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Solitary intraventricular tumors in dogs and cats treated with radiotherapy alone or combined with ventriculoperitoneal shunts: A retrospective descriptive case series

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Abstract

Background: Intraventricular tumors are rare, optimal treatment is not defined. Symptomatic patients often exhibit life-threatening hydrocephalus. With several months time-to-effect after radiotherapy (RT), increased intracranial pressure is concerning. This increase in pressure can be overcome by ventriculoperitoneal shunting (VPS).

Objectives: Retrospective evaluation of outcome and complications in dogs and cats with intracranial tumors treated with either RT or VPS/RT.

Animals: Twelve client-owned cats and dogs.

Methods: Dogs and cats with symptomatic intraventricular tumors treated with definitive-intent RT or VPS/RT were included in a retrospective, descriptive case series. Complications, tumor volume evolution, time-to-progression, and survival time were determined.

Results: Twelve animals were included: 1 cat and 5 dogs treated with single-modality RT and 4 cats and 2 dogs treated with VPS/RT. Neurological worsening seen in 4/6 animals during single-modality RT and 2/6 died during RT (suspected brain herniation). All dogs with VPS normalized clinically by the end of RT or earlier. Complications occurred in 4/6 animals, all but 1 were successfully managed surgically. Imaging follow-up in 8 animals surviving RT showed a marked decrease in tumor volume. Median survival time was 162 days (95% confidence interval [CI]: 16; infinity) for animals treated with RT and 1103 days (95%CI: 752; infinity) for animals treated with VPS/RT. Median time-to-progression was 71 days (95%CI: 7; infinity) and 895 days (95%CI: 704; infinity) for each group, respectively. Two dogs died because of intraventricular metastasis 427 and 461 days after single-modality RT.

Abbreviations: CBCT, cone-beam computed tomography; CSF, cerebrospinal fluid; CT, computed tomography; GTV, gross tumor volume; ICRU, International Commission on Radiation Units and Measurements; IMRT, intensity-modulated radiation therapy; kV, kilovolt; MRI, magnetic resonance imaging; PTV, planning target volume; RT, radiation therapy; SIB, simultaneously integrated boost; ST, survival time; TTP, time to progression; VMAT, volumetric intensity modulated arc therapy; VPS, ventriculoperitoneal shunt.

Katrin Beckmann and Valeria Meier are co-first and -last authors.

Conclusions and Clinical Importance: Ventriculoperitoneal shunting led to rapid normalization of neurological signs and RT had a measurable effect on tumor volume. Combination of VPS/RT seems to be beneficial.

KEYWORDS
brain surgery, brain tumor, canine, choroid plexus tumor, endoscopic septum pellucidum fenestration, ependymoma, feline, neuronavigation-assisted, radiation therapy

1 | INTRODUCTION

Optimal treatment for intraventricular tumors in dogs and cats is not yet defined, presumably because of their rarity in that they account for only 7% of all intracranial tumors in dogs and 3.2% in cats according to necropsy studies.[1,2] Clinical signs in dogs and cats with intraventricular tumors are commonly caused by secondary internal hydrocephalus because the tumor either causes outflow obstruction or increased cerebrospinal fluid (CSF) production.[3,4] Internal hydrocephalus, if it is obstructive and acute, is associated with increased intracranial pressure that can lead to brain herniation and sudden respiratory arrest or death.[5] This outcome can be prevented by ventriculoperitoneal shunt (VPS) surgery.[6]

Although VPS surgery is an effective way to evacuate CSF into the abdominal cavity, it mainly has been described to treat cats and dogs with congenital hydrocephalus.[7,8] Palliative VPS surgery was described in 4 dogs with tumors of the third ventricle and obstructive hydrocephalus.[9] All 4 dogs showed rapid recovery of neurological signs, but recurrence developed within 7 months because of new dilatation of the contralateral lateral ventricle. Ventriculoperitoneal shunting surgery also was reported in 8 dogs with either intraventricular tumors or tumors leading to secondary compression of the ventricular system. Two of those dogs were treated using a combined approach with radiation therapy (RT) with a markedly hypofractionated (palliative) protocol.[10] A recent case report described a cat treated with VPS and definitive-intent RT. This cat experienced rapid amelioration of its neurological signs and a reduction in tumor volume at the 6-month follow-up.[11]

Antitumor treatment is crucial even for benign brain tumors because an intracranial increase in volume inevitably will lead to clinical signs. Surgical removal of an intraventricular tumor has been described in 1 cat and 1 dog, but it is a challenging surgery associated with high risk of hemorrhage because of the highly vascular surgical field.[12,13]

To our knowledge, response to RT and outcome of intraventricular tumor patients after RT has not yet been described in >3 pets per study. Progression-free survival was 265 days and 558 days in 2 cats treated with RT and 10 months in 1 cat treated with VPS/RT.[11,14] Tumor size, evolution and outcome for choroid plexus tumors was not mentioned separately in the 1 to 3 dogs included in previous reports of irradiation of different brain tumors.[15-18] One dog was alive 35 months after stereotactic radiosurgery.[18]

Our objective was to describe outcome and complications during and after VPS placement and RT, clinical signs, and tumor evolution in a group of dogs and cats with an imaging diagnosis of presumed intraventricular tumor treated with definitive-intent RT or VPS surgery followed by RT. Time to normalization of clinical signs, time to progression and overall survival time were the outcomes of interest.

2 | MATERIALS AND METHODS

2.1 | Study design

This single-center, descriptive case series retrospectively included cats and dogs presented to the Division of Radiation Oncology and the Section of Neurology of the Vetsuisse Faculty, University of Zurich, Switzerland between January 2012 and January 2022.

2.2 | Inclusion criteria and patient characteristics

Eligible cases were client-owned cats and dogs with presumed magnetic resonance imaging (MRI) diagnosis of an intraventricular tumor presented for RT. Only animals with presumed imaging diagnosis of a solitary intraventricular tumor according to previous guidelines,[19] treatment with RT (any definitive-intent protocol) or combined treatment with VPS/RT were included. Ethical approval was not required, but written owner consent for anonymous data usage was obtained. Dogs and cats the owners of which declined treatment with definitive-intent RT or VPS/RT were excluded.

Information on signalment, tumor volume, location, clinical signs, MRI findings, CSF results, medical treatment and treatment outcome were retrieved from the electronic medical records, phone calls to owner or veterinarians.

