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Incidence, risk factors, and outcomes for early postoperative seizures in dogs with rostrotentorial brain tumors after intracranial surgery

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Abstract

Background: Seizures in the early postoperative period after intracranial surgery may affect outcome in dogs.

Objectives: To determine the incidence of early postoperative seizures (EPS) in dogs with brain tumors, identify specific risk factors for EPS, and determine if EPS affects outcome.

Animals: Eighty-eight dogs that underwent 125 intracranial surgeries for diagnosis and treatment of rostrotentorial brain tumors.

Methods: Retrospective cohort study. All patients with a diagnosis of rostrotentorial brain tumor from 2006 to 2020 were included. Early postoperative seizures were diagnosed by observation of seizure activity within 14 days of neurosurgery. Previously diagnosed structural epilepsy, perioperative anticonvulsant drug (ACD) use, magnetic resonance imaging (MRI), and tumor characteristics were evaluated. Outcome measures included neurologic and nonneurologic complications, duration of hospitalization, and survival to discharge.

Results: Dogs with rostrotentorial brain tumors had EPS after 16/125 (12.8%) neurosurgical procedures (95% confidence interval [CI], 7%-19%). Presence of previous structural epilepsy was not associated with EPS risk ($P = 1$). Perioperative ACD use also was not associated with EPS ($P = .06$). Dogs with EPS had longer hospitalization ($P < .001$), were more likely to have neurologic complications postsurgery ($P = .01$), and were less likely to survive to discharge ($P = .01$).

Conclusions and Clinical Importance: It is difficult to predict which dogs are at risk of EPS because the presence of previous structural epilepsy and the use of perioperative ACDs was not associated with EPS. However, seizures in the early postoperative

Abbreviations: ACD, anticonvulsant drug; EPS, early postoperative seizure; KPS, Karnofsky Performance Scale; PHS, primary histiocytic sarcoma; SBB, stereotactic brain biopsy.

period are clinically important because affected dogs had prolonged hospitalization, more neurologic complications, and decreased short-term survival.

KEYWORDS
brain biopsy, canine, craniotomy, intracranial neoplasm, neurosurgery

1 | INTRODUCTION

Seizures are a known complication of intracranial surgery in dogs.[1-3] Postoperative seizures may occur in animals with previously diagnosed structural epilepsy, or they can develop postoperatively.[1] The occurrence of seizures in the postoperative period may be related to surgical complications and can affect perceived quality of life. Recent studies investigating complications associated with stereotactic brain biopsy or treatment intent craniotomy or craniectomy in dogs suggest that early postoperative seizures (EPS) are rare.[4,5]

In humans undergoing intracranial surgery for brain tumors, the development of postoperative seizures is an important prognostic indicator. Postoperative seizures have been recognized in humans with various tumor types, including glioma and meningioma.[6,7] Early postoperative seizures are variably described as occurring anytime in the first week to first month after surgery, and are often of a different underlying pathophysiology than late postoperative seizures.[6,8,9] Seizures in the early postoperative period are considered acute symptomatic seizures, and are reported to occur in 1% to 18% of humans undergoing craniotomies.[10] A human patient experiencing seizures early in the postoperative period would require a repeat diagnostic evaluation, because such seizures may indicate a surgical complication.[7] Early postoperative seizures in humans are linked to a worse Karnofsky Performance Score (KPS), prolonged hospitalization, and delay of adjuvant treatment.[7] Seizures in the early postoperative period also are associated with increased risk for future hospitalizations to manage seizures associated with the development of structural epilepsy.[8] The use of perioperative prophylactic anticonvulsant drugs (ACDs) to prevent perioperative seizures in human patients has been the subject of a Cochrane review.[10] Currently, the cumulative evidence suggests that perioperative ACD do not decrease the risk of EPS, but the topic remains controversial because of the limited number of studies, numerous indications for the performance of intracranial surgery, and highly variable ACD protocols.[10,11]

Our objectives were to determine the incidence of EPS in dogs with rostrotentorial tumors, identify risk factors for the development of EPS in this cohort, and determine if EPS were associated with other postoperative adverse events. Early postoperative seizures were defined as occurring withing the first 14 days after surgery in our cohort. We hypothesized that: (1) dogs with preexisting structural epilepsy would be more likely to experience EPS than dogs with no history of seizures; (2) the risk for EPS would be higher in dogs with tumors located in the frontal and temporal or piriform lobes of the cerebrum compared to other locations; (3) the use of an additional perioperative ACD would be associated with lower risk of EPS; and (4) the presence of EPS would negatively influence acute outcomes by prolonging hospitalization or increasing the risk of death before hospital discharge.

