INVITED REVIEW—NEUROIMAGING RESPONSE ASSESSMENT CRITERIA FOR BRAIN TUMORS IN VETERINARY PATIENTS

JOHN H. ROSSMEISL, JR., PAULO A. GARCIA, GREGORY B. DANIEL, JOHN DANIEL BOURLAND, WALDEMAR DEBINSKI, NIKOLAOS DERVISIS, SHAWNA KLAHN

The evaluation of therapeutic response using cross-sectional imaging techniques, particularly gadolinium-enhanced MRI, is an integral part of the clinical management of brain tumors in veterinary patients. Spontaneous canine brain tumors are increasingly recognized and utilized as a translational model for the study of human brain tumors. However, no standardized neuroimaging response assessment criteria have been formulated for use in veterinary clinical trials. Previous studies have found that the pathophysiologic features inherent to brain tumors and the surrounding brain complicate the use of the response evaluation criteria in solid tumors (RECIST) assessment system. Objectives of this review are to describe strengths and limitations of published imaging-based brain tumor response criteria and propose a system for use in veterinary patients. The widely used human Macdonald and response assessment in neuro-oncology (RANO) criteria are reviewed and described as to how they can be applied to veterinary brain tumors. Discussion points will include current challenges associated with the interpretation of brain tumor therapeutic responses such as imaging pseudophenomena and treatment-induced necrosis, and how advancements in perfusion imaging, positron emission tomography, and magnetic resonance spectroscopy have shown promise in differentiating tumor progression from therapy-induced changes. Finally, although objective endpoints such as MR imaging and survival estimates will likely continue to comprise the foundations for outcome measures in veterinary brain tumor clinical trials, we propose that in order to provide a more relevant therapeutic response metric for veterinary patients, composite response systems should be formulated and validated that combine imaging and clinical assessment criteria.

Key words: brain tumor, MRI, neurology, oncology.

Introduction

CROSS-SECTIONAL IMAGING TECHNIQUES such as CT and magnetic resonance (MR) imaging are invaluable tools in neuro-oncology. In both veterinary and human medical practice, MR is the modality of choice for the presumptive antemortem diagnosis, morphologic characterization, and therapeutic response assessment of diseases of the brain, including brain tumors.[1–5] However, CT remains widely used for stereotactic biopsy procedures, image-guided interventional techniques, radiotherapeutic planning, and emergency evaluation of clinically unstable patients with intracranial disease.[5–7]

In recent years, the translational research potential of spontaneous canine brain tumors has been recognized in the comparative neuro-oncology community.[8] It has been shown that canine and human intracranial tumors share many similar clinicopathologic, diagnostic imaging, molecular, and cytogenetic features.[2,3,9–12] Additionally, the anatomy and physiology of the dog brain allow for development, testing, and translation of biomedical technologies and devices without the need for extensive engineering or manufacturing modifications prior to human applications.[12] As a result, the relationship between veterinary and human neuro-oncology is mutually beneficial, with spontaneous canine brain tumors an increasingly exploited preclinical model for evaluation of novel brain tumor therapies, and the continued off-label use of efficacious human therapies in veterinary patients with brain tumors.[12–14]

Assessment of therapeutic response in neuro-oncology presents unique and evolving challenges. Since the

From the Department of Small Animal Clinical Sciences (Rossmeisl, Daniel, Dervisis, and Klahn), Virginia-Maryland Regional College of Veterinary Medicine,VA 24061; Biomechanical Systems and Veterinary and Comparative Neuro-oncology Laboratories (Rossmeisl, Garcia), Department of Biomedical Engineering, Virginia Tech-Wake Forest University School of Biomedical Engineering and Sciences, VA 24061; Department of Radiation Oncology (Bourland), Brain Tumor Center of Excellence, Thomas K. Hearn Brain Tumor Research Center, Department of Neurosurgery, Radiation Oncology and Cancer Biology (Debinski), Wake Forest School of Medicine Medical Center Blvd., Winston-Salem, NC 27157.

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Address correspondence and reprint requests to Dr. John Rossmeisl at the above address. E-mail: jrossmei@vt.edu

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incorporation of superconducting magnets and gadolinium-enhanced MR imaging in the early 1980s in human neuro-oncology, there has been an extensive body of literature demonstrating the advantages of MR for the assessment of therapeutic responses in brain tumor patients.[4,5,15–20,22–29] MR is noninvasive, widely available, and can provide objective and quantitative outcome measures. Magnetic resonance-based therapeutic response criteria, along with clinical evaluations, have become crucial in human and veterinary neuro-oncology, especially in Phase II studies. Currently, imaging-based response assessments are considered as acceptable surrogates of therapeutic effect.[12,15–20,30] However, despite the widespread use of imaging-based response assessments in human neuro-oncology and in clinical and research studies of canine brain tumors,[1,2,12,21] the authors are unaware of any veterinary reports evaluating quantitative measures of tumor burden in serial imaging studies or describing methods in sufficient detail that would allow for accurate reproduction of results or standardization of imaging-based response assessments. Additionally, numerous challenges have been and continue to be identified that preclude the ability of MR to replace histopathological examination as a definitive means of phenotypic characterization of brain lesions.[2,3,17,24] Thus, brain biopsy remains fundamental for brain tumor diagnosis, and may be required in parallel with neuroimaging to confirm therapeutic responses or tumor progression.[17]

The diagnostic challenges associated with brain tumors are becoming increasingly recognized in veterinary practice.[2,3,7] Imaging-based response assessment has important implications for the management of brain tumors in daily practice and the promotion of evidence-based medicine by incorporation of optimum protocols in clinical trial design. Veterinary radiologists, neurologists, oncologists, and researchers need to be aware of the approaches used for, and spectrum of issues associated with, imaging-derived response assessments for brain tumors.

Here we review and illustrate the techniques, advantages, and challenges associated with published imaging-based brain tumor therapeutic response criteria using veterinary case examples with histopathologically confirmed intracranial tumors, discuss the potential applications of functional neuroimaging for the characterization of brain tumor therapeutic responses, and propose a systematic approach for the evaluation of veterinary brain tumors.

Imaging-based Response Assessment Criteria in Human Neuro-oncology

There are two fundamental methodologies for objective evaluation of tumor responses from serial imaging studies: one-dimensional diameter-based measurements and volumetric methods. To date, the most widely used response systems in human neuro-oncology are the Macdonald criteria, response evaluation criteria in solid tumors (RECIST), and response assessment in neuro-oncology (RANO) criteria, which use diameter-based measurements.[15,17,25–27] However, volumetric techniques offer distinct benefits over diameter-based methods, can be performed using commercial image-analysis software platforms, and are becoming increasingly advocated for use in clinical trials.[27] Although the majority of literature devoted to imaging-based therapeutic response assessments in humans has been focused on and validated in high-grade gliomas, the criteria described below can be described to other solid brain tumors.

The Macdonald and World Health Organization (WHO) Criteria

Both methodologies utilize a dimensional method of tumor measurement, the product of perpendicular (orthogonal) diameters, obtained from a single, postcontrast axial image representing the largest area of the tumor. The Macdonald system was developed in 1990 and originally described for use with CT images, but has been widely adopted for use with the contrast-enhancing lesion burden on both CT and MR images.[15–18] For multiple target lesions, the product measurements (sum products of diameters; SPD) from each lesion are summed (Fig. 1, Table 1). The Macdonald criteria do not address assessment of cystic or necrotic regions of contrast-enhancing lesions, and do not evaluate the nonenhancing lesion burden (Fig. 2).[15] The major difference between the WHO and Macdonald criteria is that the Macdonald criteria also incorporate assessment of clinical data and corticosteroid requirements into evaluation of therapeutic response.

Response Evaluation Criteria in Solid Tumors Criteria

The response evaluation criteria in solid tumors criteria were originally published in 2000 and subsequently updated in 2009 (RECIST 1.1) for global use in clinical oncology to replace the WHO scheme described in 1981.[25,26,28] The response evaluation criteria in solid tumors criteria were developed to allow for a simplified, standardized assessment of solid cancers. They conservatively classify therapeutic responses in brain tumors based on a one-dimensional tumor measurement, the longest diameter across a contrast-enhancing lesion in an axial plane. In cases where multiple lesions are present, a sum of the longest diameters of up to two measurable lesions is obtained (Fig. 1, Table 1).[27]

The response evaluation criteria in solid tumors criteria have been used in human and veterinary clinical trials studying systemic solid tumors.[26,27,29,30] However, there has not been widespread use of RECIST in brain tumor trials, partially due to the description and historical use