2.3 | Ventriculoperitoneal shunt—procedure

Ventriculoperitoneal shunt surgery was recommended to all owners before the start of RT if the animal showed signs of increased intraventricular pressure based on MRI (e.g., elevated corpus callosum and presence of a deformed intermediate mass, periventricular edema, dilatation of the olfactory recess, thinning of sulci or subarachnoid space or both).[20] Unilateral shunts were placed by a board-certified

veterinary neurologist (KB) under general anesthesia as previously described.[21] Information about shunt-related complications as well as the time points when they appeared after shunt placement were retrieved from the medical records.

2.4 | Radiation therapy—protocols and procedure

Animals were positioned using a rigid patient positioning system (custom-made vacuum cushion [BlueBag BodyFix, Elekta AB, Stockholm, Sweden], maxillary bite block [President The Original, Putty Soft, Coltène, Whaledent AG, Altstaetten, Switzerland]) and planning computed tomography (CT) and MRI images were fused for planning and contouring of organs at risk and target volumes, which was performed as previously described.[14,22] Target volumes and expansion margins were contoured according to the attending radiation oncologist's preference. Anesthesia, daily image guidance (kilovolt [kV]-kV orthogonal radiographs or kV cone beam CT [CBCT]) and treatment were performed and delivered using a 6 MV linear accelerator (Clinac iX, Varian, Palo Alto) and according to the attending board-certified veterinary radiation oncologists' preferences. Starting in 2016, institutional guidelines regarding image guidance were established: CBCT was mandatory before each fraction of a 3-fraction protocol, CBCT was mandatory at least 4 times for a 10-fraction protocol, and orthogonal kV-kV radiographs were mandatory before the remaining fractions. Beforehand, image guidance with orthogonal kV-kV radiographs was performed. Computer-based coplanar treatment planning was performed using an external beam planning system (Eclipse Planning System, version 10.0.28 or 15.1 Varian Oncology Systems, Palo Alto, California), analytical anisotropic algorithm (AAA), and heterogeneity correction with either 3-dimensional conformal RT, dynamic intensity-modulated radiation therapy (IMRT) or volumetric intensity modulated arc therapy (VMAT). Dose was prescribed to 100% of the mean. Dose coverage of 95% to 98% of the volume of the planning target volume with at least 95% of the prescribed dose was targeted. The primary goal was optimal target coverage and the secondary goal was optimal sparing of organs at risk. Dose specification adhered to the International Commission on Radiation Units and Measurements (ICRU) report 62 or the IMRT version adapted for veterinary medicine.[23,24] All IMRT and VMAT plans were dosimetrically verified before the start of treatment using an Octavius-Phantom (PTW, Freiburg, Germany) and each treatment plan was approved by a medical physicist as required by federal guidelines. Medical records were searched for complications during RT.

2.5 | Time to progression and survival

Regular clinical evaluations were recommended. Time until complete clinical normalization was extracted from the medical records and counted from the start of RT (as it was the recommended neurological reevaluation time point after surgery). Animals that showed complete normalization of clinical signs before RT therefore had a time to normalization of 0. Time-to-progression (TTP) and survival time (ST) were documented as described below.

2.6 | Tumor volume evolution

Reimaging was recommended every 6 months after RT or in the event of newly emerging neurological signs. Computed tomography and MRI reevaluation images (studies with contrast agent) were retrospectively imported into the RT planning system. The new tumor volume was contoured, and the percentage of size reduction or increase computed using the irradiated initial or (if available) smallest reevaluation tumor volume as baseline. Progressive disease was defined as either an increase in tumor size of >25% or metastatic disease with new intracranial or spinal space-occupying lesions based on previous studies.[25,26]

2.7 | Statistical analysis

Data were analyzed using R (version 4.0.5, www.R-project.org) with use of Gmisc, dplyr, ggplot2, and DescTools packages.[27-30] Confidence intervals for binomial proportions were computed using the Jeffreys method.

Kaplan-Meier plots were used to display the time to event outcomes with the package Survminer.[31] Time-to-progression was documented from the start of RT until recurrent neurological signs or progressive disease based on imaging (whichever came first). Animals were censored for TTP if they were still alive and free of progression at the time of analysis, if they died without any signs of progressive disease or were lost to follow-up. Survival time (ST) was documented from the start of RT until death of any cause. Animals were censored if they were still alive or lost to follow-up. Death was scored as tumor-related (local progressive disease or metastatic disease according to imaging or recurrent neurological signs) or nontumor-related (confirmed other cause of death).

Changes in relative tumor volumes over time were plotted and visualized using a spreadsheet program (Microsoft Excel for Mac 2011, version 14.3.2).

3 | RESULTS

3.1 | Patients—numbers and characteristics

Five cats and 7 dogs fulfilled the inclusion criteria and were included in the study. These animals were presented between 2014 and 2022. No dog received VPS surgery without subsequent RT. Two cats and 4 dogs had participated in previous trials for various brain tumors.[14,22]

Information on signalment, tumor volume and location, clinical signs, and MRI findings of all animals at diagnosis are shown in Tables 1 and S1. All animals received prednisolone PO after diagnosis with a median dose of 1 mg/kg/day (range, 0.5-1.16). Four of