2 | MATERIALS AND METHODS

2.1 | Study design

Ours was a single center, retrospective cohort study. The search terms brain biopsy, brain tumor, craniectomy, craniotomy, dog, and intracranial neoplasm were used to identify medical records of dogs with brain tumors that were managed by surgery from 2006 to 2020. Among records identified using these search criteria, dogs were included if they had a histologically-confirmed diagnosis of a rostrotentorial neoplasm coded in the master problem list, a complete medical record, and preoperative brain magnetic resonance imaging (MRI) examinations available for review. Only rostrotentorial tumors were included because caudal fossa tumors are less likely to cause seizures.[1,2] Dogs were excluded if medical records were incomplete or unavailable for review, or if they underwent surgical treatment for their brain tumor at another institution.

2.2 | Data collection

Data retrieved from the medical records included signalment, duration and type of clinical signs present before surgery, presence or absence of structural epilepsy before surgery, types and dosages of ACD being administered, results of preoperative physical and neurological examinations, and preoperative modified KPS for dogs.[5,12,13] In our study, any of the following semiologies were classified as seizures in dogs diagnosed with preoperative structural epilepsy or that experienced EPS: (1) intermittent focal or generalized seizures or both, (2) cluster seizures (≥2 seizures in a 24-hour period), or (3) status epilepticus.[14] Perioperative ACD drug usage was defined as the addition of a new ACD or an increase in the dosage of a previously prescribed maintenance ACD in the 24 hours before intracranial surgery that was continued for at least 7 days after surgery or until death in those dogs that did not survive to discharge. The early postoperative period was defined as the 14 days after performance of intracranial surgery. Postoperative adverse effects were characterized as seizures (ie, EPS), neurological complications (transient vs permanent neurologic deficit), and nonneurologic complications (eg, aspiration pneumonia, corneal ulceration, uroabdomen, infection, pulmonary thromboembolism).[4]

The duration of hospitalization and survival to discharge also were recorded.[5]

2.3 | Diagnostic imaging

Magnetic resonance images were reviewed by at least 1 board-certified neurologist (JR or RS) and the following data recorded as previously described: tumor circumferential location relative to the neuraxis (intra-axial, extra-axial, both), tumor location within the cerebrum (designated by lobe), the total T2-weighted (T2W) tumor volume, the total T2W brain volume, the total tumor: brain volume, and the extent (none, mild, moderate, marked) of contrast enhancement.[5] The following imaging features were scored as present or absent: peritumoral edema, midline shift >3 mm, and subfalcine, transtentorial, and foramen magnum herniations.[5] Quantitative measurements were performed using Osirix MD (v. 12.0.03, Pixmeo SARL, Switzerland).

2.4 | Surgical procedures

Dogs were hospitalized for either a diagnostic (stereotactic brain biopsy [SBB]) or therapeutic intent (craniotomy or craniectomy) surgery, or both procedures. Stereotactic brain biopsy procedures were performed as previously described using a minimally invasive technique.[15,16] The therapeutic craniotomy or craniectomy approaches used were variable depending on the location and extent of the tumor. In all cases, surgery was performed by a board-certified neurologist. Anesthesia was supervised by a board-certified or residency-trained anesthesiologist.

Histopathology of tissue samples was performed on each animal to determine tumor type. The histopathology samples were reviewed by a board-certified veterinary pathologist. Tumors were classified using the canine glioma classification system, previously reported criteria for canine histiocytic sarcomas, and the 2016 WHO brain tumor classification system for all other tumor types.[17-19] If gliomas had previously been classified under another system, they were reclassified.

2.5 | Statistical analyses

Summary data are presented as median and range, with mean and SD (Supplemental Table S1) for continuous measures and count and percentage for categorical measures. Each dog underwent 1 or 2 surgical procedures, and when a single surgical procedure was examined per dog, only the second procedure was included for analysis. A Fisher's exact or χ^2 test was used to compare each categorical risk factor with EPS using the single procedure per dog.