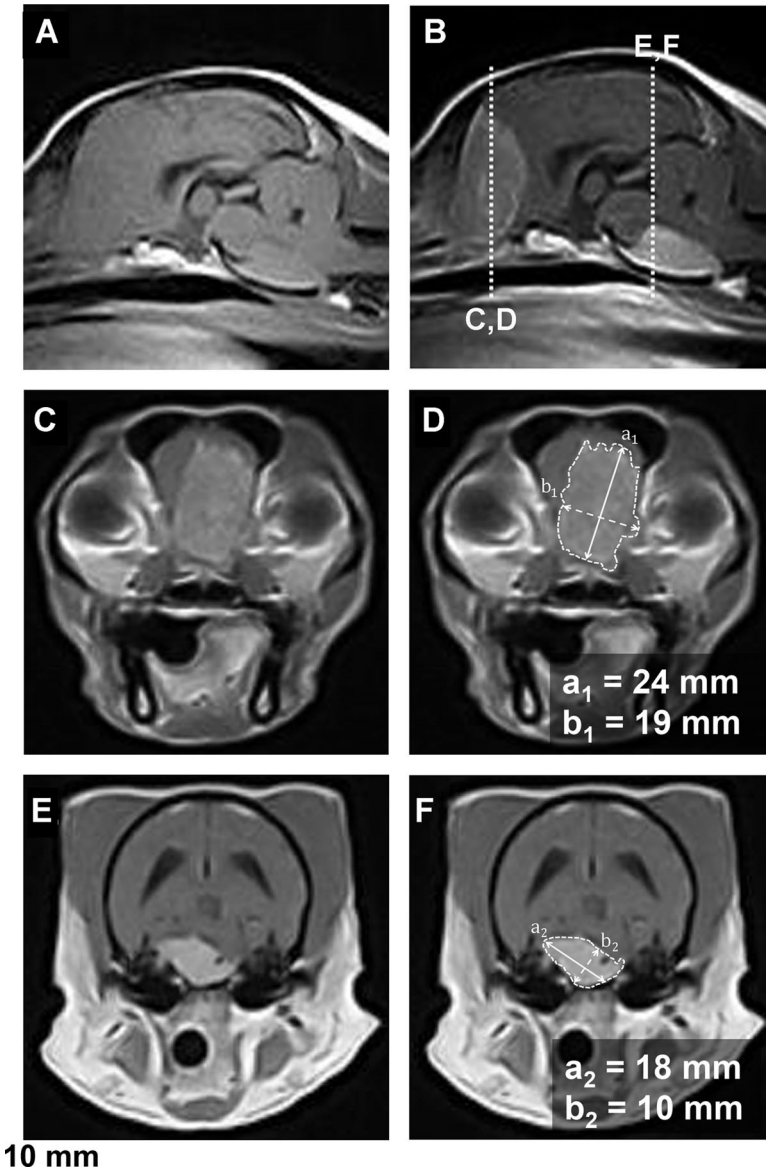

FIG. 1. Target lesion measurement using dimensional criteria in a dog with multiple Grade I meningiomas that are isointense to mildly hyperintense to the brain on the sagittal T1-weighted image (A). Both lesions are of sufficient size and demonstrate uniform enhancement on sagittal (B) and transverse (C–F) postcontrast T1-weighted images to allow for ready assessment with response evaluation criteria in solid tumors (RECIST), Macdonald, response assessment in neuro-oncology (RANO), or volumetric criteria. Using RECIST criteria, the sum of longest diameters (SLD) is represented by 24 mm (a_1) + 18 mm (a_2) = 42 mm. In both the Macdonald and RANO systems, the sum products of diameters is determined by 24 mm (a_1) × 19 mm (b_1) + 18 mm (a_2) × 10 mm (b_2) = 636 mm^2.

of the Macdonald criteria prior to the introduction of RECIST.[15,25] The technical implementation of RECIST is also confounded by many pathophysiologic features common to human and veterinary brain tumors, such as cysts, necrotic foci, and leptomeningeal lesions, all of which are considered unmeasurable.[2,3,16,17,25,31] However, the RECIST system offers the advantage of the use of a single diametric measurement that can be performed easily and rapidly, and has performed comparably to other two-dimensional and volumetric systems in brain tumor studies.[32,33]

Response Assessment in Neuro-oncology Criteria

The response assessment in neuro-oncology criteria was presented in 2010 as a continually evolving development. They were designed to address specific shortcomings of RECIST or Macdonald criteria in MR-based imaging assessment of high-grade gliomas.[17,26,27] The response assessment in neuro-oncology system relies on two-dimensional diameter-based measurement of contrast-enhancing lesions (sum products of diameters), but specifically excludes incorporation of cystic or necrotic portions of

contrast-enhancing lesions into measured target lesions. The response assessment in neuro-oncology criteria indicate that contrast-enhancing lesions should only be measured in instances where a discrete, nodular portion $\geq$ 10 mm in diameter can be isolated and measured without encroachment upon any cystic or necrotic areas.[27] Approaches for defining target and nontarget lesions, and measurement of target lesions using the RANO criteria are presented in Figs. 1–3.

The response assessment in neuro-oncology criteria attempts to account for the presence of and changes associated with the nonenhancing lesion burden. Nonenhancing lesions visible on T2 and/or fluid-attenuated inversion recovery sequences can be seen in a significant proportion of low-grade gliomas and some anaplastic astrocytomas.[2,3,17,27] As T2 and fluid-attenuated inversion recovery lesions are difficult to measure and nonenhancing tumor cannot be differentiated from other comorbid pathologies that are T2 or fluid-attenuated inversion recovery hyperintense, the current RANO criteria consider T2 and fluid-attenuated inversion recovery abnormalities to be nontarget lesions (Fig. 3, Table 1) that are qualitatively evaluated.[17,27] However, qualitative assessment of T2 and fluid-attenuated inversion recovery (FLAIR) abnormalities is important when assigning therapeutic responses, as interpretation of the nontarget lesion burden in parallel with target lesions will often result in reduction of response rates and progression-free survivals in clinical trials.[18–20,27]

Volumetric Methods

Several methods of volumetric tumor measurement have been described in the human and veterinary brain tumor literature.[2,12,13,21,24,32–36] Some protocols describe manual measurements using hand-drawn regions of interest from postcontrast T1-weighted, T2-weighted, or postcontrast CT images. Others have calculated volumes obtained from three-dimensional diameter measurements or extrapolated a volume from single diameter, which assumes that the tumor is represented by a sphere ($V = 4/3\pi r^3$; Table 1).[2,12,21,32] Variably automated, computer-assisted tumor segmentation algorithms have also been described. Volumetric or perimeter-based analyses can be performed on image stacks using combinations of morphologic filtering and intensity thresholding. Fully automated software platforms further facilitate volumetric analyses through coregistration and fusion of pre- and postcontrast image sequences with statistical normalization of the intensity of enhancement using anatomic fiducials.[35] The generation of accurate coregistered images can be challenging and is subject to variability and error due to system- and patient-inherent distortions, as well as differing scan protocols and patient positioning techniques between modalities.

Computer-assisted approaches have distinct benefits. They allow for calculation of total tumor volumes, as well as independent, quantitative assessments of contrast-enhancing, and nonenhancing lesion burdens. As a result, volumetric approaches can be applied in instances of tumors whose shape, margin delineation, or extent and degree of contrast-enhancement precludes or complicates the use of RECIST, Macdonald, or RANO criteria (Fig. 4).[15,26,27] Although volumetric techniques have shown promise for use in neuro-oncology, there are insufficient data to recommend replacement of dimensional assessment methods.[27] A definite advantage of volumetric methods is the quantitative assessment of target volume statistics, such as the dose–volume histogram, before and after intervention, which cannot be performed without three-dimensional segmentation of the target volume.

Categorical Definitions of Therapeutic Responses

The response evaluation criteria in solid tumors, Macdonald, and RANO systems assign therapeutic response into four basic categories: complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), although these systems each have their own definitions for the possible categorical responses (Table 1)[4,5,15–20,26,27] Ultimately, criteria used to determine these categorical assignments may also vary depending on the tumor type being treated, as well as the endpoints used in the clinical trial. The response evaluation criteria in solid tumors system does not incorporate clinical information into categorical assignment of tumor response (Table 1). The Macdonald and RANO systems combine clinical data, namely the patient's neurological status trend and corticosteroid requirement, with imaging findings when defining therapeutic responses (Table 1), as it has been previously demonstrated that corticosteroid therapy can diminish tumor enhancement.[37,38]

Specifically related to imaging of contrast-enhancing tumors, a complete response is defined as the disappearance of all measurable and nonmeasurable contrast enhancing tumor (Fig. 5), regardless of the system used.[15,25–27] A partial response results when a predetermined decrease in the contrast-enhancing lesion burden is seen on follow-up imaging when compared to baseline (Fig. 6). The response assessment in neuro-oncology system also requires that any T2/fluid-attenuated inversion recovery abnormalities remain stable or improve, and no new lesions develop to attain complete or partial responses.[17,27] Stable disease includes imaging changes that do not meet specified criteria for complete response, partial response, or progressive disease, and is also termed noncomplete response/nonprogressive disease in RECIST 1.1 system (Fig. 7).[15,25–27] Patients with nonmeasurable contrast-enhancing or nonenhancing (nontarget lesion) brain

TABLE 1. Comparison of Published and Response Criteria Used in Neuro-oncology

	RECIST[25,26] (1D)	Macdonald and WHO[15] (2D)	RANO[17,27†] (2D)	Volumetric Extrapolated[18]	
Complete response*	Elimination of all enhancing tumor	Elimination of all enhancing tumor	Elimination of all enhancing tumor; Stable or decreased T2/FLAIR lesion burden; No new lesions	Elimination of all enhancing tumor	Imaging
	NA	Stable or improved clinical status; Patient not receiving steroids	Stable or improved clinical status; Patient not receiving steroids; All of the above required for complete response	Stable or improved clinical status; Patient not receiving steroids	Clinical
Partial response*	≥30% decrease in sum of SLD	≥50% decrease in enhancing tumor SPD	≥50% decrease in enhancing tumor SPD; Stable or decreased T2/FLAIR lesion burden; No new lesions	≥65% decrease in enhancing volume	Imaging
	NA	Stable or decreased steroid dose; Stable or improved clinical status	Stable or decreased steroid dose; Stable or improved clinical status; All of the above required for partial response	Stable or decreased steroid dose; Stable or improved clinical status	Clinical
Stable disease	All other findings	All other findings	<50% decrease or <25% increase in enhancing tumor SPD; Stable or decreased T2/FLAIR lesion burden; No new lesions	All other findings	Imaging
	NA	Stable or decreased steroid dose; Stable or improved clinical status	Stable or decreased steroid dose; Stable or improved clinical status; All of the above required for stable disease	Stable or decreased steroid dose; Stable or improved clinical status	Clinical
Progressive disease	> 20% increase in sum of SLD	≥25% increase in enhancing tumor SPD	≥25% increase in enhancing tumor SPD Increase in T2/FLAIR tumor burden; New lesion(s) present	≥40% increase in enhancing volume	Imaging
	NA	Clinical deterioration	Clinical deterioration; Any of the above qualify for progressive disease	Clinical deterioration	Clinical

NA, not applicable; FLAIR, fluid-attenuated inversion recovery; SLD, sum longest diameter; the single longest diameter of the lesion or sum of the longest diameters for multiple lesions; SPD, Sum of products of diameters; the product of orthogonal diameters on postcontrast image section with largest tumor area or the sum of products if multiple lesions present.