TABLE 1 Baseline characteristics, clinical signs, and MRI characteristics

	Radiation therapy	VPS and radiation therapy	All animals included
Number of animals	6	6	12
Age in years (median [IQR])			
Dogs	8.2 (6.5-8.3)	8.2 (6.5-8.3)	7.5 (6.3-8.3)
Cats	14.9	9.8 (8.2-11.2)	11 (8.5-12)
Weight in kg (median [IQR])			
Dogs	17.8 (8.3-23.0)	24.9 (22.4-27.4.0)	19.8 (13-26)
Cats	2.8	4.6 (4-5.2)	4.3 (3.2-5)
Sex (n [%])			
Female	0	2 (33%)	2 (17%)
Male	0	1 (17%)	1 (8%)
Female spayed	1 (17%)	2 (33%)	3 (25%)
Male castrated	5 (83%)	1 (17%)	6 (50%)
Tumor volume in cm^3 (median [IQR])	1.11 (0.31-2.01)	0.75 (0.08-3.91)	0.98 (0.08-3.91)
Tumor location (n [%])			
Lateral ventricle	2 (33%)	2 (33%)	4 (33.3%)
Third ventricle	4 (67%)	2 (33%)	6 (50%)
Fourth ventricle	0	1 (17%)	1 (8.3%)
Lateral and third ventricle	0	1 (17%)	1 (8.3%)
Brain MRI characteristics (n [%])			
Caudal transtentorial herniation only	6 (100%)	2 (33%)	8 (66.7%)
Caudal transtentorial and foramen magnum herniation	0	4 (67%)	4 (33.3%)
Periventricular edema	6 (100%)	6 (100%)	12 (100%)
Hydrocephalus internus	6 (100%)	6 (100%)	12 (100%)
Clinical signs (n [%])			
Cranial nerve deficits	4 (66%)	6 (100%)	10 (83.3%)
Lethargy	5 (83%)	4 (67%)	9 (75%)
Decreased alertness	4 (67%)	4 (67%)	8 (66.7%)
Behavior changes	4 (67%)	4 (67%)	8 (66.7%)
Collapse	3 (50%)	4 (67%)	7 (58.3%)
Circling	2 (33%)	4 (67%)	6 (50%)
Epileptic seizures	3 (50%)	2 (33%)	5 (41.7%)
Abnormal gait	1 (17%)	3 (50%)	4 (33.3%)
Blindness	1 (17%)	2 (33%)	3 (25%)
Head pressing	0	2 (33%)	2 (16.7%)
Inappetence	2 (33%)	0	2 (16.7%)
Polyuria/polydipssia	2 (33%)	0	2 (16.7%)
Dyspnea	0	1 (33%)	1 (8.3%)
CSF protein concentration (n [%])			
Normal (<0.3 g/L)	0	2 (33%)	2 (16.7%)
Increased (>0.3 g/L)	2 (33%)	2 (33%)	4 (33.3%)
Not measured	4 (67%)	2 (33%)	6 (50%)
Nucleated cell count per µL (median [IQR])	15 (8-22)	2.9 (1.2-5)	2.9 (1.1-5.8)

Abbreviations: CSF, cerebrospinal fluid; IQR, interquartile range; MRI, magnetic resonance imaging; VPS, ventriculoperitoneal shunt.

12 animals received antiseizure medications PO after diagnosis (Table S1). Only 50% (6/12) of animals had CSF analysis available, for the others it was noted in the medical record that CSF analysis was not recommended (MRI signs of brain herniation [n = 4] or not evaluable [blood contamination because of VPS surgery, n = 2]). The CSF was collected directly from the shunt during VPS placement in 5 animals and in 3, an atlantooccipital CSF tap was performed after MRI. Protein concentration was >0.3 g/L in 4/6 animals (Table 1). In none of the animals did protein concentrations exceed 0.8 g/L, a concentration previously identified as a cut-off for choroid plexus carcinomas (vs papillomas).[3]

3.2 | VPS surgery and complications

Two dogs and 4 cats underwent VPS surgery before RT. Time from surgery to start of RT ranged from 3 to 15 days. Unilateral VPS with low to medium pressure valves (PaediGAV, Christoph Miethke GmbH & Co KG, Potsdam, Germany) were used in all animals: 9/24 cm/H_2O in dogs and 4/14 cm/H_2O in cats.[21] Antibiotics were prescribed PO according to the attending neurologist's preference.

In 1 cat, a second shunt was placed 1217 days after the initial surgery. Routine follow-up MRIs (892 and 1029 days after first RT) had already shown progressive enlargement of the contralateral right ventricle with mass effect indicating complete obstruction at the level of the interventricular foramen (the cat still was neurologically normal). Neurological deterioration was seen 1200 days after the first RT and follow-up MRI showed an increase in the size of the ipsilateral left ventricle and the contralateral right ventricle (Figure 1). In this cat, an endoscopic septum pellucidum fenestration was performed through a right occipital burr hole (Figure 2). The dura was incised and the endoscope (18 cm length, 30°, 2.7 mm Hopkins II with matching cystoscope urethroscope shaft and working channel, Karl Storz, Tuttlingen, Germany) was introduced using neuronavigation (StealthStation S8 Surgical Navigation System, Medtronic, Minneapolis) into the right ventricle. A blunt fenestration of the septum pellucidum was performed using the StealthStation EM Flexible Stylet (Medtronic, Minneapolis) creating hole of approximately 5 mm diameter. The new shunt was placed through the burr hole used for the endoscopic approach leading again to complete remission of clinical signs.

Complications were seen in 3 cats and suspected in 1 dog. In cats, disconnection (n = 3, 22-105 days), coiling (n = 1, 45 days), kinking (n = 1, 32 days), and dislocation of the abdominal part of the shunt (n = 1, 8 days) were seen, and all were successfully corrected surgically. Ninety days after surgery, 1 cat had pruritus of the head over approximately 10 weeks, which was suspected to be caused by overshunting and successfully treated using oclacitinib (Apoquel 3.6 mg, Zoetis, Delémont, Switzerland) 0.8 mg/kg PO q12h and cat nail caps. One dog initially showed rapid and complete neurological remission but had sudden onset of neurological deterioration and died 3 weeks after shunt placement. Emergency MRI of the brain and cervical spine at the practice of the referring veterinarian (0.33 T MRI, Paramed) showed hydrocephalus and no detectable metastases in the brain and cervical spinal cord, but no contrast agent had been administered and only a few MRI sequences were available. Culture of the CSF showed no evidence of bacterial infection. This dog had shown increased protein concentration and atypical myeloid cells on CSF analysis at the time of shunt placement. The cells had been considered bone marrow progenitor cells originating from the skull and were suspected to be associated with contamination of the drill hole during surgery. In this dog, shunt complications were suspected because of the initial rapid neurological improvement after the surgery and the acute deterioration 3 weeks later indicated a sudden increase in intracranial pressure. However, progressive disease (metastasis) could not be ruled out.