After exploratory Fisher's exact or χ^2 testing, multivariable analysis was performed to further characterize the primary hypotheses. All 125 surgical procedures were analyzed. Because of the correlated data structure, logistic regression incorporating generalized estimating equations with exchangeable correlation matrix was utilized to identify the risk factors for EPS. It was originally planned to include previous structural epilepsy, tumor location, additional perioperative ACD use, duration of hospitalization, survival to discharge, tumor contrast enhancement, and tumor type in the model. However, because of the sparse cells, the 95% confidence intervals (CIs) of odds ratios (ORs) for previous structural epilepsy and tumor type were too wide. These 2 independent variables then were removed from the model. Therefore, the final multivariable model analyzed the associations of postoperative seizure for all 125 procedures with tumor location, additional perioperative ACD use, duration of hospitalization, survival to discharge, and tumor contrast enhancement.

3 | RESULTS

3.1 | Animals

A total of 88 dogs met the inclusion criteria. Breeds represented included Boxer (16), Boston terrier (9), mixed breed (9), American Staffordshire terrier (6), French bulldog (6), Golden retriever (5), Labrador retriever (5), English bulldog (4), American Eskimo (2), German Shepherd (2), and Miniature Schnauzer (2), with the remaining 22 dogs each representing another unique breed. There were 46 females (3 intact, 43 spayed) and 42 males (4 intact, 38 neutered). The median age, body weight, KPS, and duration of clinical signs at diagnosis were 8 years (range, 3-14 years), 24 kg (range, 3-82 kg), 80 (range, 40-90), and 55 days (range, 11-245 days), respectively. Mean and SD for age, body weight, KPS, and duration of clinical signs are provided in Supplemental Table S1. Forty-one of 88 (46.6%) dogs had a normal interictal neurologic examination, 37/88 (42.0%) dogs had neurological examination findings consistent with a focal forebrain lesion, and 10/88 (11.3%) dogs had neurological examination abnormalities consistent with multifocal intracranial disease. All 88 dogs were treated with corticosteroids PO before surgery.

A preoperative diagnosis of structural epilepsy was established in 64/88 (72.7%) dogs. All dogs with structural epilepsy were receiving ACD therapy before surgery. Seizure phenotypes historically reported in the 64 dogs with preoperative structural epilepsy included generalized seizures only in 23/64 (35.9%), focal and generalized seizures in 19/64 (29.6%), focal seizures only in 11/64 (17.1%), cluster seizures in 6/64 (9.3%), and status epilepticus in 5/64 (7.8%). In the 6 dogs with cluster seizures, 2/6 (33.3%) initially manifested focal seizures that secondarily generalized and 4/6 (66.6%) dogs had generalized cluster seizures. All 5 dogs with status epilepticus had generalized convulsive seizures.

3.2 | Surgical procedures

In the 88 dogs, 125 intracranial surgical procedures were performed. Diagnostic SBB procedures only were performed in 20/88 (22.7%)

dogs, 31/88 (35.2%) dogs had a therapeutic surgical treatment only, and 37/88 (42.0%) dogs had both SBB and therapeutic procedures. No dogs underwent >2 procedures, and all dogs that had 2 procedures performed had SBB first, followed by a therapeutic procedure. Those dogs that underwent 2 surgical procedures were further subdivided, with 18 dogs having the second surgery 2-3 days after the SBB and 19 dogs having the 2 surgeries >14 days apart.

3.3 | Incidence and phenotypes of EPS

Early postoperative seizures were observed after 16/125 (12.8%; 95% CI, 7%-19%) neurosurgical procedures in 16/88 (18.2%; 95% CI, 10%-26%) dogs. In the EPS dogs, the first postoperative seizure occurred ≤6 hours after recovery from anesthesia in 12/16 (75.0%) dogs, and between 6-24 hours after recovery from anesthesia in 4/16 (25.0%). All dogs that experienced EPS were found to have a seizure within the first 24 hours of surgery. In total, during the 14-day follow-up period, 9 dogs with EPS experienced a single generalized seizure, 3 dogs experienced 2 generalized seizures separated by ≥24 hours, 1 dog experienced 3 generalized seizures each separated by ≥24 hours, 1 dog experienced cluster seizures, and 2 dogs experienced status epilepticus.