*Assignment of complete response or partial response ideally confirmed with serial imaging studies performed at least 4 weeks apart; if not confirmed with repeat imaging, an assignment of stable disease is given.

†The same criteria are employed in the proposed response assessment in veterinary neuro-oncology (RAVNO) system.

tumors can only be qualitatively assessed. Thus nonenhancing or nonmeasurable tumor burdens cannot be assigned a categorical response of complete response or partial response using existing RANO criteria.[27] Progressive disease is assigned when a specified fractional increase in the contrast-enhancing lesion burden is observed when compared to the lesion burden nadir, there is unequivocal progression of the target lesion (Fig. 8), or when an unequivocal new lesion is identified.[15,17,27] Definitions for new lesions are typically defined on a per-protocol basis. It should be noted that in the absence of corroborating imaging or clinical evidence, an increased corticosteroid requirement does not constitute grounds for assignment of progressive disease.[15,17,27] In human neuro-oncology, for response criteria assignments of complete response, partial response, and progressive disease, confirmation with repeated imaging studies at least 4 weeks later is recommended, especially in clinical trials with imaging-defined endpoints.[15–20,27]

Defining the Tumor Burden—Technical Considerations

The primary technical areas that need to be considered when defining the tumor burden include standardization of image acquisition and selection of appropriate regions of interest for lesion measurement. As veterinary medical practice is confounded by both inherent (wide variability in anatomical conformation) and acquired (routine use of low- and high-field magnets) inconsistencies, only general recommendations regarding image acquisition are made in this review.[39] The fundamental aspects of image acquisition that should be consistent for serial patient examinations include image modality, magnetic field strength,

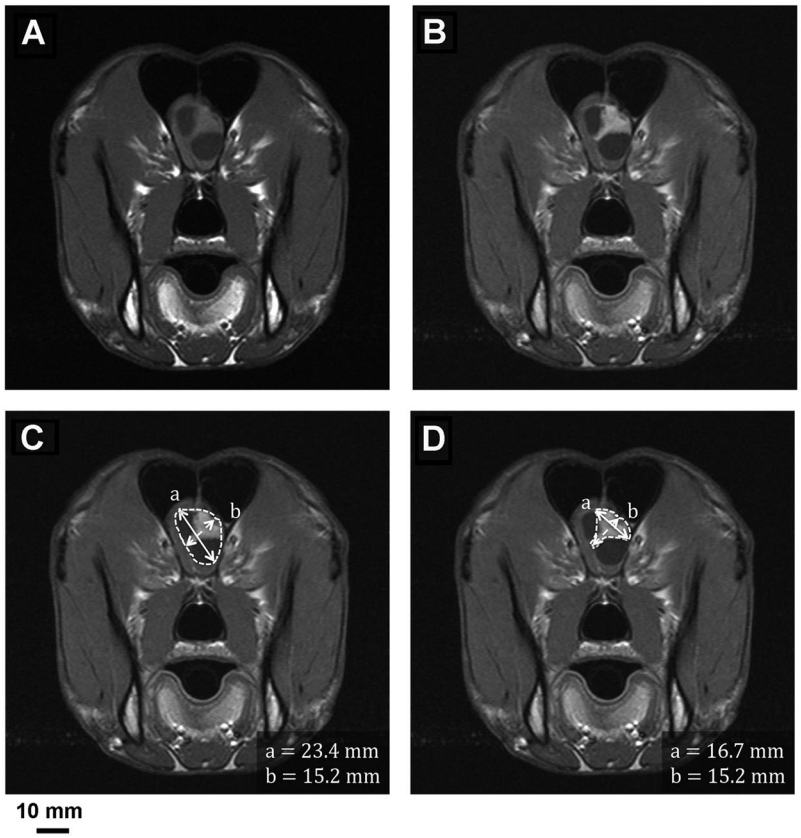

FIG. 2. Transverse MR images from a dog with a Grade I cystic meningioma in the left fronto-olfactory region. There is a sharply demarcated island of mildly hyperintense soft-tissue interposed between two cystic regions on the T1-weighted image (A) that demonstrates marked enhancement on postcontrast T1-weigted images (B–D). Using the Macdonald criteria, to encompass the largest area of tumor, measurements would cross the cystic regions (C). The response assessment in neuro-oncology criteria specify measurement of target lesions should be limited to regions of discrete contrast enhancement that do not contain cysts (D).

sequence or scan acquisitions parameters, patient positioning, and dose and timing of contrast agent administration.[40] Extensive technical reviews of standards for image acquisition in tumor response assessment protocol design are available.[15,17,25–27,39–42]

Although the Macdonald and RECIST criteria were designed and described for use with CT, current standards of care in neuro-oncology recommend MR-based imaging for objective tumor assessments, and cross-modality comparisons between CT and MR images be avoided.[5,16,26] If comparisons of CT and MR images are necessary, only a therapeutic response assessment of unequivocal progressive disease can reliably be applied (Fig. 8).

Serial MR scans used for therapeutic response assessments should be ideally acquired on magnets with identical field strengths using standardized image acquisition parameters and patient positioning techniques.[26] In humans, it is recommended that cross-sectional image slices be < 5 mm thick with no interslice gap when obtained for the purposes of comparative tumor quantification.[17,25–27] In veterinary medicine, image acquisition parameters are modified to optimize the signal-to-noise ratio and minimize acquisition time, but in general slices should be 1–5 mm in thickness depending on head size, with no interslice gap. If CT is used for serial scanning, it is also important to consider the radiation exposures when designing protocols. To avoid volume averaging, measurable lesions should to be at least 10 mm in diameter, or at least twice as large as the slice thickness, and also account for any interslice gaps present.[4,5,15–20,25–27] Most manufacturers of low- and high-field magnets have proprietary three-dimensional high-resolution ($\cong$1 mm slice thickness) T1-weighted sequences, which are predominantly gradient echo images with a three-dimensional Fourier transformation, that can be obtained practically in veterinary patients.[39,41] The use of these sequences pre- and postcontrast in multiple planes should be considered for incorporation into protocols evaluating brain tumor therapeutic responses. The dose of contrast agent administered, as well as the administration rate and timing of acquisition of postcontrast images should also be standardized and optimized for the scanner platform and tumor type being studied.[40]

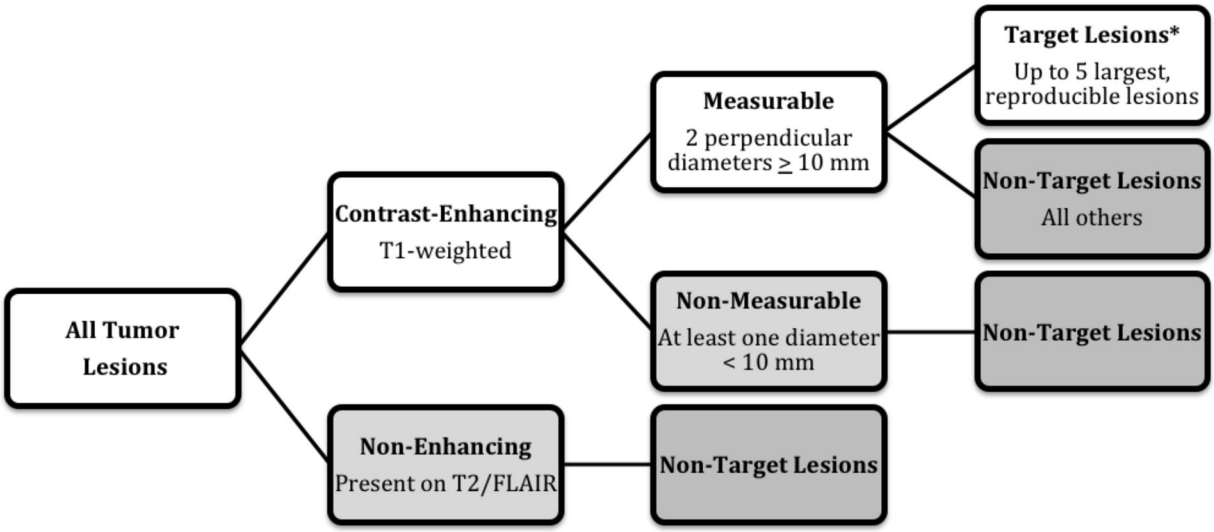

FIG. 3. Algorithm for defining lesions with MRI using RANO criteria. *The sum product diameters is determined for all target lesions at each timepoint, and follow-up measurements compared with baseline or nadir sum product diameters.