3.3 | RT and complications

All animals underwent RT as defined by the inclusion criteria. Protocols varied: 1 cat and 3 dogs were treated with 10 × 4 Gy (Monday-Friday; 1/3 with VPS/RT), 3 dogs were treated with 10 × 4 Gy to the planning target volume (PTV) with a simultaneously integrated boost (SIB) of 10 × 4.45Gy to the gross tumor volume (GTV), (Monday-Friday; 1/3 with VPS/RT), 1 cat with 10 × 4.2 Gy (Monday-Friday; with VPS/RT), 1 dog with 20 × 2.5 Gy (Monday-Friday, no VPS), and 3 cats with 3 × 8 Gy (q48h; all with VPS/RT).

Two dogs died during single-modality RT. One dog died suddenly at home approximately 1.5 hours after its third fraction (2 days after initiation of RT; 10 × 4 Gy intended protocol) after normal recovery from anesthesia. Respiratory arrest caused by foramen magnum herniation was suspected, but not evident on visual inspection during necropsy. Histopathological examination indicated no signs of herniation and a well-differentiated choroid plexus tumor with some atypia, and malignant transformation was not ruled out. The second dog showed worsening of neurological status in the afternoon after its 12th fraction (16 days after initiation of RT; intended protocol 20 × 2.5 Gy) and experienced respiratory arrest on return to the hospital the next morning. The dog was successfully resuscitated, but MRI showed progression of the hydrocephalus and the owners elected euthanasia. Necropsy identified a choroid plexus papilloma, but no signs of herniation were found.

3.4 | Normalization of clinical signs

Nine animals experienced complete normalization of their clinical signs at some point during the study period. Overall, median time to normalization (from the start of RT) for all animals that showed clinical signs at the start of RT and that finished RT was 11 days (range, 1-29). Of the animals that had VPS surgery, 2/6 experienced complete normalization of clinical signs before the start of RT and the other 4/6 normalized by the end of RT. None showed worsening of neurological signs during RT.

Of the animals that underwent single-modality RT, 2/6 experienced normalization of clinical signs with medical treatment before the start of RT. However, 4/6 dogs experienced worsening of

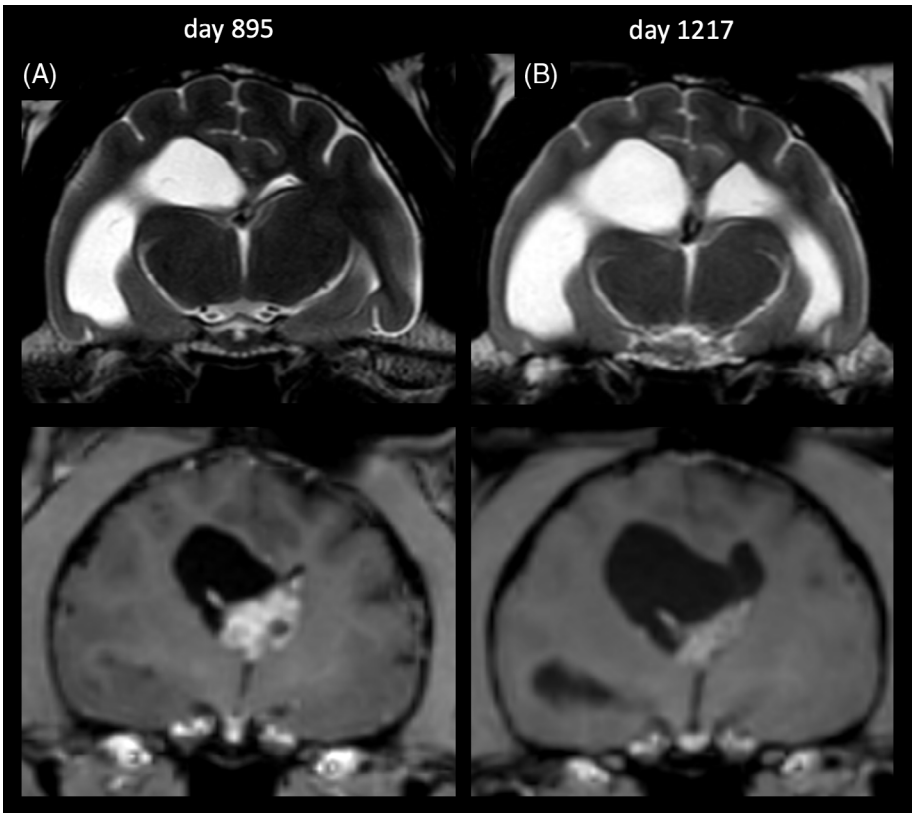

FIGURE 1 Comparison of the MRI of 1 cat 895 (A, C) and 1217 days (B, D) after the first RT. The cat had undergone a second RT 902 days after the first RT and was presented on day 1217 for relapse of neurological signs. Transverse T2 weighted magnetic resonance image at the level of the dorsum sellae (A, B) showing a moderately dilated right ventricle and slit-like left sided ventricle (asterisks) (A), progressing to a severely dilated right and a mildly increased left ventricle (asterisks) (B) indicating shunt failure. The transverse T1 postcontrast at the level of the hypophysis (C, D) show the reduction of the intraventricular mass (white arrows) on day 1217 (D) in comparison to day 895 (C) as result of RT

neurological signs during RT and 2/4 dogs died during RT (described above). Of the 4 animals that survived single-modality RT, 2/4 experienced complete normalization of clinical signs (1 dog at the start of RT, 1 dog 29 days after the start of RT). One cat experienced amelioration of clinical signs, but cranial nerve deficits remained and 1 cat was euthanized 49 days after starting RT. The latter cat experienced neurological worsening during the course of single-modality RT and newly occurring epileptic seizures before its death. Follow-up MRI and VPS placement were declined by the owner.

3.5 | Time to progression and survival

Ten of 12 animals were classified as showing progressive disease either clinically or based on diagnostic imaging. One dog was alive and free of clinical signs of its suspected choroid plexus tumor at the time of data collection 1043 days after VPS surgery and RT (10 × 4 Gy with SIB of 10 × 44.5 Gy to the GTV) and therefore was censored for TTP and survival analysis. One cat was lost to follow-up and therefore censored 423 days after treatment with VPS/RT (10 × 4.2 Gy). Median TTP for all animals was 332 days (95%CI: 19; infinity), 71 days (95%CI: 7; infinity) for animals using single-modality RT and 895 days (95%CI: 704; infinity) using VPS/RT (Figure 3).