3.4 | Risk factors for EPS

Of the 64 dogs previously diagnosed with structural epilepsy, 12 developed EPS (12/64 or 18.8%). Twenty-four dogs had no history of structural epilepsy and 4 of those had EPS (4/24 or 16.7%). A history of structural epilepsy before surgical treatment was not linked to the occurrence of EPS ($P = 1$; Supplemental Tables S2-S4). The effect of maintenance ACD on EPS was evaluated. The maintenance ACDs used before surgery were none (4/24 or 16.7% developed EPS), phenobarbital (1/21 or 4.7% dogs with EPS), levetiracetam or zonisamide (4/11 or 36.4% dogs with EPS), or ≥2 drugs (7/32 or 21.8% dogs with EPS). For further description of maintenance ACDs used, see Supplemental Table S2). The presurgical maintenance ACD protocol was not associated with the presence of EPS ($P = .13$).

A cohort of dogs (17/88, 19.3%) was started on an additional perioperative ACD, or had their maintenance ACD dose increased in the day before surgery. Eight of the 17 dogs (47.1%) had not previously received ACDs and none of these dogs had a previously documented seizure. Nine of the 17 (52.9%) were previously treated with maintenance ACDs, and all of these dogs had previously documented structural epilepsy. Of those 17 dogs, all were either started on or treated with a dose increase of phenobarbital (5/17, 29.4%) or levetiracetam (12/17, 70.6%). Justifications for use of an additional perioperative ACD or increase in maintenance ACD dose were not provided in the records of 8/8 (100.0%) dogs that had not experienced a seizure before surgery, and in 3/9 (33.3%) dogs with previously diagnosed structural epilepsy. In 6/9 (66.6%) dogs with structural epilepsy, clinician use of additional perioperative ACD or alteration in maintenance ACD treatment was initiated because of an interictal interval <9 days in 2/6 (33.3%) dogs, preoperative serum phenobarbital concentration below the lower limit of the reference interval (<15 μg/mL) in 2/6 (33.3%) dogs, and clinician perceived administration of a subtherapeutic dose of levetiracetam (< 20 mg/kg PO q8h or q12h) in 2/6 (33.3%) dogs. Among the dogs in which an additional perioperative ACD was administered, 6/17 (35.3%) (including 1/5 [20.0%] of phenobarbital-treated dogs and 5/12 [41.6%] dogs treated with levetiracetam) experienced EPS, and 10/71(14.1%) dogs not treated with additional perioperative ACD experienced EPS. The addition of perioperative anticonvulsants was not statistically associated with EPS ($P = .06$).

When comparing the KPS for a single procedure per dog, dogs that did not have EPS had a median KPS of 80 (range, 40-90) and dogs that had EPS had a median of 70 (range, 60-90). The preoperative KPS was significantly associated with EPS ($P = .05$).

Fifty tumors were intra-axial, 36 were extra-axial, and 2 were located in both intra- and extra-axial locations. Tumor location was further classified as affecting the frontal lobe (22/88, 25.0%), piriform or temporal lobes (20/88, 22.7%), or other (46/88, 52.2%). Dogs that developed EPS included 5/22 (22.7%) dogs with frontal tumors, 1/20 (5.0%) dogs with piriform or temporal tumors, and 10/46 (21.7%) with tumors in other locations, including 1/7 (14.3%) olfactory, 1/14 (7.1%) parietal, 2/8 (25.0%) occipital, and 6/14 (42.3%) multifocal tumors. Overall, tumor location was not significantly associated with development of EPS ($P = .23$).

Median T2W tumor volume was 3.22 cm^3 (range, 0.19-17.84 cm^3), and median tumor: brain volume ratio was 0.045 (range, 0.01-0.29). The T2W tumor volume was not associated with EPS ($P = .4$). The tumor: brain ratio also was not associated with development of EPS ($P = .3$). Mass effect was identified in 81/88 (92.0%) cases, with 57/88 (64.8%) dogs having ≥1 brain herniations. Early postoperative seizures occurred in 3/31 (9.7%) dogs with no herniations, 8/33 (24.2%) dogs with subfalcine herniations, 3/15 (20.0%) dogs with transtentorial herniation, 1/3 (33.3%) dogs with foramen magnum herniation, and 1/6 (16.6%) dogs with ≥2 herniations. Brain herniation was not associated with the development of EPS ($P = .44$).