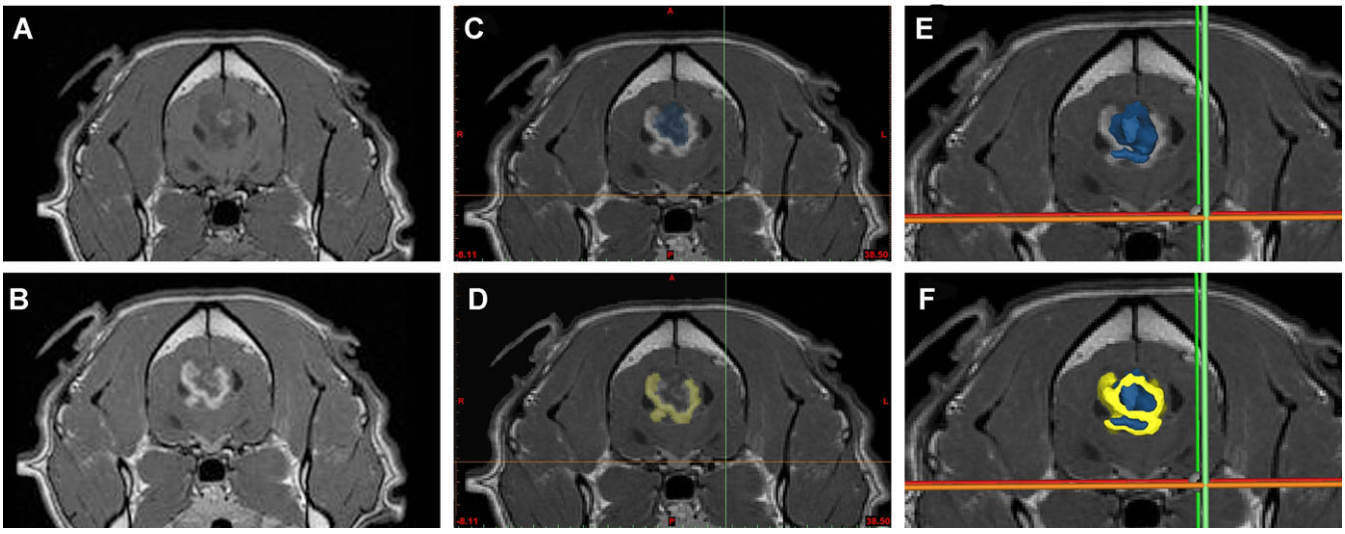

FIG. 4. Volumetric MR measurement of a canine Grade IV astrocytoma. Native pre- (A) and postcontrast (B) T1-weighted transverse images demonstrating large central necrohemorrhagic region and irregular peripheral ring enhancement that complicates quantitative measurement using RECIST, Macdonald, or RANO criteria. (C–F) Transverse postcontrast T1-weighted images used for semiautomated segmentation (Mimics 14.2, Materialise, Leuven, BG) of the tumor. The central necrotic (C, E) and contrast-enhancing tumor (D) regions are individually traced in each of the slices and segmented according to intensity values. Solid three-dimensional representations (E, F) of the contrast-enhancing volume (4199 mm^3), necrotic lesion volume (E; 2372 mm^3), and entire tumor volume (F; contrast enhancing + necrotic core = 6543 mm^3) are then calculated.

Determination of the lesion burden is also heavily dependent on the selection of appropriate regions for lesion quantification. Measurement of target lesions should not include normal anatomy or equivocal regions. Lesion measurement has traditionally been performed in the transverse plane when assessing brain tumors, but theoretically with MR, it could be performed in any plane.[15–20,26] Irrespective of the plane used, serial dimensional measurements of target lesions should always account for the longest representative diameter of the tumor, even if this requires use of different slice levels or diameter vectors than those used for the baseline assessment.[26]

In summary, when defining the tumor burden using diameter-based criteria, quantitative assessments are limited to those cases in which large (>10 mm in diameter), contrast-enhancing lesions are present (Fig. 3). All other abnormalities should be considered nontarget lesions and qualitatively evaluated. It is important to note that when performing a quantitative assessment using RANO criteria, both a reduction (or resolution) in the size of target lesions and stable or decreased nontarget lesion burdens must be present in order to attain a response assignment of partial or complete responses. Qualitative evaluations should incorporate comparisons of the size, shape, location,

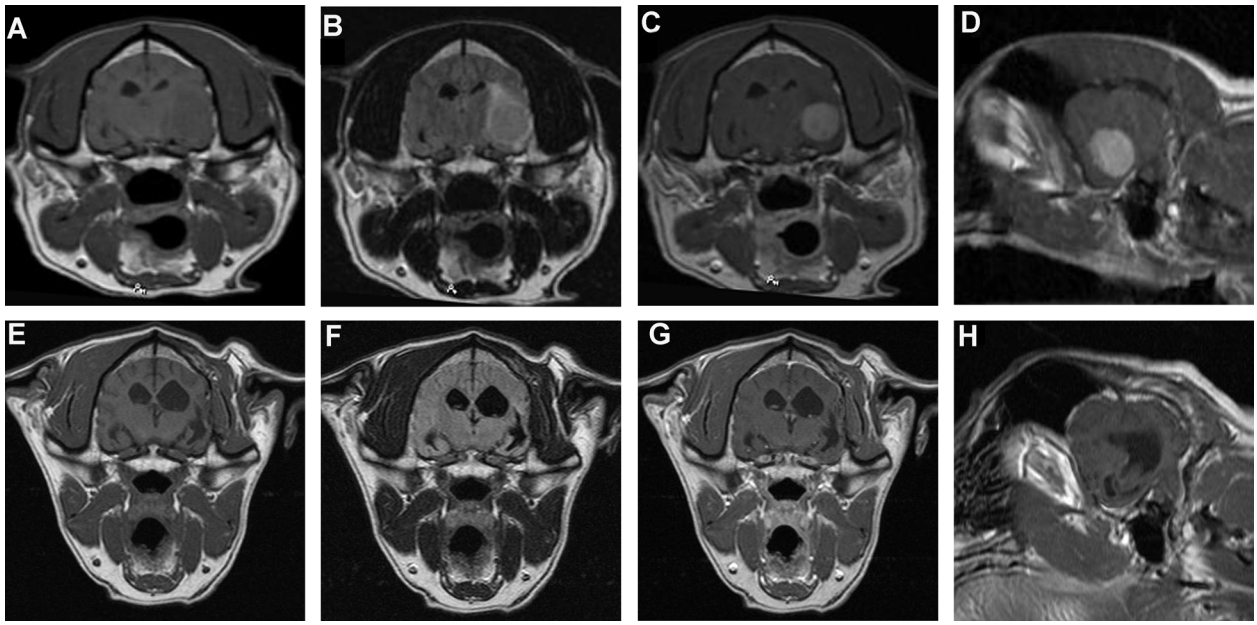

FIG. 5. Transverse MR images from a dog with a Grade I meningioma demonstrating imaging criteria compatible with a complete response to surgery. Preoperative images (A–D) illustrate a spherical, well-delineated mass in the left temporal lobe that is hypointense on T1-weighted (A), hyperintense on fluid-attenuated inversion recovery (B), and homogenously contrast enhancing (C and D). On images obtained 1 year following surgery, there is no evidence of tumor on T1-weighted pre- (E) and postcontrast T1-weighted (G and H) or fluid-attenuated inversion recovery (F) images, although a resection cavity is visible underlying the craniectomy defect.

and number of any observed abnormalities observed on T2 and FLAIR images between scans, and any new lesions identified.

Comparisons of Dimensional and Volumetric Response Criteria in Brain Tumors

Several studies have compared diameter-based and volumetric methods for the assessment of therapeutic response in human with gliomas.[32–36,42] At least three retrospective studies have concluded there were no statistically significant differences between diameter-based or volumetric methods when defining therapeutic response by a reduction in tumor size.[33,36,42] However, an additional study demonstrated that a computer-assisted volumetric method of measurement was superior to linear methods for the early detection of progressive disease, especially for smaller tumors.[32] In a large retrospective study comparing volumetric to RECIST measurement of gliomas, the response rate was more favorable when volumetric criteria were used (17% partial response versus 8%), but the statistical significance of this finding was not reported.[42]

Current Challenges with Brain Tumor Response Criteria

The accurate determination of tumor burden is confounded by inherent clinico-pathological features of brain tumors as well as the incorporation of imaging into the response assessment. A principle limitation of currently used response criteria is the universal dependence upon contrast enhancing lesion burdens for lesion quantification. Abnormal contrast enhancement is not limited to neoplastic tissue and can result from a variety of secondary effects associated with brain tumors, including meningeal or parenchymal inflammation, necrosis, seizure-induced changes, and infarction.[4–6,15–20,25–27]

An additional limitation is the lack of a clearly defined or accepted method describing a cutoff value for the quantification of tissue contrast enhancement with MR. Mathematical models based on the initial peak enhancing signal increase have been formulated, but have not been widely adapted.[43,44] Most often the definition of abnormal contrast-enhancing tissue is qualitative and based on expert opinion.[43,44]

There is conflicting evidence as to the degree and significance of the inter- and intraobserver variability with different methods of response assessment. Studies evaluating these factors cannot be readily compared owing to different methods of both scan acquisition and tumor measurement.[26,27,32,42] The majority of the measurement systems described to date are not fully automated. It is not surprising that studies have demonstrated inherent variability when using user defined regions of interest, even among expert reviewers.[25,36] Computer automation of volumetric measurement techniques have shown promise for improving variability associated with user defined regions of interest.[35]

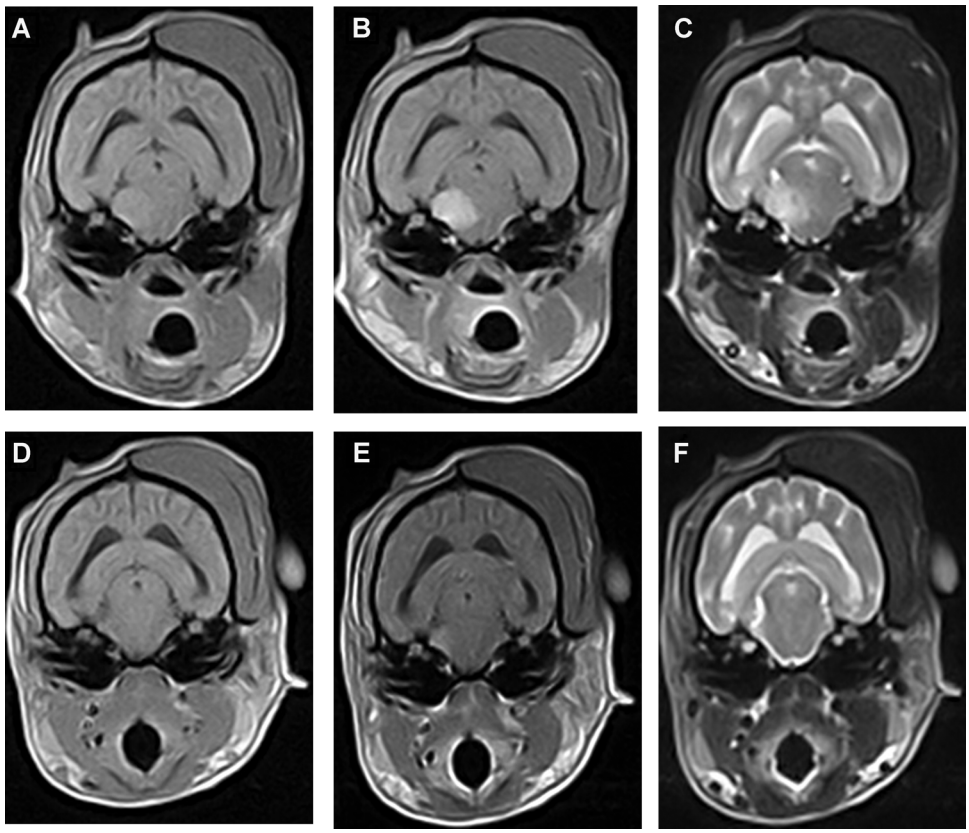

FIG. 6. Transverse MR images from a dog with a trigeminal nerve sheath tumor before (A–C) and 6 months after (D–F) fractionated radiotherapy demonstrating a partial response. There is marked unilateral atrophy of the right temporalis muscle. An ovoid, extra-axial mass is present in the right mesencephalon that is isointense on T1-weighted images (A), heterogeneously hyperintense on T2-weighted images (C), and enhances uniformly on postcontrast T1-weighted images (B). Posttreatment images show a poorly marginated area of contrast enhancement (E) in the region of the original tumor site that is too small to measure, and near complete resolution of the T2-hyperintensity within the right mesencephalon (F).

