



Canine intracranial gliomas: Relationship between magnetic resonance imaging criteria and tumor type and grade

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ABSTRACT

Limited information is available to assist in the ante-mortem prediction of tumor type and grade for dogs with primary brain tumors. The objective of the current study was to identify magnetic resonance imaging (MRI) criteria related to the histopathological type and grade of gliomas in dogs. A convenience sample utilizing client-owned dogs ($n = 31$) with gliomas was used. Medical records of dogs with intracranial lesions admitted to two veterinary referral hospitals were reviewed and cases with a complete brain MRI and definitive histopathological diagnosis were retrieved for analysis. Each MRI was independently interpreted by five investigators who were provided with standardized grading instructions and remained blinded to the histopathological diagnosis.

Mild to no contrast enhancement, an absence of cystic structures (single or multiple), and a tumor location other than the thalamo-capsular region were independently associated with grade II tumors compared to higher grade tumors. In comparison to oligodendrogliomas, astrocytomas were independently associated with the presence of moderate to extensive peri-tumoral edema, a lack of ventricular distortion, and an isointense or hyper-intense T1W-signal. When clinical and MRI features indicate that a glioma is most likely, certain MRI criteria can be used to inform the level of suspicion for low tumor grade, particularly poor contrast enhancement. Information obtained from the MRI of such dogs can also assist in predicting an astrocytoma or an oligodendroglioma, but no single imaging characteristic allows for a particular tumor type to be ruled out.

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Introduction

The magnetic resonance imaging (MRI) features of gliomas and other intra-axial primary brain tumors in dogs have been described (Kraft et al., 1990, 1997; Lipsitz et al., 2003; Snyder et al., 2006; Cervera et al., 2011; Ródenas et al., 2011; Wolff et al., 2012), but only recently have associations between the MRI appearance and the tumor type or the tumor grade been studied (Young et al., 2011). Typical canine intracranial gliomas are intra-axial, T1W-iso- to hypo-intense, T2W-iso- to hyper-intense mass lesions with varying perilesional edema and contrast enhancement (Kraft et al., 1997; Snyder et al., 2006; Ródenas et al., 2011; Young et al., 2011).

Some MRI features have been related to type and grade of canine glioma. The presence of contrast enhancement was significantly associated with tumor grade (Young et al., 2011). Cysts and areas of necrosis have not been significantly related to grade, but are common in higher grade tumors (Lipsitz et al., 2003; Young et al., 2011). Differentiation between areas of necrosis, and single and multiple cystic structures has not been previously studied in glioma in dogs; however, a technique for describing either a single cyst or at least one intra-tumoral accumulation of fluid (ITF) has been reported for meningioma (Sturges et al., 2008). Regarding tumor type, surface contact was reported to be significantly more common with oligodendrogliomas (Young et al., 2011), but distortion of ventricles has not yet been reported to be significantly more common (Kraft et al., 1997; Ródenas et al., 2011; Young et al., 2011).

For glioma in humans, various MRI features can be used to predict tumor type and grade (Dean et al., 1990; Watanabe et al., 1992; Provenzale et al., 2006; Jenkinson et al., 2007). Accordingly,

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using MRI to predict the type and grade of canine tumors may be possible. As surgery is expensive and invasive, and canine gliomas are routinely treated with modalities such as radiation therapy without histopathological confirmation (Brearley et al., 1999; Bley et al., 2005), information that can be used to better predict tumor type and grade could be useful. Canine gliomas are not routinely managed based on a division between low grade glioma (grades I and II) and high grade gliomas (grades III and IV), although this is standard in human medicine (Dean et al., 1990; Watanabe et al., 1992; Cavaliere et al., 2005). Higher grade tumors can be suspected based on imaging characteristics such as irregular or ring-like contrast enhancement or signal intensity in humans, and this can be used to guide therapy (Watanabe et al., 1992; Forbes et al., 2011; Rao et al., 2013).

Based primarily on a review of the MRI literature relating to canine gliomas (Kraft et al., 1990, 1997; Lipsitz et al., 2003; Polizopoulou et al., 2004; Snyder et al., 2006; Sturges et al., 2008; Cervera et al., 2011) and a pilot study (Bentley et al., 2010), and secondarily to studies of human gliomas (Dean et al., 1990; Provenzale et al., 2006; Jenkinson et al., 2007), we hypothesized that increasing tumor grade is related to increasing degree of contrast enhancement, the formation of single cysts or multiple ITFs, and T2*-weighted gradient echo (GRE) signal voids. Regarding tumor type, we hypothesized that ventricular distortion is more common with oligodendrogliomas than astrocytomas.

Materials and methods

Animals and tumors

The medical records of dogs admitted to two veterinary teaching hospitals (Purdue University, University of Minnesota) between 30 July 2007 and 10 October 2010 were reviewed and cases for which histology confirmed intracranial structural lesions, and for which a complete MRI of the brain was performed before histological diagnosis, were retained for analysis. Only dogs with a histopathological diagnosis of glioma were included as cases. The MRIs of 25 dogs with structural intracranial lesions other than gliomas were also retained as distractors. These were provided to the investigators reading the MRIs mixed with the MRIs of gliomas in a blinded fashion; the results were not used in the statistical analyses.

One veterinary pathologist (GOS, MAM) at each institution provided a histological diagnosis using previously described criteria (Koestner et al., 1999; Louis et al., 2007). Hematoxylin and eosin (H&E)-stained sections and glial fibrillary acidic protein (GFAP) immunohistochemistry were available for all cases. Grading was performed according to the 2007 WHO classification of human tumors (Louis et al., 2007) and a numerical grade was then applied to each tumor as described for canine gliomas (Young et al., 2011).