Contrast enhancement after IV gadolinium administration was observed in 75/88 (85.2%) tumors. Early postoperative seizures occurred in 1/13 (7.7%) dogs with no contrast enhancement, in 1/25 (4.0%) with mild, in 4/17 (23.5%) with moderate, and in 10/33 (30.3%) with marked contrast enhancement. Presence of contrast enhancement was associated with the development of EPS ($P = .04$). Peritumoral edema was present in 61/88 (69.3%) tumors and not observed in 27/88 (30.6%) tumors. Two of the 27 (7.4%) dogs with tumors that did not show peritumoral edema had EPS, whereas 14/61 (22.9%) with peritumoral edema present had EPS. Peritumoral edema was not associated with EPS ($P = .13$).

The effect of neurosurgical treatment type on EPS was evaluated. One dog experienced EPS after SBB (1/20, 5.0%), and the remaining 15 experienced EPS after therapeutic intent surgical treatment (15/68, 22%). Three dogs that experienced EPS had both SBB and resection surgery, but each only experienced EPS after the

resection surgery. These 3 dogs had >2 weeks between the initial SBB and the second surgery. The overall risk of developing EPS after SBB or therapeutic surgical treatment was not significant ($P = .11$).

Histopathologic tumor diagnoses included 17 astrocytomas (5 low-grade, 12 high-grade), 32 oligodendrogliomas (11 low-grade, 21 high-grade), 1 low-grade undefined glioma, 29 meningiomas (18 Grade I, 11 Grade II), 5 primary histiocytic sarcomas (PHS), 2 diffuse large B-cell lymphomas, 1 choroid plexus papilloma, and 1 granular cell tumor. Overall, 5/50 (10.0%) dogs with gliomas; 5/29 (17.2%) dogs with meningiomas, and 6/9 (66.7%) dogs with other tumors developed EPS. Of the 5 dogs with PHS, all 5 developed EPS (100%). Comparison of tumor type was categorized into meningioma, glioma, or other for the purpose of statistics. The presence of EPS was associated with tumor type ($P = .0003$). When glioma vs meningioma were compared, no significant difference was found ($P = .48$), but when glioma vs other were compared, a significant difference was found between tumor type and the development of EPS ($P = .001$).

3.5 | Outcomes

The median duration of postoperative hospitalization was 2 days (range, 1-12 days). The duration of hospitalization was significantly longer for dogs that experienced EPS (median, 5.5 days; range, 2-12 days) compared to dogs that did not (median, 2 days; range, 1-6 days) when all procedures were included ($P < .001$). We evaluated the risk of other neurologic deficits occurring in conjunction with EPS. Dogs with EPS were more likely to also have a postoperative neurologic complication, which included either a transient or permanent neurologic deficit. Neurologic deficits were variable and neuroanatomically associated with tumor location (eg, head turn or circling ipsilateral to lesion, hemiparesis contralateral to lesion, thalamocortical visual deficits). They occurred in 8/16 (50.0%) dogs with EPS vs 12/72 (16.7%) dogs that did not have EPS ($P = .01$). However, no difference was found in the incidence of postoperative nonneurologic complications, which occurred in 1/16 (6.3%) dogs with EPS and 13/72 (18.1%) dogs without EPS ($P = .27$). Nonneurologic complications included aspiration pneumonia, corneal ulceration, uroabdomen, infection, and pulmonary thromboembolism.

Six of 88 (6.8%) dogs did not survive to discharge. Dogs with EPS (4/16; 25.0%) were less likely to survive to discharge than dogs without EPS (2/72; 2.8%; $P = .01$). Tumor types in 4/16 dogs with EPS that failed to survive to discharge consisted of gliomas (2/4; 50.0%), meningioma (1/4; 25.0%), and histiocytic sarcoma (1/4; 25.0%). Dogs with EPS that did not survive to discharge were euthanized directly related to EPS (2/4; 50.0%), EPS with a concurrent neurological complication (1/4; 25.0%), or EPS associated with a nonneurologic complication (1/4; 25.0%). Both dogs without EPS that failed to survive to discharge had gliomas; 1/2 (50.0%) died of a nonneurologic complication and 1/2 (50.0%) was euthanized for an undetermined reason.