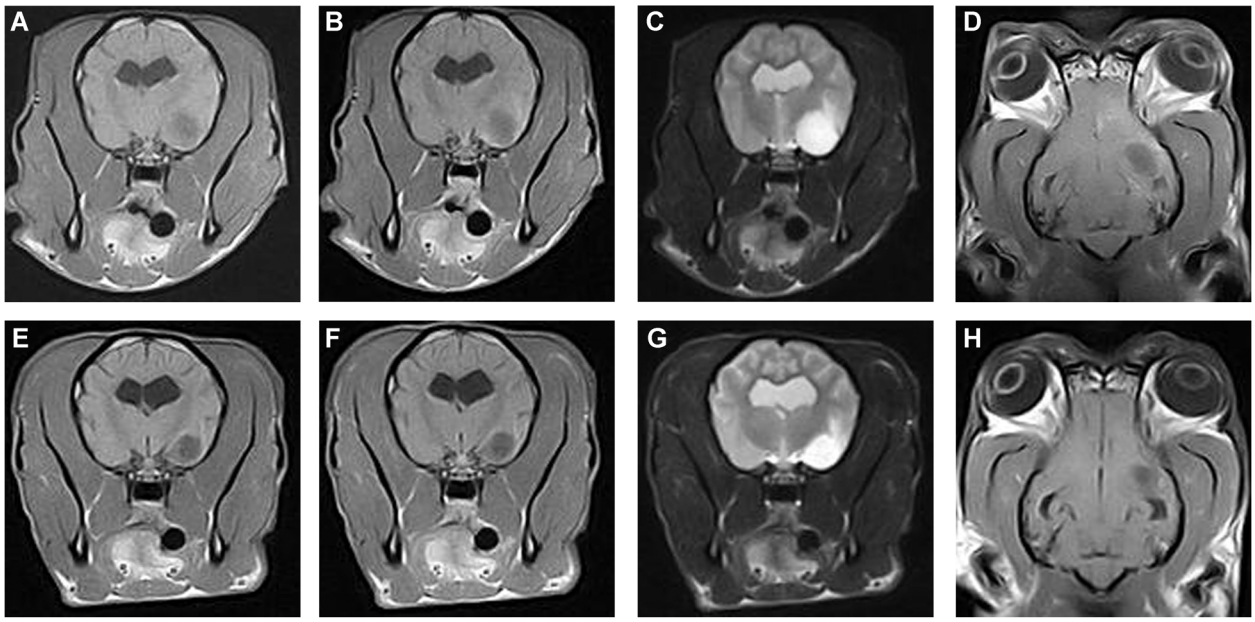

FIG. 7. MR images from a dog with a Grade II oligodendroglioma in the left piriform lobe before (A–D) and 6 months after (E–H) fractionated radiotherapy. The ovoid, intraaxial mass appears hypointense on T1-weighted images (A, E), homogenously hyperintense on T2-weighted images (C, G), and demonstrates scant peripheral contrast enhancement (B, D, F, and H). These characteristics qualify for RANO definition of the tumor as a nontarget lesion, and as such the qualitative reduction in tumor size on posttreatment images defined as stable disease.

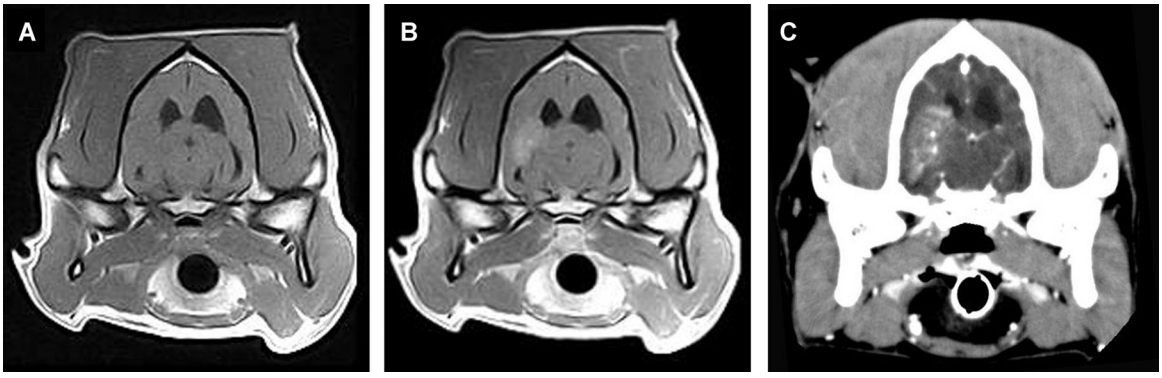

FIG. 8. Serial transverse images from a dog with a Grade III astrocytoma in the right parietotemporal region and progressive disease. There is an ellipsoidal intraaxial mass attenuating the lateral ventricle that is isointense on T1-weighted images (A) and demonstrates mild and heterogeneous contrast enhancement (B). Although direct quantitative comparison of target lesions is not recommended between CT and MRI, there is an unequivocal increase in the tumor size on the postcontrast CT image (C) obtained one month later, which occurred in association with clinical deterioration.

There are also the significant issues of the ideal timing of follow-up imaging protocols and therapeutic response confirmation. These are especially pertinent in veterinary medicine considering our current poor understanding of brain tumor biology, the efficacy of conventional therapies on clinical outcomes of patients with histologically confirmed brain tumors, and the requirement for general anesthesia to obtain diagnostic MR studies. The frequency of posttreatment imaging should ideally take into account the interval during which a response might be detected, as well as an approximation of the likely duration of response, which are often unknown variables in clinical trials of investigational therapies. In addition, as novel therapies continue to emerge that use cytostatic approaches that would not be expected to result in significant changes in tumor size, consideration should be given as to whether serial responses should be based on purely morphologic or both morphologic and physiologic (functional) imaging criteria.[16,18,19]

Considering the above limitations, we acknowledge that the optimal interval for posttreatment imaging in veterinary patients is currently unknown and will be influenced by the both the tumor type and therapy being investigated. However, based on the human experience, it is recommended that acute postoperative MR studies be obtained within 72 h of resective or ablative therapies to allow for optimal serial evaluation of tumor responses.[17,26,27,45] The goal of this acute postoperative scan is to define the limits and appearances of resection cavities and any other surgical induced changes prior to the administration or evaluation of additional therapies. Baseline imaging studies should also be obtained within 2 weeks of entry into a clinical trial prior to initiation of protocol treatment, especially in those cases with clinical or imaging evidence tumor progression following prior therapies.[17,25] In veterinary medicine, it may be possible to prolong the interval between baseline imaging and entry into clinical trials to 4–6 weeks for patients with slow growing tumors, such as meningiomas. In canine patients with glial tumors, we strive to obtain follow-up imaging every 8–12 weeks, which corresponds to the therapeutic cycle interval method commonly used in humans with high-grade gliomas.[4,19,33,34] Confirmation of therapeutic responses with repeat imaging at 4 weeks is recommended in the RECIST, Macdonald, and RANO criteria and is designed to avoid overestimating the response rate in clinical trials.[15,26,27] When therapeutic responses are not confirmed in this manner, this should be clearly and explicitly stated in reported results.

Therapy Induced Alterations in Brain Tumor Imaging: Resection Cavities, Pseudophenomena, and Treatment-Related Brain (Radiation) Necrosis

Reliance on conventional MR sequences, especially gadolinium enhanced images, for quantification of tumor burden is also complicated by the effects of prior therapies. In some instances, the differentiation of therapy-induced changes from alterations in tumor burden requires stereotactic biopsy.[35,45]

Resection cavities present unique and dynamic geometric and enhancement challenges to lesion quantification. Current assessment criteria state that resection cavity margins should not be included in target lesions. However, differentiation of a contrast-enhancing margin of a surgical resection cavity from residual tumor can be impossible. As such, it is recommended that postoperative MR scans be obtained within 72 h of tumor resection to minimize any possible interference with target lesion measurement from contrast-enhancing resection cavity margins.[26,27,45] In the acute postoperative setting, T1-hyperintensities resulting from blood in the resection site can complicate interpretation of gadolinium-enhanced MR images. The collapse of a resection cavity over time presents unique geometric challenges to serial quantification of the tumor burden using dimensional methods.[35,46] Because of the challenges associated with resection cavities, volumetric approaches have

been demonstrated to be beneficial when evaluating target lesions in postoperative patients.[35]

The widespread use of antiangiogenic agents in humans with recurrent high-grade glioma has resulted in the recognition of an imaging phenomenon that has been termed pseudoresponse.[16–18,25–27,46,47] Antiangiogenic agents and platelet-derived growth factor receptor inhibitors, most notoriously bevacizumab, function to inhibit vascular endothelial growth factor. When administered to humans with malignant gliomas, vascular endothelial growth factor inhibitors can result in a rapid decrease in the degree and extent of contrast enhancing tumor, and may also result in improvement in T2 and fluid-attenuated inversion recovery peritumoral hyperintensity resulting from edema. These imaging changes can be noted as early as 24 h after drug administration, and occur due to the decrease in capillary permeability induced by the antiangiogenic agent, and are not due to tumor cytotoxicity.[16–18] In humans with recurrent glioblastoma multiforme treated with vascular endothelial growth factor inhibitors, there is a relatively high response rate that is not associated with a significant survival benefit, part of which has been attributed to pseudoresponsivness.[47] As canine meningiomas and gliomas have also been associated with vascular endothelial growth factor overexpression, there is some rationale for use of vascular endothelial growth factor inhibitors in veterinary neuro-oncology, and we have observed the pseudoresponse in dogs with recurrent gliomas treated with bevacizumab (Fig. 9).[48,49]