Imaging-confirmed progressive disease was diagnosed as follows: local progression was seen in 2/10 and distant progression 2/10 animals (described below). Progressive disease or tumor-related worsening of clinical signs was suspected but not confirmed in 6 animals. Two dogs died during single-modality RT because of suspected internal hydrocephalus with brain herniation (termed progressive disease [tumor-related incident] although MRI showed stable disease in 1/2 dogs). Four of 10 animals showed new or recurrent neurological signs. In 1/4 these were suspected to be caused by VPS failure because the reservoir no longer filled properly (reimaging and possible new VPS placement were declined by the owner), in 2/4 neurologic signs were suspected to be a consequence of internal hydrocephalus rather than progression of the primary tumor, because clear worsening of neurological signs was seen shortly after beginning single-modality RT (7 days) or neurological signs never resolved completely after RT and suddenly worsened (126 days). One dog died 21 days after VPS placement because of possible shunt failure as described above. Because local or distant progressive disease could not be ruled out, those 4 animals were considered progressive in our analysis.

Ten animals died during the study period and in 9/10 animals, death was confirmed or suspected to be tumor-related. Median overall survival of all animals was 427 days (95%CI: 49; infinity). It was 162 days (95%CI: 16; infinity) for animals treated with single-modality RT and 1103 days (95%CI: 752; infinity) for those treated with VPS/RT (Figure 4). Comparison of survival curves between treatment modalities using log-rank test was not possible because of small case numbers and heterogeneous baseline characteristics.

Two animals died during RT because of suspected brain herniation. Two died because of intraventricular metastasis based on

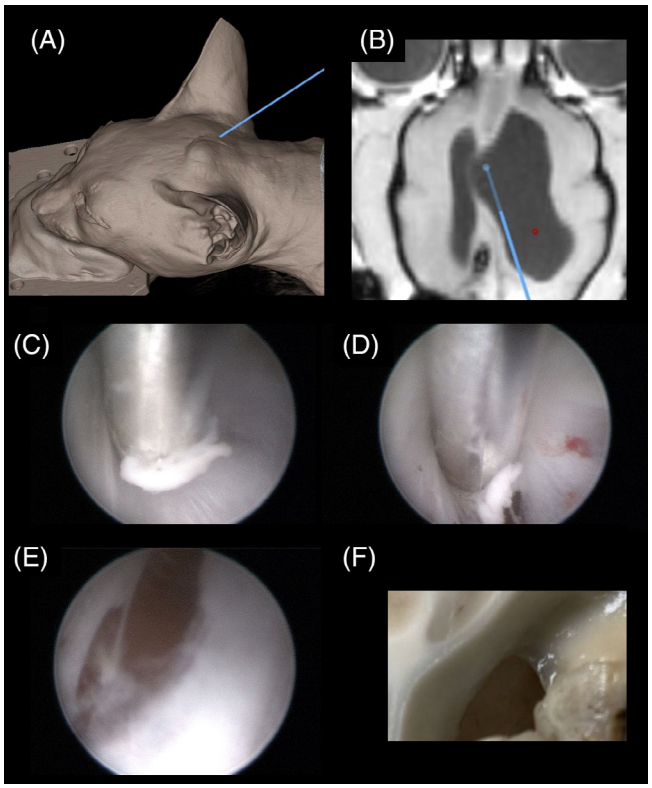

FIGURE 2 Neuronavigation-assisted endoscopic septum pellucidum fenestration. Trajectories of the approach (blue line) can be seen in the 3D view (A) and in the MRI dorsal view (B) generated using the neuronavigation system (StealthStation S8 Surgical Navigation System, Medtronic, Minneapolis). Images C, D and E show the endoscopic view after introduction of the endoscope in the right vertical before (C), during (D) and after (E) fenestration of the septum pellucidum. The last image (F) shows the fenestrated septum pellucidum in a postmortem image of the brain after mid sagittal dissection 182 days after the endoscopic fenestration

follow-up MRI 427 days and 461 days after RT (both treated with single-modality RT with 10 × 4 Gy with SIB as described above), while the primary tumor showed a marked decrease in size. Five of 10 died because of recurrent or progressive neurological signs 28 days (dog treated with 10 × 4 Gy, neurological worsening started 6 days after RT), 49 days (dog treated with RT with 10 × 4 Gy, neurological worsening started during RT), 276 days (cat treated with RT with 10 × 4 Gy, neurological worsening started 126 days after RT), 752 days (cat treated with VPS/RT with 3 × 8 Gy), and 1392 days (cat treated with VPS/RT with 8 × 3 Gy, retreated with 10 × 4 Gy 895 days after the first RT session) after the start of RT. One cat died of heart failure associated with its previously known obstructive hypertrophic cardiomyopathy 1103 days after the end of RT (VPS/RT with 3 × 8 Gy). Necropsy MRI indicated local progressive disease despite the absence of neurological signs.

Of the 4 dogs with increased CSF protein concentration, 1 dog still was alive at the time of data collection 2.6 years after VPS/RT. One dog died 21 days after combined VPS/RT because of suspected VPS complications.

3.6 | Tumor volume evolution

Five dogs and 4 cats underwent follow-up imaging. One dog was excluded from imaging response analysis because tumor size could not be evaluated (no contrast study available), 1 dog because it died during RT (stable tumor volume). Contouring of the tumor on follow-up diagnostic imaging indicated a decrease in primary tumor volume at 1 point in all 7 animals that survived RT (Figure 5). Despite the primary tumor being markedly smaller, 2 dogs (single-modality RT) showed intraventricular metastasis (427 and 461 days post-RT) and therefore overall progressive disease. Two cats experienced local progressive disease. One cat experienced a decrease in tumor size by 44% when reimaged 722 days after VPS/RT (3 × 8 Gy) but local progressive disease (increase of 167%) without neurological signs when reimaged at necropsy after it had died because of heart failure (known obstructive hypertrophic cardiomyopathy) 1103 days after treatment. One cat treated with VPS/RT (3 × 8 Gy) experienced progressive disease of the primary tumor (increase of 213%) 895 days after RT; the cat was retreated with RT (10 × 4 Gy) and tumor size decreased again by 36% at 130 days and by 44% at 297 days after the second RT. Progressive disease was detected 488 days after the second RT course with an increase in tumor volume of 120%.