A multivariable analysis was used to further evaluate the significance of factors from our primary hypotheses. After refinement of the model, the factors included were tumor location, additional perioperative ACD, duration of hospitalization, survival to discharge, and tumor contrast enhancement on MRI. For tumor contrast enhancement, non- and mildly enhancing tumors were grouped and compared to moderate and markedly enhancing tumors. Tumor location including other vs frontal ($P = .65$), tumor location of temporal or piriform vs frontal ($P = .64$), and additional perioperative ACD use ($P = .34$) were not significantly associated with EPS. However, duration of hospitalization was significantly associated with EPS (OR, 3.53; 95% CI, 1.63-7.63; $P = .01$). The probability of survival to discharge also was significantly associated with EPS (OR, 0.06; 95% CI, 0.01-0.37; $P = .002$). Additionally, presence of no or mild tumor contrast enhancement vs moderate to marked contrast enhancement was significantly associated with EPS (OR, 3.59; 95% CI, 1.01-12.75; $P = .05$).

4 | DISCUSSION

The incidence of EPS in dogs was 12.8% when all intracranial procedures were included and 18.2% for individual dogs. A previous study reported seizures in 11.3% (18/160) of all dogs undergoing surgery for intracranial masses, with 3.1% (5/18) of those dogs experiencing new onset seizures.[1] This finding is similar to reported early seizure occurrence in human neurosurgical patients, where the reported incidence of EPS is between 1% and 18%.[10] We hypothesized that previously diagnosed structural epilepsy would be related to increased risk for EPS, but, in the current cohort of dogs, no association was found between historical structural epilepsy and EPS. In the population of dogs already diagnosed with structural epilepsy, we also evaluated the maintenance ACD regimen and found that the drug or combination of drugs used for maintenance ACD treatment did not alter the risk for EPS. Previous reports evaluating maintenance ACD protocols in structural epilepsy have not identified a difference among various treatment protocols.[20] However, the underlying pathophysiology of EPS may be different because of factors related to surgical intervention or anesthesia.[21,22] Studies of human patients indicate that brain hemorrhage, meningitis, edema, or systemic complications increase the risk for EPS.[7,8] The data suggests that regardless of previous structural epilepsy or maintenance ACD treatment, dogs undergoing neurosurgery should be monitored for EPS and additional diagnostic testing may be recommended if EPS occurs.

The assessment of whether a dog had a seizure was performed by evaluation of clinical signs of seizures only. Seizures were not confirmed by electroencephalography in our study, and thus it is very likely that some seizures were missed. It is reported that observation of the clinical signs of seizures markedly underestimates electroencephalographic seizure frequency.[23] All dogs in our case series that had EPS had their first seizure within 24 hours of surgery and thus, for the dogs that developed EPS, the first seizure was observed in the hospital. Some seizures may have occurred later in the postoperative period and were not observed either at home or in hospital.

One of the primary questions of our study was whether or not introduction of an additional perioperative ACD before surgery would alter the incidence of EPS in our patient population. The use of perioperative ACDs is common in human medicine, despite few studies

suggesting that they are effective.[9-11,24-26] We hypothesized that additional perioperative ACD use would decrease the risk of EPS, but we did not detect a difference in EPS between groups that did or did not receive additional ACDs. Therefore, we did not detect a clear benefit of additional perioperative ACDs in this cohort of dogs. Although our sample size was relatively small, our findings are similar to larger studies in humans, that have not documented a clear benefit to perioperative ACD prophylaxis.[10,11] Updated neuro-oncology guidelines conclude that there is insufficient evidence that ACDs are useful in preventing seizures in human neurosurgical patients without previous epilepsy.[11] It is possible that the use of a perioperative ACD other than levetiracetam or phenobarbital would be more effective for preventing EPS. However, a study comparing the effectiveness on various ACDs, including levetiracetam, phenobarbital, or a combination of the 2, did not identify a benefit of 1 ACD protocol vs another when managing structural epilepsy of various causes in dogs.[20] One consideration when adding ACDs for any patient is whether adverse or unintended effects will occur and what additional patient monitoring will be necessary. It is possible the introduction of a new ACD with the potential to cause sedation or ataxia just before surgery in dogs undergoing neurosurgical procedures may result in prolonged recovery from anesthesia or confound the assessment of postoperative adverse events. In this instance, we found no evidence of benefit with the addition of a perioperative ACD.