An additional imaging phenomenon, referred to as pseudoprogression, is a well-recognized entity that develops in 20–50% of human glioblastoma patients treated with radiotherapy and temozolamide chemotherapy.[18,47] Pseudoprogression is characterized by a posttreatment increase in the contrast-enhancing portion of a lesion and/or peritumoral edema without true tumor progression, and typically occurs within 3–6 months of completion of radiotherapy (Table 2). Thus, operational definitions of pseudoprogression imply that the observed changes improve or resolve without treatment. Although pseudoprogressive lesions stabilize or may decrease in size on subsequent MR studies, the temporal period that defines lesion stabilization consistent with pseudoprogression is not standardized. Pseudoprogression is clinically asymptomatic in 66% of humans with malignant glioma, and occurs as a result of treatment-induced inflammation and vascular permeability.[17,18,27,46,47] Considering the incidence in which it is observed following radiotherapy, it postulated by some sources to represent a mild, self-limiting variant of radiation necrosis. However, pseudoprogression may evolve into radiation necrosis, which some authors suggest should be referred to as treatment-related necrosis in patients that have received combinatorial therapies including radiation.[50] Although pseudoprogression is most commonly noted and best described following temozolomide chemoradiotherapy, similar transient increases in contrast enhancing tissue followed by prolonged periods of tumor control have been observed in humans with brain tumors treated with other locally delivered genetic, immunologic, and intracavitary therapies.[47,50–52] In these instances, the observed imaging changes have also been termed the flare phenomenon.

Radiation necrosis is the most significant, and often irreversible, manifestation of late radiation induced injury to the brain, occurring months to years after tumor treatment (Table 2).[50] Radiation necrosis is a complex, temporally and spatially dynamic process believed to result from cellular membrane and deoxyribonucleic acid damage, with significant effects on the vasculature and oligodendroglial progenitor cells. Thus, the phenotypic hallmarks of late-delayed radiation induced brain injury are necrosis and leukoencephalopathy, with an associated inflammatory response (Table 2).[50,53,54] The pathophysiology, imaging features, and pathology of radiation necrosis has been reviewed in depth elsewhere.[50,53–56] The true incidence of radiation necrosis is difficult to determine, as definitive diagnosis requires histopathologic examination of representative tissue, and most human patients with pathologic change consistent with radiation necrosis have received multimodal therapies (treatment-related necrosis).[54] In addition, there can be significant discordance between clinical and imaging indicators of treatment-related necrosis. Although treatment-related necrosis has been rarely reported in veterinary medicine, it has been estimated to occur in 3–24% of humans with malignant glioma, and is significantly higher in patients receiving chemoradiotherapy.[54–56] Although there is currently a lack of data describing the clinical and temporal features of radiation toxicity in animals with spontaneous brain tumors, radiation induced brain injury may manifest earlier than in humans, at least in part due to typical usage of larger dose per fraction in veterinary medicine.

A significant limitation of conventional MR is its inability to discriminate treatment-related necrosis from tumor progression.[17,27,46,50,54–56] The MR features of treatment-related brain injury will vary in relation to the timing following treatment (Table 2). Late treatment-related necrosis can result in lesions with T2-weighted and contrast-enhancement characteristics and mass effect indistinguishable from recurrent glioma, and may occur in the vicinity of or remote from the original tumor.[50] Some authors have reported that "soap-bubble" or "swiss-cheese" patterns of gadolinium enhancement are more predictive of radiation necrosis, but at the present time there are no standardized imaging techniques that can reliably distinguish recurrent glioma from treatment-related change.[53] We have observed treatment-related necrosis in dogs associated with both necrosis and diffuse leukoencephalopathy (Fig. 10).[55]

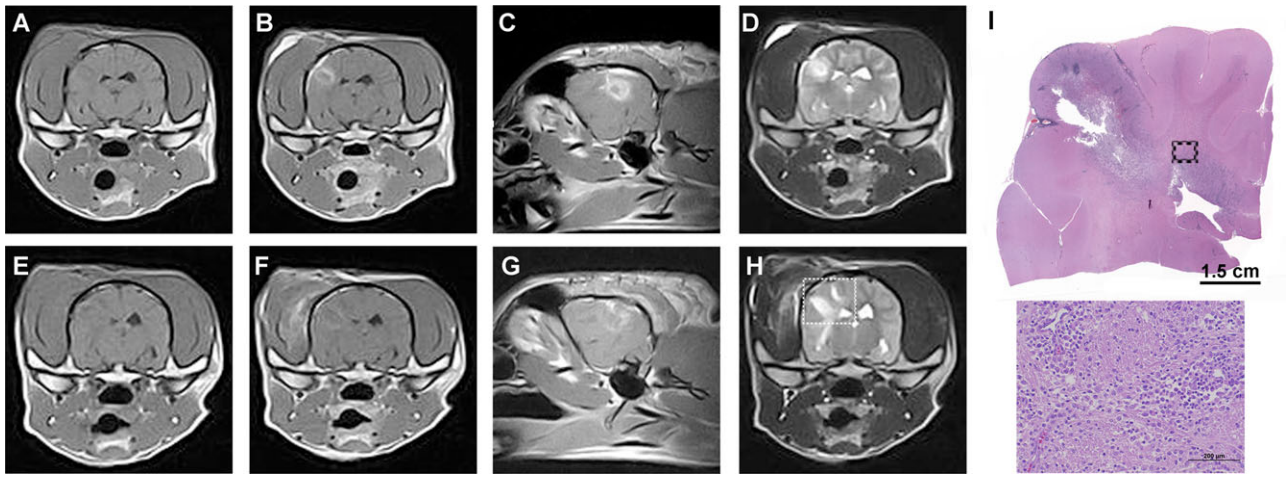

FIG. 9. Bevacizumab induced pesudoresponse in a dog with a recurrent Grade III astrocytoma in the right parietal lobe following surgical resection. (A–D) MR images of recurrent tumor prior to antiangiogenic therapy. An ovoid intraaxial mass adjacent to the previous craniectomy appears iso- to hypointense on transverse T1-weighted images (A), demonstrates heterogeneous ring enhancement on transverse (B) and sagittal (C) postcontrast T1-weighted images, and is heterogeneously hyperintense on transverse T2-weighted images (D). (E–H) MR images corresponding to panels (A–D), obtained 5 weeks after tumor biopsy and initiation of bevacizumab therapy. There is a reduction in the contrast-enhancing tumor (F, G), which would qualify as stable disease using Macdonald and RECIST criteria. However, there is an increase in perilesional T2 hyperintensity extending into the adjacent white matter (H) associated with a falx shift and attenuation of the right lateral ventricle (E, F, H). (I) Transverse brain necropsy specimen, representing area depicted in panel H inset (H&E stain). Progressive disease is characterized by viable tumor in the nonenhancing and T2-hyperintense regions at the original tumor site, accompanied by extensive infiltration of nonenhancing tumor into the white matter of the internal capsule, corona radiata (inset), and corpus callosum; H&E stain.

TABLE 2. MR and Pathologic Characteristics of Radiation-Associated Brain Injury[45,46,49,52,53,55]

		Acute injury	Early delayed	Pseudoprogression	Late delayed	Recurrent tumor
Temporal onset		Coincident with RT	Weeks to 3–4 months post-RT	Weeks to 3–4 months post-RT	Months to years post-RT	Weeks to years post-RT
Putative mechanism		Transient BBB disruption	Reversible demyelination	Multiple, non-progressive?	Multiple, irreversible	Treatment refractory disease
Imaging features	**Contrast enhancement**	No	No	Yes	Yes	±
	Mass effect	No	No	Yes	Yes	±
	Edema	±	±	±	±	±
Pathologic features	**Necrosis**	No	No	Yes	Yes	±
	Demyelination	No	Yes	?	Yes	No
	Endothelial cell proliferation	No	No	No	No	Yes
	Edema	Yes	Yes	Yes	Yes	Yes
	Macrophages	?	Yes	±	±	±

BBB, blood-brain barrier; RT, radiation therapy; ?, unknown or controversial.

Functional Neuroimaging in Neuro-oncology

The previously identified shortcomings of conventional MR in neuro-oncology have resulted in an extensive and growing body of literature dedicated to the use of functional and physiologic imaging. The vast array of specific modalities, agents, techniques, and indications for functional imaging are beyond the scope of this review. However, in relation to brain tumors, the majority of studies to date have attempted to use functional imaging to identify indiscriminate brain lesions as neoplastic, to noninvasively grade-specific tumor types, facilitate image-based therapeutic targeting, differentiate recurrent tumor from treatment-related change, or use functional parameters to predict therapeutic outcomes.[4,5,57,58] At this time, functional neuroimaging techniques should be considered complimentary to conventional MR imaging for the evaluation of therapeutic responses.