3.7 | Necropsy

Necropsy was performed in 4 animals. Two dogs (1 with suspected brain herniation and a well differentiated choroid plexus tumor with some atypia and 1 with a choroid plexus papilloma) are described above. Two cats were diagnosed with ependymoma at necropsy. No metastases were found during necropsy.

4 | DISCUSSION

We evaluated a small group of dogs and cats with imaging diagnosis of solitary intraventricular tumor treated using either single-modality RT or VPS/RT. The VPS placement led to rapid amelioration of neurological signs in all animals, and although there was a high complication rate, most were easily managed with revision surgery. No deaths occurred during RT in the group with combined treatment and most animals experienced prolonged survival. In contrast, 2 deaths occurred in the group that received single-modality RT. Imaging follow-up showed a marked decrease in primary tumor volume at some time point in all animals surviving RT.

All animals in our study had neurological signs, most commonly cranial nerve deficits, lethargy, decreased alertness and behavior changes, as previously described.[9,32] However, in 58.3% owners reported episodes of sudden collapse. In 3/4 of dogs, these episodes were associated with physical activity. In 1 dog, the owners reported that it collapsed when it was exited and barking at other dogs. In the other dogs, the type of activity leading to collapse was not specified by owners. In the 3 cats, it was not reported whether the collapsing

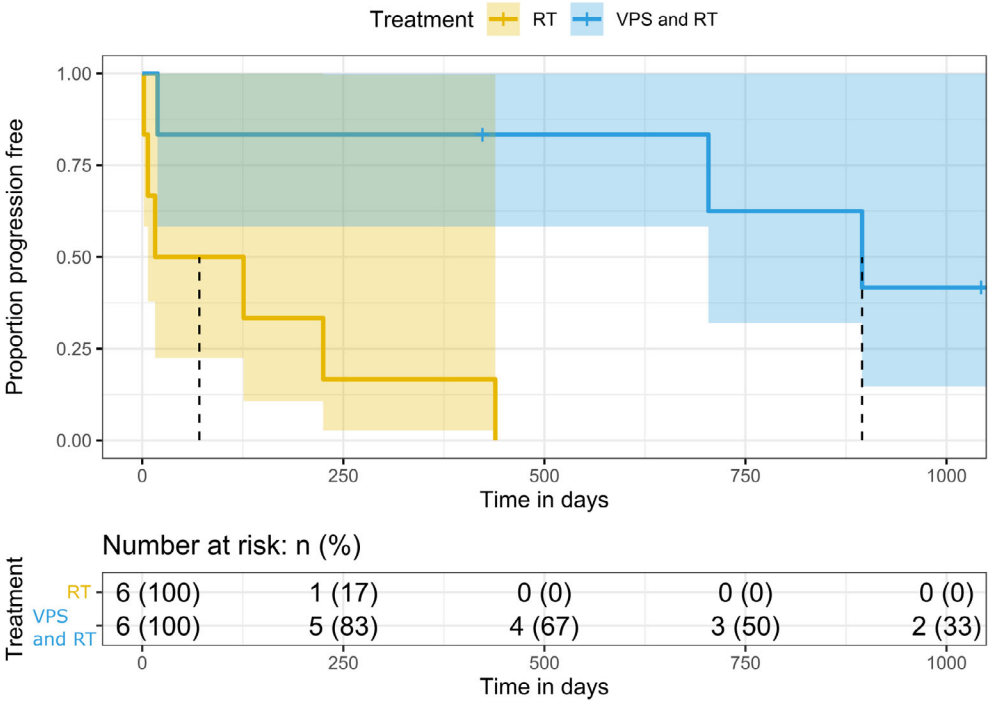

FIGURE 3 Kaplan-Meier time to progression (TTP) curves of cats and dogs split by treatment modality: the yellow line represents single-modality radiation therapy (RT) with median TTP of 16 days (95%CI: 0; 158), the blue line pets treated with ventriculoperitoneal shunt and RT with median TTP of 895 days (95%CI: 496; 1293). Tick marks represent censored cases, the shaded area the CI

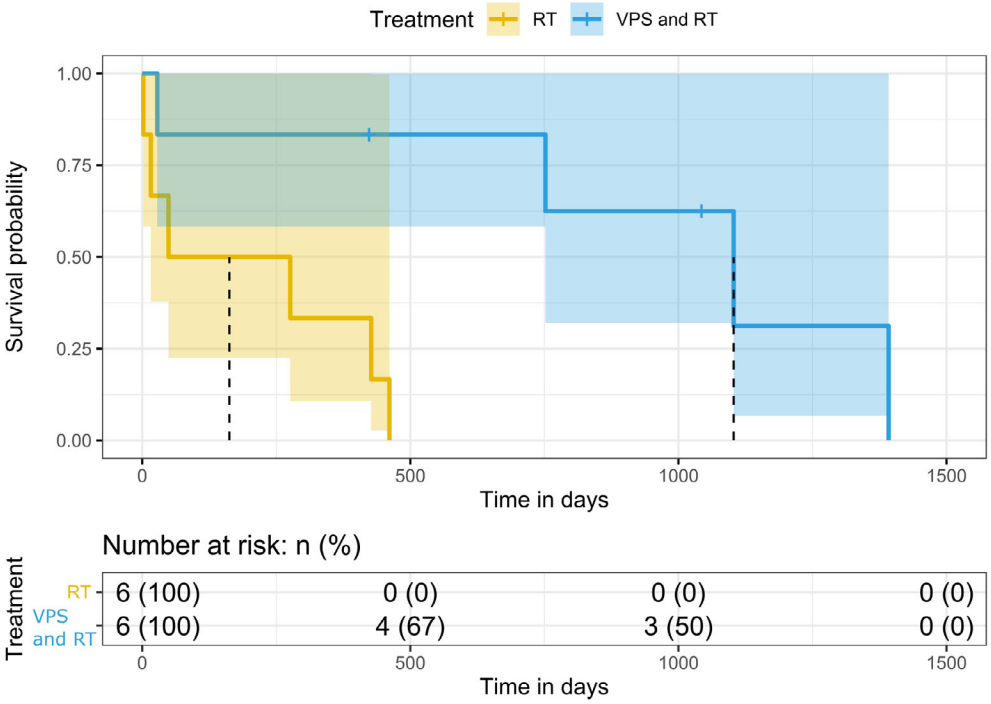

FIGURE 4 Kaplan-Meier survival time (ST) curves of dogs and cats split by treatment modality: the yellow line represents pets treated with single-modality radiation therapy (RT) with median ST of 49 days (95%CI: 0; 361), the blue line the pets treated with ventriculoperitoneal shunt and RT with median ST of 1103 days (95%CI: 562; 1643). Tick marks represent censored cases, the shaded area the CI

