoplasia or systemic disease (eg, hyperadrenocorticism). Dogs were excluded from the present study specifically if their preoperative MRI scans were not of an appropriate sequence type (T2- or post–gadolinium administration T1-weighted sequences) for performance of tumor volume measurements.

Medical records review

Data were collected from the medical records regarding dog age, sex, and breed; date of MRI scanning; date of surgery; date of death; and histologic tumor type and grade. As part of the externally funded studies these dogs participated in, each dog was monitored by communication with the owner, referring veterinarian, or both after each immunotherapy appointment and at recheck MRI appointments. All dogs were followed for 1 year after surgery or until death, which in uncommon situations exceeded 1 year after surgery. After their dogs died, owners were requested to submit the brain for evaluation of tumor regrowth to determine whether the death was disease related.

Tumor volume measurements

Existing MRI scans were used for tumor volume measurements. The advanced imaging had been performed at several referral institutions by use of scanners with magnet strengths that ranged between 0.5 and 3.0 T. Either T2-weighted or post–gadolinium administration T1-weighted image sequences were used. The primary author (JDM) analyzed images in the axial and sagittal planes (images in the coronal or dorsal plane were not available for all dogs). A second observer (ACD) reviewed the scans in the axial plane alone. Dogs were then excluded from further analysis if images of sufficient resolution in either type of sequence in both axial and sagittal planes were unavailable.

Values for tumor volume as a proportion of total calvarial volume were determined in both the axial and sagittal planes by the primary author, who used a previously described planimetry technique.[3] For each dog, tumor area was traced slice by slice in both axial and sagittal planes. The sum of area measures was multiplied by the sum of slice thickness and gap in each plane to yield tumor volume. The same scans were traced slice by slice to measure the entire volume within the calvarial vault, including the brain parenchyma, tumor, CSF, and meninges. Tumor volume was calculated as a percentage of the total calvarial volume to control for variation in dog size.

Statistical analysis

Data regarding treatment adjunctive to surgical debulking as well as survival data were used in the analysis, which was performed with the aid of statistical software.[a] The degree of agreement between observers was assessed by calculation of an agreement index value by use of the following equation[8]:

$$\text{Agreement index} = 1 - (x_a - x_b)/([x_a + x_b]/2)$$

where x_a is the mean of the first operator's measurements and x_b is the mean of the second operator's measurements. As the agreement index value approaches 1, the 2 compared volume measurements are less variable and therefore more reliable. Six-month, 1-year,

and > 2-year survival rates (from completion of surgery and adjuvant immunotherapy) were calculated for each 2% increase in tumor volume. The χ^2 and Goodman-Kruskal γ tests were performed to assess the effect of each 2% fraction of tumor volume on survival rate. Several Cox proportional hazard regression models were fit with the response variable as the survival status of the dog after the surgery. The assumption of proportionality in the Cox proportional hazard models was verified by visual inspection of the survival curves. A simple model was proposed initially, involving only data from the axial plane and dividing those values into 2 categories: small and large tumor volume. Complexity was then added by stratifying on the adjunctive treatment covariate and testing other options for the tumor volume variable. For each model, ORs and 95% confidence intervals were calculated. Values of $P < 0.05$ were considered significant.

Results

Sixty dogs that underwent craniotomy and adjunctive treatment for primary glial cell tumors during the study period were assessed. Of those dogs, 13 (22%) were excluded from the analysis owing to inadequate availability of required preoperative imaging sequences, leaving 47 dogs in the study. A definitive histologic diagnosis for all tumors was provided by several board-certified veterinary pathologists with consultation from a human-medicine neuropathologist. Tumor type and grade were reported as grade 2 astrocytoma (n = 3), grade 3 anaplastic astrocytoma (11), grade 3 anaplastic oligodendroglioma (17), grade 4 glioblastoma multiforme (15), and grade 4 primitive neuroectodermal tumor (1). Three (6%) tumors were therefore considered low grade, and 44 (94%) were considered high grade.

All included dogs had undergone surgical debulking of the intra-axial tumor with curative intent and received adjuvant treatment with autologous tumor lysate vaccine–based immunotherapy. All but 3 (ie, 94%) dogs had died or been euthanized at the owner's request by the time of statistical analysis. Postmortem examination of the brain was performed on all but 4 dogs. Twenty-nine dogs had evidence of recurrent disease, and 3 dogs had pathological changes in the brain parenchyma attributable to the immunotherapy. One dog was euthanized after an episode of status epilepticus that responded to treatment but no brain lesions were identified on postmortem examination. Other dogs with no tumor recurrence were euthanized for other unrelated causes, such as necrotizing pancreatitis or other neoplasia.