Magnetic Resonance Diffusion Weighted Imaging

This physiologic technique is based on the movement of water, and has been reviewed extensively.[59–62] Diffusion data are typically reported as the apparent diffusion coefficient, with lower apparent diffusion coefficient values corresponding to decreased movement of water. As water movement is more restricted in the intracellular compartment, necrosis, and cellular lysis will increase apparent diffusion coefficient values, as will edema, due to expansion of

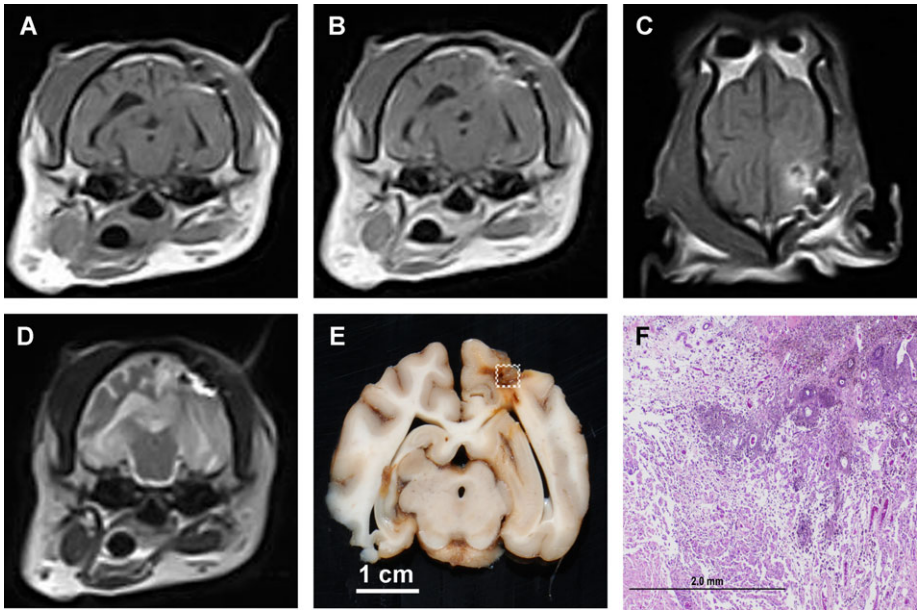

FIG. 10. Diffuse treatment-related brain necrosis in a dog with a Grade III oligoastrocytoma following combinatorial treatment with irreversible-electroporation and fractionated radiotherapy.[53] On the pre- (A) and postcontrast (B, C) T1-weighted MR images, there is a distortion of the cerebrocortical architecture in the left parieto-occipital lobe underlying the craniectomy defect that is heterogeneously iso- to hypointense and contrast enhancing. The dorsal postcontrast T1-weighted image (C) shows a focal ring-enhancing lesion with a "soap-bubble" appearance. On the T2-weighted image (D) there is a heterogeneous T2 hypo- and hyperintense lesion in the left parieto-occipital lobe, as well as bilateral periventricular and hippocampal hyperintensities. (E) Gross brain specimen at the level of the tympanic bullae demonstrating focal, tan discolored area of cortical necrosis in the left parieto-occipital region in the vicinity of the original tumor. (F) Photomicrograph of area depicted in panel E inset demonstrating pathologic features of treatment-related coagulative necrosis: course calcium deposits, hyalinized vasculature, and vascular telangiectasia; H&E stain.

the extracellular fluid compartment volume that facilitates movement of water. In contrast, areas of increased cellular density, such as infiltrative tumor foci, serve to restrict water movement and will result in lower apparent diffusion coefficient values.[59] These features highlight the utility of diffusion-weighted imaging as a complimentary technique to conventional MR sequences for the evaluation of brain tumor progression. Voxel-wide changes in apparent diffusion coefficient values in an individual patient over time can be assessed using functional diffusion maps, which can facilitate detection of subtle changes in tumor cell density both within and outside of areas of contrast enhancement and for evaluation of tumor progression following anti-angiogenic treatment.[59–62]

Another technique used with diffusion-weighted imaging for the evaluation tumor progression is apparent diffusion coefficient histogram analyses. Currently, this application has primarily been used to predict the treatment response to bevacizumab in the setting of recurrent glioblastoma, and has retrospectively demonstrated that tumors with low apparent diffusion coefficient values were more likely to progress by 6 months than tumors with high apparent diffusion coefficient values.[63] Although this technique has shown promise as a predictive biomarker in retrospective studies, it has not yet been rigorously and prospectively evaluated.[63,64]

Perfusion Imaging

Multiple methods of acquiring perfusion data with CT or MR have been developed, which involve serial acquisition of images in the same anatomic location during intravenous contrast administration. The two most commonly used perfusion techniques are dynamic susceptibility contrast and dynamic contrast enhanced imaging. Dynamic susceptibility contrast generates maps of relative blood volume or flow in a target tissue, and in the case of brain imaging, this is referred to as the relative cerebral (or tumor) blood volume, and relative cerebral blood flow. Dynamic contrast enhanced imaging is primarily used to assess capillary permeability.[5,16,27,65] There are numerous reports describing the roles of perfusion imaging in the evaluation of brain tumors.[65–71] In veterinary medicine to date, dynamic contrast enhanced-CT and dynamic contrast enhanced-MRI have been primarily evaluated as a noninvasive means to differentiate various histopathologic types of brain tumors.[70,71] In humans with astrocytomas, the potential utility of perfusion imaging for the assessment of therapeutic responses to radiotherapy, temozolamide, and vascular endothelial growth factor inhibitors has been evaluated in several studies. The maximal relative cerebral blood volume has been shown to have prognostic significance, with high or increasing relative cerebral blood volume

being a negative prognostic indicator irrespective of astrocytoma grade.[67]

For human patients with glioblastoma who receive standard of care chemoradiotherapy, the percentage change in relative cerebral blood volume from pre- to posttreatment measurements is predictive of 1-year survival.[67–69] In addition, perfusion imaging has demonstrated utility in discriminating treatment-related necrosis from glioma recurrence, with increases in relative cerebral blood volume being much more commonly associated with recurrent or progressive tumor.[65,72] Hyperperfusion noted with tumor recurrence reportedly occurs as a result of increased metabolic activity and tumor neoangiogenesis, while radiation necrosis will result in ischemic injury secondary to progressive intrinsic and obstructive vasculopathy.[65,67,72]

Positron Emission Tomography and Single Photon Emission Computed Tomography

Both positron emission tomography and single photon emission CT imaging have been used to evaluate intracranial neoplasia in humans and animals. Single photon emission CT imaging utilizes conventional or single gamma emitting radionuclides such as ^{99m}Technetium (^{99m}Tc). The traditional technetium-based radiopharmaceutical such as ^{99m}Tc-diethylene triamine pentaacetic acid (^{99m}Tc-DTPA) or ^{99m}Tc-glucoheptonates (^{99m}Tc-GHA) were commonly used to detect intracranial neoplasia before the availability of CT and MR.[73] These agents would localize in tumors based on a disrupted or incompetent blood brain barrier.

The next generation of technetium-based radiopharmaceuticals were ^{99m}Tc-hexamethylpropylenamine oxime (^{99m}Tc-HMPAO) or ^{99m}Tc ethyl cysteinate dimer (^{99m}Tc ECD). These are lipophilic agents that readily cross the blood-brain-barrier and react with intracellular glutathione that converts them to a hydrophilic compound that cannot diffuse out of the cells. The radiopharmaceutical is thereby fixed in the brain cells, and the cerebral distribution reflects a snapshot of cerebral blood perfusion. These perfusion agents are generally not useful for detection of intracranial malignancies because they typically have normal or decreased uptake in the area of the tumor.[74] Other conventional radiopharmaceuticals, such as Thallium-201 or ^{99m}Tc-methoxyisobutylisonitrile (^{99m}Tc-MIBI) have had limited use in detecting intracranial neoplasia.

Positron emission tomography imaging agents use positron-emitting radionuclides such as Fluorine-18 (^{18}F) or Carbon-11 (^{11}C). These low atomic number elements can be incorporated into biologically active molecules. The most commonly used radiopharmacetical in positron emission tomography is 2-deoxy-2 [^{18}F] fluoro-D-glucose (^{18}FDG).[75]

2-Deoxy-2 [^{18}F] fluoro-D-glucose is able to detect alterations in tissue glucose metabolism and higher ^{18}FDG uptake is often associated with higher grade malignancies. There have been mixed and conflicting results in studies investigating the utility of 2-deoxy-2 [^{18}F] fluoro-D-glucose positron emission tomography for evaluation of intracranial neoplasia because of the high 2-deoxy-2 [^{18}F] fluoro-D-glucose uptake by normal brain tissue.[47,75–77] The normal brain will have much higher uptake in gray matter than white matter (Fig. 11). In people, low-grade gliomas (WHO Grade 1 and II) will have 2-deoxy-2 [^{18}F] fluoro-D-glucose uptake similar to white matter where as Grade III gliomas will uptake equal to gray matter. High grade (WHO Grade IV) will often have 2-deoxy-2 [^{18}F] fluoro-D-glucose uptake more intense than gray matter. 2-deoxy-2 [^{18}F] fluoro-D-glucose uptake has been shown to discriminate between glioma recurrence, pseudorecurrence, and treatment-associated brain pathologies.[47,75–77] In humans with glioma, the sensitivity and specificity of 2-deoxy-2 [^{18}F] fluoro-D-glucose positron emission tomography is low when attempting to differentiate treatment-associated necrosis from recurrence, which has been at least partially attributed to the fact that altered glucose metabolism is a nonspecific finding associated with numerous pathologic processes.[47,75]

Amino acid positron emission tomography, such as ^{11}C-methionine (MET-PET) and ^{18}F-O-(2) fluoroethyl-L-tyrosine (FET-PET), have recently gained widespread use in human neuro-oncology. Compared to 2-deoxy-2 [^{18}F] fluoro-D-glucose, uptake of both ^{11}C-methionine (MET) and ^{18}F-O-(2) fluoroethyl-L-tyrosine (FET) is relatively low in normal brain tissue, but robust in brain tumors, thus providing high tumor to normal tissue contrast.[76] In gliomas, the uptake of ^{11}C-methionine (MET) correlates well with WHO tumor grading and the Ki-67 cellular labeling index, and therefore is considered an optimal marker of tumor proliferative activity. ^{11}C-methionine (MET) has been also shown to be superior to 2-deoxy-2 [^{18}F] fluoro-D-glucose for defining the gross tumor volume and identification of recurrence in humans with gliomas.[76–78] , ^{11}C-methionine (MET) has also been identified as valuable for the volumetric definition of skull-based meningiomas and brainstem metastases for radiation planning.[77] Considering its ability to provide information regarding tumor volume and proliferative activity, ^{11}C-methionine (MET) positron emission tomography is considered the standard of care in positron emission tomography in humans with gliomas. However, the practical limitations associated with the short (20 min) half life of ^{11}C-methionine (MET) prompted the development of ^{18}F-labeled amino acid analogs, including ^{18}F-O-(2) fluoroethyl-L-tyrosine (FET).[76,77]