episodes were related to physical activity. In none of these patients was a cardiac cause found. Neither electroencephalography nor ECG was performed during these episodes in any patient. None of these animals continued to show these episodes after VPS or RT, suggesting an association with the increased intracranial pressure. In veterinary medicine, episodes of collapse rarely have been reported as a feature of increased intracranial pressure.[33] In human medicine however, syncope was described occasionally with valsalva-type maneuvers in patients with increased intracranial pressure. The proposed mechanism is a temporary impeding of cerebral blood flow by a sudden increase in intracranial pressure.[34,35] The high frequency of episodic collapse in our study and the response to treatment should increase awareness for increased intracranial pressure with valsalva-type maneuvers as a possible cause of syncope in dogs and cats in the absence of cardiovascular disease.

Because of the rarity of intraventricular tumors, optimal treatment and outcome in cats and dogs with intraventricular tumors are not well described. Previously, efforts to gain more insight into this

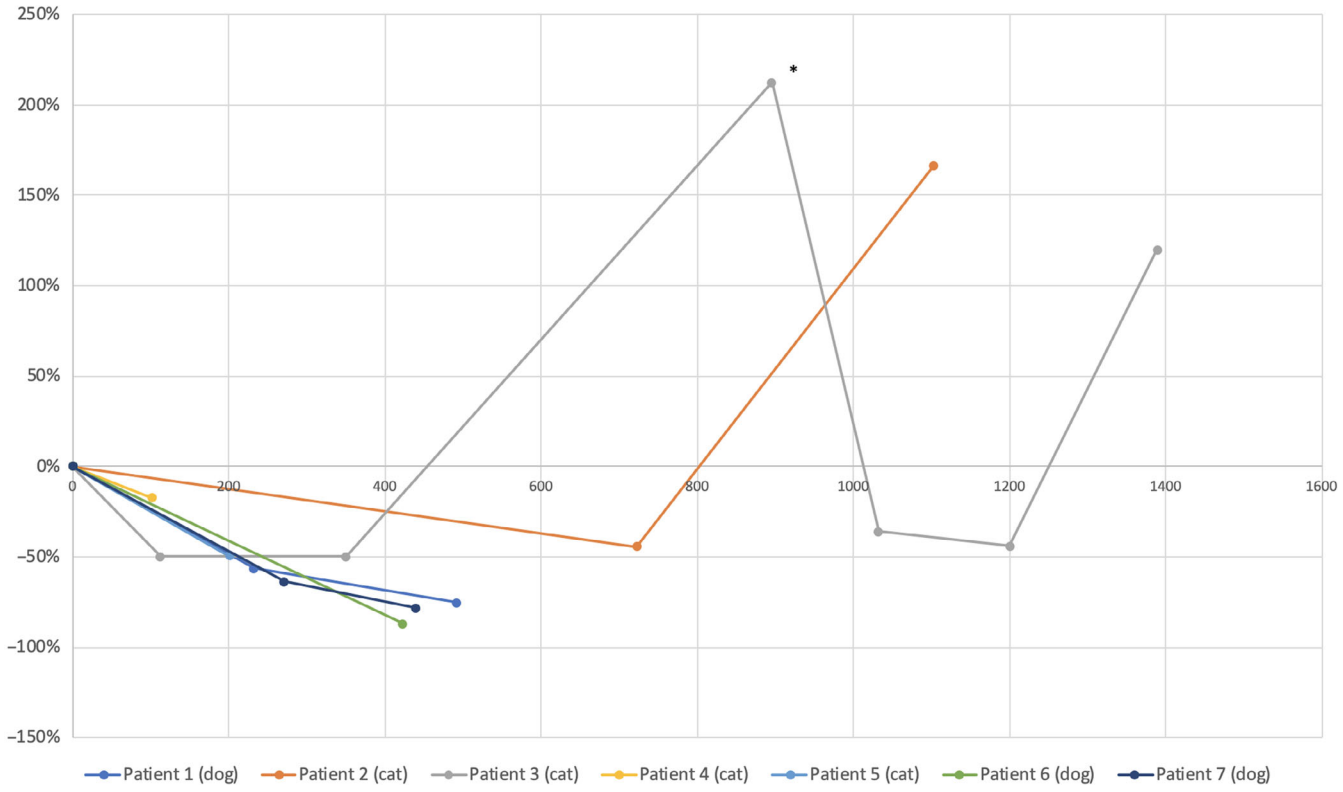

FIGURE 5 Radiation response of presumed primary intraventricular tumors (metastasis not included): Each follow-up computed tomography or MRI dataset was retrospectively imported into the treatment planning system and the new tumor volume was contoured. The y-axis depicts the tumor volume in percentage, the x-axis the time after radiation therapy (RT) in days. Time point and volume zero represents the initial tumor volume at the time of RT. Each dot corresponds to an imaging follow-up time point for an individual pet. Cat number 3 (asterisk) was retreated with RT (10 × 4Gy) 895 days after the initial treatment