The overall MST for the 47 dogs in the study was 185 days (range, 2 to 802 days). No significant differences in survival rate or MST were identified among the various tumor types for dogs with high-grade tumors. However, the 3 dogs with low-grade tumors had numerically longer survival times than did dogs with high-grade tumors, surviving at least 532, 727, and 802 days after surgery. Because of the low number of dogs with low-grade tumors, statistical comparison with dogs with high-grade tumors was not performed.

Agreement between observers was comparable to that of the previous study[3] involving brain tumor measurement in dogs, with a mean ± SD agreement index value of 0.90 ± 0.07. Mean ± SD tumor volume as a proportion of total calvarial volume was 4.70 ± 3.07% (range, 0.80% to 12.20%) in the axial plane and 4.56 ± 3.04% (range, 0.50% to 11.70%) in the sagittal plane.

When the data were stratified by relative tumor volume, in 2% incremental increases, size of tumor had no association with 6-month or 1- or 2-year survival rates (χ^2 test, $P = 0.78$; Goodman-Kruskal γ test, $P = 0.28$; **Table 1**). To improve statistical power by increasing the number of dogs (and, thus, tumors) in each comparison group, the analysis was repeated with tumors reclassified into 2 broader volume groups on the basis of a natural separation that was noted in the number of dogs relative to tumor volume as a percentage of total calvarial volume. These 2 groups were small (tumor volume < 4% of total calvarial volume; n = 24) and large (tumor volume ≥ 4% of total calvarial volume; 23). Despite the increase in the number of dogs per group, no significant difference was found between the survival curves for dogs with small and large tumor volumes **(Figure 1)**.

Table 1—Number (%) of dogs that survived to 6 months and 1 and 2 years after surgical debulking and subsequent adjunctive immunotherapy for treatment of primary intracranial glioma as a function of relative tumor volume.

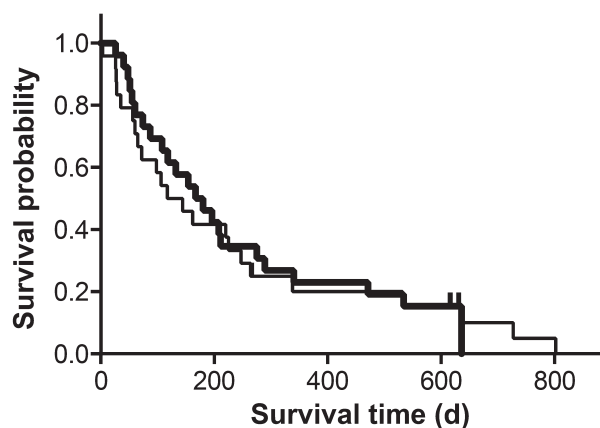| Relative tumor volume (%)	6 months	1 year	2 years
0–2.0 (n = 8)	4 (50)	1 (12)	0
2.1–4.0 (n = 17)	7 (41)	4 (24)	2 (12)
4.1–6.0 (n = 9)	3 (33)	2 (22)	0
6.1–8.0 (n = 5)	2 (40)	1 (20)	0
8.1–10.0 (n = 4)	3 (75)	2 (50)	0
> 10 (n = 4)	3 (75)	2 (50)	1 (25)
Total (n = 47)	**22 (47)**	**12 (25)**	**3 (6)**

Figure 1—Kaplan-Meier survival curves for 47 dogs with glioma grouped on the basis of whether the tumor volume was ≥ 4% (thick line) or < 4% of the total calvarial volume. Survival time was calculated relative to completion of surgical debulking. Vertical tick marks on the curves represent dogs that were still alive (n = 3) at the time of analysis and were therefore censored.

Discussion

The results of the present study suggested that tumor size measured as tumor volume as a proportion of total calvarial volume was not significantly associated with survival time of dogs with primary intracranial glioma following surgical debulking and adjunctive immunotherapy. The data used in this study were from dogs referred to the University of Minnesota for enrollment in clinical trials that involved surgery and primarily adjuvant immunotherapy. All MRI scans were reviewed by the director of the clinical trials program prior to referral, and owners were offered enrollment of their dogs if the tumor appeared to be intra-axial and was deemed operable. As such, an inherent selection bias existed. No dogs with tumors in the brainstem were enrolled because of the extremely high mortality rate following surgical resection of brainstem meningioma. None of the referred dogs had previously undergone biopsy of their intracranial lesions; therefore, dogs were enrolled with the presumptive diagnosis of glioma.