Evaluation of magnetic resonance imaging

The MRIs were independently evaluated by five investigators, including Board-certified radiologists (CPO, KLA, DAF, JFN) and a Board-certified neurologist (RTB). Each investigator was masked to the histopathological diagnosis and provided standardized grading instructions. The MRIs were graded on 18 criteria similar to those used in previous studies (Kraft et al., 1997; Lipsitz et al., 2003; Snyder et al., 2006; Ródenas et al., 2011) and further developed in our pilot study (Bentley et al., 2010). For 17 criteria, investigators chose one option from a list of 2–5 options (Table 1). Investigators were instructed to provide a free-response description of the anatomic location of the tumor for the final criterion. Following data collection, tumors were grouped into four locations; Location 1 (frontal or fronto-olfactory); Location 2 (parietal lobe or adjacent corpus callosum, temporal lobe); Location 3 (diencephalic or any portion of the internal capsule); and Location 4 (caudal fossa). Both cortical lesions and subcortical lesions were included within the frontal, parietal and temporal classifications (Locations 1 or 2), respectively. Tumors were ascribed to multiple locations as appropriate.

Specific instructions were supplied to the investigators for some MRI criteria. If margins were indistinct, they were considered poorly defined; clear tumor margins were divided into smooth and irregular margins. For mass effect, all features were considered, including ventricular distortion and brain herniations. Both T1W- and T2W-intensities were considered with respect to normal grey matter and the signal from the largest fraction of the tumor was recorded. For T1W- and T2W-homogeneity, tumors were only considered homogenous if nearly all the tumor displayed matching signal intensity. Peri-tumoral edema restricted to one brain division was given an objective grade, while edema of an entire cerebral hemisphere or of

multiple brain divisions was graded as extensive. For contrast enhancement severity, only the most severely enhancing portion of the tumor was considered. For brain herniations, the most severe herniation present was selected.

Statistical analysis

Inter-observer agreement for each MRI criterion was assessed by calculating the value for linearly weighted kappa (κ) for each pair of investigators, providing a total of 10 κ values for each criterion (PROC FREQ, SAS 9.2, SAS Institute). The overall level of agreement for each criterion was summarized by the median kappa value for the 10 investigator pairs; values of 0.81–1.00 were considered to indicate excellent agreement; 0.61–0.80, good agreement; 0.41–0.60, moderate agreement; 0.21–0.40, fair agreement; 0.01–0.20, poor agreement, and 0.00, chance agreement (Landis and Koch, 1977), as previously applied to canine brain MRI studies (Wolff et al., 2012).

Statistical analysis of the relationship between the MRI criteria and the tumor type and grade was performed in two stages, a preliminary univariate analysis and a final multivariate analysis. For the preliminary univariate analysis, contingency tables were developed. Grade II tumors were compared to grade III and IV tumors for consistency with prior studies (Young et al., 2011), thus dividing the cases into low-grade and high-grade glioma as in studies of human tumors (Rao et al., 2013). Separately, astrocytomas were compared to oligodendrogliomas. Each contingency table was analyzed using a Fisher's exact test (PROC FREQ, SAS 9.2, SAS Institute) and $P < 0.01$ was considered significant, because of the high number of putative variables examined. Patterns of contrast enhancement were further investigated post hoc by determining associations with no contrast enhancement and with partial or complete ring enhancement.

For multivariate analysis, forward stepwise logistic regression (PROC LOGIST, SAS 9.2, SAS Institute) was used. Again, grade II tumors were compared to grades III and IV and astrocytomas were compared to oligodendrogliomas. A P value to enter of <0.20 and to remain of <0.05 was used. Investigators were entered as dummy variables and the final logistic regression model fit was evaluated using the Hosmer–Lemeshow goodness-of-fit test.

Results

Cases

Thirty-one cases of glioma were evaluated, providing 155 MRI interpretations by five investigators. The five investigators additionally evaluated the MRIs of 25 distractors which were not included in the statistical analysis. The 31 cases included 17 astrocytomas and 14 oligodendrogliomas, composed of grade II to IV tumors (Table 2). One brainstem oligodendroglioma exhibited diffuse infiltration of neoplastic GFAP negative glial cells in the prosencephalon, consistent with gliomatosis cerebri. Fifteen astrocytomas and 10 oligodendrogliomas were diagnosed by surgical biopsy. The histopathologically-confirmed distractors not used in statistical analysis were meningiomas ($n = 11$), other extra-axial tumors ($n = 4$), meningoencephalitis ($n = 5$), primitive neuroectodermal tumors (PNET; $n = 3$), benign intraparenchymal hemorrhage ($n = 1$) and radiation therapy-induced necrosis following treatment of a nasal tumor ($n = 1$).

Magnetic resonance imaging

Time between MRI and histological diagnosis was variable but was <47 days, except for one case that underwent surgery 140 days after MRI. Some MRI studies were performed at other institutions leading to variability in MRI sequences. Images were acquired in transverse, sagittal and dorsal planes. Field strength for both cases and distractors was 0.2–0.5 T ($n = 3$), 1.0 T ($n = 13$), 1.5 T ($n = 29$) or 3.0 T ($n = 11$); all studies included pre-contrast T1W, T2W and post-contrast T1W images. The intravenous gadolinium-based contrast agent administered varied according to institution, but was either 0.11 mL/kg of gadodiamide (Omniscan, 287 mg/mL, GE Healthcare) or 0.2 mL/kg of gadopentetate dimeglumine (Magnevist, 469 mg/mL, Bayer Healthcare Pharmaceuticals) for most cases. T2-weighted Fluid Attenuation Inversion Recovery (FLAIR) images were acquired on 30/31 cases and T2*-weighted GRE images were attained on 24.

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