The distribution within and intensity of uptake of ^{18}F-O-(2) fluoroethyl-L-tyrosine (FET) within primary brain tumors has been shown to comparable to ^{11}C-methionine (MET).[79] Although ^{18}F-O-(2) fluoroethyl-L-tyrosine (FET) has a high-sensitivity for the detection of high-grade brain

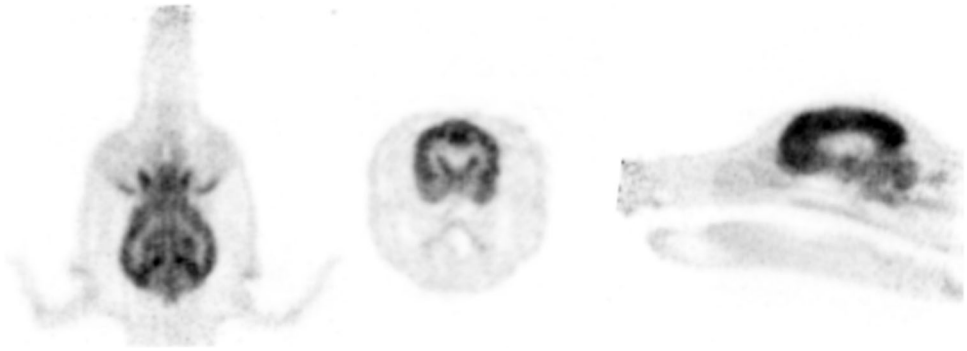

FIG. 11. Dorsal, transverse, and sagittal plane images of 2-deoxy-2 [^{18}F] fluoro-D-glucose positron emission tomography scan of normal canine brain demonstrating high tracer uptake in gray matter.

tumors, its specificity is somewhat limited by the passive leakage of tracer into non-neoplastic lesions that disrupt the blood-brain-barrier, such as encephalitis.[80,81] The use of ^{18}F-O-(2) fluoroethyl-L-tyrosine (FET) has been shown to valuable when attempting to differentiate glioma recurrence form treatment-related necrosis. Nonneoplastic contrast enhancing tissue noted on MRI due to radionecrosis is typically negative on ^{18}F-O-(2) fluoroethyl-L-tyrosine (FET) positron emission tomography, while biologically active sites of tumor recurrence will demonstrate tracer uptake.[81]

A number of other radiopharmaceutical agents have been developed and investigated for positron emission tomographic imaging of the biological features of brain tumors. A consistent feature among high-grade gliomas are regions of hypoxia. The microenvironment of these hypoxic regions have been shown to essential for the promotion of neovascularization, tumor proliferation and propagation, and conferring radio- and chemo-resistance.[82,83] ^{18}F-fluoromisonidazole (FMISO), a nitroimidazole derivative, and 2-(2-nitro-1H-imidazol-1-yl)-*N*-(2,2,3,3,3–^{18}F-pentafluoropropyl)-acetamide (^{18}F-EF5) have been demonstrated to be useful agents for the evaluation the hypoxic regions of gliomas, and subsequent radiotherapeutic planning and prediction of therapeutic response.[82,83] Numerous molecularly targeted imaging tracers have also been developed for positron emission tomographic imaging evaluation of brain tumors. The majority of these agents function by binding to protein targets, such as epidermal growth factor or vascular endothelial growth factor, that are typically overexpressed on brain tumors relative to normal brain.[84]

The deoxyribonucleic acid-based tracer 3'-deoxy-3'-[^{18}F] fluorothymidine (^{18}FLT) is a more specific marker of cellular proliferation. 3'-deoxy-3'-[^{18}F] fluorothymidine has the potential of being a better imaging agent for intracranial neoplasia because uptake of 3'-deoxy-3'-[^{18}F] fluorothymidine by normal brain tissue is much lower than for 2-deoxy-2 [^{18}F] fluoro-D-glucose.[84] 3'-deoxy-3'-[^{18}F] fluorothymidine uptake is high in proliferating cells and low in quiescent cells. Although the absolute uptake of 3'-deoxy-3'-[^{18}F] fluorothymidine in gliomas is lower than 2-deoxy-2 [^{18}F] fluoro-D-glucose, the tumor to nontumor ratio is much higher than for 2-deoxy-2 [^{18}F] fluoro-D-glucose. 3'-deoxy-3'-[^{18}F] fluorothymidine was reported to be a robust predictor of glioma progression in preliminary studies.[85,86]

Magnetic Resonance Spectroscopy

Proton MR spectroscopy has been widely studied as a method to noninvasively diagnose and grade brain tumors and discriminate between radiation necrosis and recurrence.[5,16,18,47,85–90] The MR spectroscopic metabolic signatures of a small number of canine brain tumors has been investigated and shown to parallel those of analogous human tumors.[87] In humans with gliomas, treatment-related necrosis has been shown to significantly reduce *N*-acetyl aspartate, with less predictable alterations in choline (Cho) and creatine (Cr).[86,88,89] Elevations in choline have been correlated with tumor progression, while low creatine is more consistently reported with radiation injury.[86,90,91] A study with gold-standard histopathologic confirmation of lesions has demonstrated improved discriminatory ability between tumor progression and radiation necrosis through the calculation of choline/*N*-acetyl aspartate, *N*-acetyl aspartate/creatine, and *N*-acetyl aspartate/choline ratios.[86]

A Proposal for Response Assessment in Veterinary Neuro-oncology

As objective, imaging-based endpoints will likely remain essential components of brain tumor clinical trials, we believe that adoption of a system closely modeled after the RANO criteria (Table 1, Fig. 3), which we term the response assessment in veterinary neuro-oncology system, represents a necessary step toward the standardization of outcome assessments. Similar to what has been observed

in human neuro-oncology, implementation of the response assessment in veterinary neuro-oncology (RAVNO) system is practical in veterinary medicine and offers distinct advantages over RECIST and Macdonald criteria. Serial clinical neurological examinations and recording of corticosteroid dose requirements are routine parts of follow-up examinations of animals with brain tumors. The process for selection of target lesions and performance of dimensional measurements requires modest training and can be readily accomplished using electronic calipers available in virtually all proprietary and open-source digital imaging and communications in medicine image viewers. The response assessment in veterinary neuro-oncology criteria allow for evaluation of noncontrast enhancing tumors, which is common in canine low-grade gliomas, and incorporates both clinical and imaging data when evaluating therapeutic response in veterinary patients.[2,3]

However, considering the technical simplicity of the RECIST criteria, extensive precedent for use of the Macdonald system, and lack of a clearly superior system in human neuro-oncology, we currently evaluate the RECIST, Macdonald, RAVNO and volumetric assessments in parallel in canine brain tumor clinical trials. Each temporal evaluation is independently performed by at least two experienced observers including neurologists, radiologists, oncologists, biomedical engineers, or medical physicists using workstation software (eFilm, Version 3.4 Merge Healthcare, Chicago, IL, for dimensional assessments, or Mimics 14.2, Materialise, Leuven, BG, for volumetric). All data are recorded on an electronic form and uploaded into a remote database.

Medication histories and neurological examinations are reviewed to allow for categorical scoring of clinical and corticosteroid dose as improved, stable, or deteriorating. Nonenhancing and nonmeasurable tumor burdens are categorically evaluated as stable disease or progressive disease. The fluid-attenuated inversion recovery/T2 (nontarget) lesion burden is classified as improved, stable, or progressive. Uni- or bidimensional quantitative lesion measurements are performed in three planes (dorsal, axial, sagittal) using three-dimensional T1-weighted image sequences and electronic calipers. Each observer selects the images demonstrating the greatest unidirectional or bidimensional product and records measurements. Volumetric quantifications are performed on transverse postcontrast T1-weighted images using semiautomated segmentation and intensity thresholding methods (Fig. 4). At our institution, experienced analysts can generate a complete dataset from each imaging examination, including quantitative dimensional and volumetric measurements, as well as a qualitative interpretation of the nontarget lesion burden, in approximately 1 h. Readers are not asked to calculate products of tumor measurement or assess therapeutic response based on quantitative or qualitative data. A research assistant or statistician performs tumor product measurement calculations.

Three sets of quantitative data from each observer and scan/visit from each patient are subsequently generated (three planar sum longest diameter [RECIST]/sum product diameters [Macdonald/RAVNO], and volumetric measurements). These data are used to quantitatively determine therapeutic response based upon percentage changes in tumor measurement according to RAVNO criteria from any of the three image planes evaluated (Table 1). Subsequently, a categorical therapeutic response is assigned according to RAVNO criteria for the visit after composite review of the clinical, steroid, and nontarget lesion data (Table 1).

Conclusions

A standardized and readily reproducible system of therapeutic response assessment is required for the evolution of evidence-based veterinary clinical neuro-oncology practice and translational research. In this review, we introduce the RAVNO system, which is modeled after the human RANO criteria and combines clinical and imaging data into therapeutic outcome assessment, and allows for qualitative evaluation of noncontrast enhancing neoplasms. As we believe that imaging-based response assessments will remain crucial for the evaluation of brain tumors, we propose that the RAVNO criteria serve as the foundation for development of quantitative and comprehensive outcome metric development in veterinary neuro-oncology. Although the RAVNO system can be readily adapted into veterinary practice and clinical trials, we readily acknowledge that the system is a work in progress that will require further extensive investigation, refinement, and validation, especially as new therapies and imaging technologies become available.

This review provides perspective on the lessons, limitations, and future potential of imaging-based response assessment in human neuro-oncology. The faithfulness of spontaneous canine brain tumors as a translational model for human disease is further illustrated with the examples of the canine pseudoresponse phenomena and treatment-induced brain necrosis. Given that similar challenges exist in the management and assessment of human and veterinary brain tumors, significant consideration should be given to the development and inclusion of functional neuroimaging studies, quality-of-life evaluations, and molecular endpoints into comprehensive therapeutic response assessment metrics for veterinary tumors.[17–19]

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