All dogs had a sudden onset of CNS signs, primarily generalized seizures or a behavioral change, that led to MRI evaluation, revealing a solitary intra-axial mass with characteristics suggestive of glioma. Many of these dogs needed aggressive supportive treatment before or after the diagnostic MRI evaluation, and dogs with a condition that could not be stabilized were likely never referred for enrollment. Dogs received appropriate palliative treatment with antiepileptic drugs to control seizures and corticosteroids to reduce cerebral edema to stabilize their condition prior to referral. Dogs that could not be stabilized following MRI evaluation were likely never referred for enrollment in the clinical trials. Therefore, owing to the study inclusion and exclusion criteria, most included dogs were in general good health with an unremarkable mental status at the time of surgery but had residual neurologic deficits such as circling, loss of conscious proprioception, and blindness. Nevertheless, a few included dogs had decompensated, were not neurologically stable immediately prior to surgery, and underwent what was considered to be emergency decompressive craniotomy as a life-saving procedure. Whether the size of tumor, some other factor (eg, degree of associated cerebral edema or herniation), or some combination of these factors led to neurologic decompensation in these dogs remains unclear.

None of the tumors could be removed en bloc because of the gelatinous consistency of most high-grade gliomas, which limited our ability to determine true tumor volume. Therefore, another limitation of the present study was the lack of data confirming the validity of the MRI tumor volume measurements. However, the only way to accurately measure tumor volume is to collect all suspected tumor tissue from the brain, separate histologically confirmed tumor from nontumor tissue, and measure the volume of actual tumor tissue. This method is an unrealistic option when dealing with clinical patients with brain tumors. It is even difficult to collect all of the excised tumor tissue given the consistency of most gliomas and the methods used to remove them.

Dogs in the present study had several types of glioma. To the authors' knowledge, no data are available on differences in survival times of dogs with various glioma types and grades. Dogs were enrolled in the clinical trials with a presumptive diagnosis of glial cell tumor on the basis of the MRI characteristics of the lesion. Histologic evaluation revealed that only 3 tumors were low grade. To determine whether any bias existed whereby small or large tumors were more likely to fall into a given histologic category, we assessed the size of the 3 low-grade tumors. One of these tumors fell into the 0% to 2% of total calvarial volume category, and the other 2 fell into the 2% to 5% category, so the low-grade tumors were in the small (< 4% total tumor volume) group. The low numbers of dogs in several of the percentage volume categories resulted in insufficient statistical power to detect associations between tumor size and survival time or rate.

Findings of the study reported here suggested that the prognosis following surgical debulking and adjunctive immunotherapy for dogs with intracranial glial cell tumors was not influenced by preoperative tumor size. Tumor size was not a factor that influenced recruitment for the clinical trials. Surprisingly, the largest tumor volume in the present study was 12% of the total calvarial volume, but many tumors had been subjectively estimated to involve 30% to 40% of the brain. In retrospect, this large tumor likely represented 30% to 40% of the total cerebral volume, which is just a portion of the total calvarial volume. Given that some of the other tumors involved regions of the brain other than the cerebral hemispheres, we believed that expression of tumor volume as a percentage of total calvarial volume was more appropriate.

Owing to the use of referral MRI scans for the preoperative analysis, we used T2-weighted images to measure tumor volume when the tumor had no gadolinium enhancement. Actual tumor volume may have been slightly overestimated in these situations if tumor-associated edema was present. Fluid-attenuated inversion recovery sequences that allow better discrimination between the tumor and edema would have been more suitable for the analysis, but this MRI sequence was not available for all dogs. Other factors such as tumor grade (given the observed differences between low- and high-grade tumors) and completeness of excision likely contributed to differences in MST in these situations. However, this information was not available to clinicians during the decision-making process for treatment. All dogs included in the present study had MRI scans repeated immediately after surgery and at intervals until death as part of the standard of care.

Other factors specific to each tumor also likely influenced both the disease-free interval and MST. Tumor metabolism and disruption of intracranial perfusion likely influenced survival time, and use of posi-

tron emission tomography to map tumor activity and cerebral perfusion as well as the extent of residual tumor after excision may help to better understand factors associated with survival time.

Although the association was not significant, the data suggested a slightly better chance of 6-month survival with a larger tumor for dogs with primary intracranial glioma in the present study. The lack of significance could have been attributable to type II error owing to the low number of dogs, which represented another study limitation. Furthermore, no attempt was made to differentiate MST in relation to minor differences in adjuvant immunotherapy protocols used. However, preliminary analysis of clinical trial data by our research group has indicated no difference among treatment protocols in survival times of dogs with high-grade glioma.

Referral for advanced imaging followed by craniotomy is currently uncommon in veterinary medicine. However, advances in surgical technique and adjunctive treatments are rapidly being developed. Findings of the study reported here can provide veterinary clinicians with basic information regarding interpretation of MRI scans for intracranial glial cell tumors in dogs and the influence of tumor size on survival following the treatment approach used.

Acknowledgments

Footnotes

a.   R, version 3.2.3, R Foundation for Statistical Computing, Vienna, Austria.

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