rare disease concentrated mainly on MRI characteristics as well as histopathological and immunohistochemical findings.[1,3,32,36] Descriptions of treatment of choroid plexus tumors or ependymomas are scarce. Single cases were treated using surgical removal, VPS or RT in the past.[9,12,15,18] Studies using combined treatment with VPS and definitive-intent RT are lacking. Successful VPS placement previously was documented in 4 dogs with tumors in the third ventricle.[9] Although VPS placement has no effect on the primary tumor itself, it quickly relieves clinical signs associated with hydrocephalus, which have been described in 75% of animals with choroid plexus tumors and were seen in 100% of our patients.[3,9] Although VPS placement led to rapid amelioration of clinical signs in all cases, a high complication rate occurred in our study. The most common complication was shunt disconnection. Although in dogs shunt disconnection seems to be a rare complication affecting only 4% of cases in a systematic review, disconnection was seen in 3/4 cats in our study.[8] In all cases, the shunt was successfully reconnected. Although the cause for this high percentage of disconnection is unknown, it also has been shown that coiling and kinking of the shunts are more common in cats than dogs.[8] We therefore suspected increased mobility of the shunt in the SC tissue of cats as a cause and adjusted the procedure by using tissue glue to secure the shunt connections and avoid further disconnections. The second most common complication in our study was shunt obstruction. Shunt obstruction was proven or suspected in 25% of cases and the rate was higher than in idiopathic hydrocephalus, with obstruction reported in only 10% of dogs and 8% of cats, but lower than in the previously reported case series of palliative shunting in dogs, where shunt obstruction occurred in 2/4 dogs.[8,9] Similar to the aforementioned study, the 2 cases with suspected shunt obstruction died or were euthanized because of related clinical deterioration. Shunt obstruction must be considered an important and possibly life-limiting complication for animals with ventricular neoplasia. Contralateral ventricle enlargement was only diagnosed in 1 of our animals, whereas it was reported in all palliative-shunted dogs in a previous study.[9] The authors of the previous study raised the question of whether 2 VPS catheters should be placed simultaneously in each ventricle routinely.[9] Because we did not diagnose contralateral ventricle enlargement in all animals, we do not recommend simultaneous shunting in all cases. One cat experienced a combination of shunt obstruction and contralateral ventricle enlargement. We decided not to simultaneously place 2 new shunts, but rather tried a different approach. We endoscopically fenestrated the septum pellucidum and created an artificial connection between both ventricles, allowing drainage from both lateral ventricles through a single shunt. Combined endoscopic septum pellucidum fenestration with placement of a single shunt therefore might be a reasonable alternative to simultaneous

shunt placement in cases of bilateral obstruction of the interventricular foramen. One cat experienced severe itching of the head ipsilateral to the shunted ventricle and brain MRI showed a slit-like ipsilateral ventricle. Itching after VPS placement has not been described either in animals or humans in the scientific literature. Only anecdotal reports exist in humans. However, the location of the itching in the absence of dermatological problems suggests a correlation.

Although none of the animals that had VPS surgery died during RT, 2 dogs with single-modality RT died during the course of RT. Brain herniation was not observed at necropsy in those 2 dogs. Nevertheless, it is likely that an acute increase in intracranial pressure with respiratory arrest took place based on previously noted hydrocephalus and characteristic sudden death.[5,37] Although case numbers are too small to compare the 2 treatment groups, the animals treated with VPS seemed to have fewer complications during RT and higher chance of long-term survival.

Two dogs showed a measurable response of the primary tumor to RT but developed multiple intraventricular contrast-enhancing masses consistent with ventricular metastasis. By coincidence, both dogs were in the single-modality RT group, potentially shortening the outcome of this group. Intraventricular or subarachnoid metastasis have been described in the past.[3,38] Although choroid plexus carcinomas were found in 67% of choroid tumors in 1 study and 35% of them already had metastasized, little is known about the actual incidence of choroid plexus carcinomas and their metastatic rate in animals. A necropsy study of primary brain tumors in dogs found 7% of all tumors to be choroid plexus tumors but did not differentiate between papillomas and carcinomas.[1] Without necropsy data, we do not know if carcinomas were evenly distributed between the 2 treatment groups.

Measurable tumor volume reduction after RT was seen in all dogs reimaged at some point during the study. This finding has not yet been described for presumed intraventricular tumors to our knowledge. Our study is a case series and conclusions cannot be drawn from such small case numbers. However, measurable tumor response to RT is crucial in considering this treatment modality. Furthermore, we observed less life-threatening complications and a rapid normalization of neurological signs in dogs that were treated with VPS placement beforehand. Although these are preliminary findings based on few cases, long-term outcome seems to be achievable using combined treatment with VPS placement as a first step (to ameliorate neurological signs rapidly) and RT as second step (to decrease tumor size).

Not all tumor responses were durable however. This observation could have different explanations, such as insufficient radiation dose. It is not possible to draw any conclusion from our small study population, because animals were treated using different protocols, follow-up imaging was only available in 7 animals, and imaging-confirmed primary tumor progression was only documented in 2/7 animals. Those 2 cats showed tumor progression 895 and 1103 days after VPS/RT using 3 × 8 Gy. Although a good outcome, tumor progression still might be a sign of insufficient radiation dose. To compare RT protocols with different total doses and fraction sizes, recalculation into 2 Gy fractions (equivalent dose in 2 Gy fractions, EQD2) is commonly performed. The resulting total dose can be used to quantify anti-tumor effect (calculation with alpha/beta ratio 10) or the risk of late radiation toxicity (alpha/beta ratio 2).[39] The above-mentioned protocol with 3 × 8 Gy has a low total (antitumor) $EQD2_{alpha/beta\ 10}$ of 36 Gy. Finely fractionated, definitive-intent radiation protocols published in dogs are 10 × 4 Gy, 10 × 4 Gy to the target volume with a boost of 10 × 4.45 Gy to the macroscopic tumor, 20 × 2.5 Gy, 15 × 3 Gy or 12 × 4 Gy with a range of $EQD2_{alpha/beta\ 10}$ between 46.67 and 56 Gy.[15,22,40,41]

Our study had some limitations. Tumor diagnosis was based on presumed imaging diagnosis in our study. Necropsy was requested but not routinely performed. Although localization in the region of the choroid plexus or ependyma, marked contrast enhancement, and ventriculomegaly are common signs of choroid plexus tumors or ependymomas, meningiomas or intraventricular gliomas cannot be ruled out.[4,19] Our case numbers were small and we included dogs and cats treated using different modalities and protocols. However, intraventricular tumors are uncommon and several of our findings raise new research questions. Randomized, controlled trials for each species and each histologically confirmed diagnosis are needed to evaluate optimal treatment (benefit of combination therapy) and prognosis. Most likely, only a multi-institutional study could provide additional insight into this very rare disease.

5 | CONCLUSION

Results of our retrospective case series must be interpreted with caution because of small case numbers. Nevertheless, our results indicate that presumed intraventricular tumors (based on imaging) seem to show a measurable response to RT. Because RT alone was associated with potentially fatal outcome and time to visible tumor response can take several months after RT, combined treatment including VPS placement is most likely the preferred treatment option. Although VPS surgery was associated with a high complication rate, complications were most often easily manageable.

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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

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

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

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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