We evaluated other presurgical risk factors for EPS. Tumor imaging characteristics previously reported to be associated with the risk of structural epilepsy in dogs include location in the frontal lobe, marked gadolinium contrast enhancement and the presence of subfalcine or transtentorial herniation.[21] Although the risk factors for EPS may be different than those for structural epilepsy from other causes because of the effects of surgical intervention in dogs with EPS, we evaluated these variables. Tumor volume and tumor: brain ratio did not affect the risk for EPS. However, the presence of moderate or marked tumor gadolinium contrast enhancement was associated with EPS. We did not find a difference between the risk of EPS and tumor location. Additionally, the severity of peritumoral edema and the presence of ≥1 brain herniations was not associated with EPS. The presence of contrast enhancement on MRI of tumors indicates an abnormal blood-brain or blood-tumor barrier, which may predispose to inflammation or meningitis and therefore increase risk for EPS.

Histopathologic tumor type was a factor in the development of EPS. This factor was significant in our initial χ^2 test, but could not be included in our multivariable model because of inadequate sample size. Studies in humans previously have shown that people with meningiomas have a higher risk for EPS than those with other tumor types, and that low-grade gliomas increase risk of EPS more than high-grade gliomas.[7,27,28] In our cohort, all 5 dogs with primary histiocytic sarcoma experienced EPS. Primary histiocytic sarcoma is a tumor type with an overall poor prognosis and short median survival time, regardless of treatment.[19,29] A recent study evaluated the role of inflammation in both primary and secondary histiocytic sarcoma.[19] The proinflammatory environment of these tumors may be a factor that predisposes dogs to EPS after surgical intervention.

The type of neurosurgical procedure performed was not a significant factor for EPS in our study cohort. One dog developed EPS after SBB, whereas the other 15 did so after therapeutic intent neurosurgical procedures. Additional studies likely will clarify whether neurosurgery type affects EPS risk. Stereotactic brain biopsy is increasingly being used in veterinary neurosurgical practice and overall is considered a relatively safe procedure.[3,5,15] It has been suggested that the extent of resection is an important risk factor for EPS in humans with primary brain tumors, with complete resection having a higher risk than partial resection or biopsy.[28] It may be that increased tissue disruption and inflammation associated with therapeutic intent procedures increase the risk for EPS in those cases.

Another objective of our study was to determine if EPS had an effect on outcome. Dogs with EPS were hospitalized for a longer period of time, were more likely to have worsening neurologic status, and were less likely to survive to discharge. Therefore, by several measures, the development of EPS results in worse short-term outcome and increased risk of death. Repeated systemic evaluation and imaging including brain MRI may be indicated in dogs that experience EPS to evaluate for an underlying cause of the EPS that can be treated. In 1 study of human patients, repeat MRI or computed tomography after EPS showed a probable cause of the seizures in 78% of patients.[7] Ability to treat the underlying cause may improve outcome, just as treatment of primary tumors leads to prolonged freedom from seizures.[30] In the dogs that did not survive to discharge, we did not separately analyze those that died spontaneously or were euthanized. Dogs that develop seizures have a worse perceived quality of life, and there also are negative effects on caregiver quality of life.[13,20,31,32] This situation may result in earlier euthanasia in the postsurgical period.

We did not assess long term outcomes in dogs with EPS, and thus we cannot evaluate whether the dogs that had EPS were likely to have worse survival after hospital discharge or whether they were more likely to develop seizures after the initial 14 day postoperative period. In humans, perioperative seizures are linked to higher likelihood of an emergency room visit within 90 days.[6] Survival in humans with EPS also is reported to be shorter.[6] In dogs with structural epilepsy, the underlying cause of epilepsy and the presence of status epilepticus were related to shorter survival.[20] Two of the dogs that experienced EPS had status epilepticus, but only 1 survived to discharge. Additional studies on EPS in dogs should evaluate the effect on long term outcomes.

5 | CONCLUSIONS

In dogs with rostrotentorial intracranial tumors, the risk of EPS was 12.8% to 18.2% and was not associated with previous structural epilepsy. The use of additional perioperative ACDs also did not provide a significant benefit against development of EPS. However, the dogs that did experience EPS were subject to prolonged hospitalizations, increased risk of neurologic complications, and were less likely to survive to discharge.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Approved by the Virginia Tech IACUC protocols 12-014, 14-235, 16-156, 17-203, 18-068, and 20-057.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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