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STANDARD ARTICLE

Comparative evaluation of a novel, moderately hypofractionated radiation protocol in 56 dogs with symptomatic intracranial neoplasia

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Background: Use of strongly hypofractionated radiation treatments in dogs with intracranial neoplasia did not improve outcomes and yielded increased rates of toxicosis.

Objectives: To evaluate safety and efficacy of a new, moderately hypofractionated radiation protocol of 10 × 4 Gy compared to a standard protocol.

Animals: Convenience sample of 56 client-owned dogs with primary symptomatic brain tumors.

Methods: Retrospective observational study. Twenty-six dogs were assigned to the control standard protocol of 20 × 2.5 Gy (group A) and 30 dogs to the new protocol of 10 × 4 Gy (group B), assigned on owners' informed consent. Statistical analysis was conducted under the “as treated” regime, using Kaplan-Meier and Cox-regression analysis. Treatment was delivered with technically advanced image-guided radiation therapy. The 2 treatment groups were compared in terms of outcome and signs of toxicosis.

Results: Overall progression-free interval (PFI) and overall survival (OS) time were favorable, with 663 (95%CI: 497;828) and 637 (95%CI: 403;870) days, respectively. We found no significant difference between the two groups: PFI for dogs in group A vs B was 608 (95%CI: 437;779) days and mean (median not reached) 863 (95%CI: 644;1083) days, respectively (P = .89), and OS for dogs in group A vs B 610 (95%CI: 404;816) and mean (median not reached) 796 (95%CI: 586;1007) days (P = .83).

Conclusion and Clinical Importance: In conclusion, 10 × 4 Gy is a safe and efficient protocol for treatment of primary intracranial neoplasia and future dose escalation can be considered.

KEYWORDS

brain tumor, dog, fractionation, neurologic signs, radiation therapy, risk

1 | INTRODUCTION

Definitive-intent radiation therapy for dogs with intracranial tumors provides a long-term tumor control with a reasonably low risk of late complications. In general, best survival outcomes involve radiation protocols with relatively small fractions sizes of 2-3 Gy in 18-22 fractions, to total doses of 45-54 Gy.[1–3] With such protocols, outcome has been attributed to be dependent on tumor size, but surprisingly neither to location or presumed known tumor type.[1–3]

Abbreviations: 3DCRT, 3-dimensional conformal radiation therapy; BED, biologically effective dose; CSF, cerebrospinal fluid; CT, computed tomography; CTV, clinical target volume; GTV, gross tumor volume; IMRT, intensity-modulated radiation therapy; NTCP, normal tissue complication probability; MRI, magnetic resonance imaging; OAR, organ at risk; OS, overall survival; PFI, progression-free interval; PTV, planning target volume; RT, radiation therapy

Attempts to shorten radiation protocols for intracranial tumors in dogs by reducing fraction number drastically, while maintaining an adequate total dose, have been made but hypofractionated treatments have not reached the same outcomes with median survival times of only 1-1.5 years,[4] compared to >2 years with more finely fractionated protocols.[1–3] Moreover, dogs treated with more coarsely fractionated protocols (and often lower total doses) have increase in toxicoses and impaired quality of life, especially when treated with older techniques.[5–8] Ideally, such a change in protocol maintains a similar efficacy with no observable or only a slight increase in risk for toxicosis. Late radiation toxicosis in the brain remains difficult to detect with no consensus in medical literature as to which criteria should be used. Diagnostic imaging after recurrence of signs of neurologic disease provides some information as to whether worsening is because of tumor progression or late radiation toxicosis.[9–11] Conventional diagnostic imaging modalities fail to reliably differentiate active neoplastic tissue from radiation necrosis.[9,12]

In radiation therapy, the risk of toxicosis can be anticipated. In a prior study, we calculated the normal tissue complication probability (NTCP) with clinical data of former dogs with brain tumor with 10 × 4.35 Gy to be safe with a low risk of radiation-induced toxicosis for most tumor sizes and locations, given an appropriate technical radiation therapy standard. This protocol provides the same biologically effective dose (BED) as the routinely used 20 × 2.5 Gy protocol, and should theoretically result in an equal tumor control.[13]

However, to implement such a new, moderately hypofractionated, 10-fraction protocol into clinical practice, we used a conservative approach: instead of using 10 × 4.35 Gy, we started with a lower dose protocol of 10 × 4 Gy. This protocol was calculated for having the "same risk" (probability estimates of late toxicosis, eg, NTCP) and hence a lower BED. As a consequence, the 10 × 4 Gy protocol was expected to have a clinically detectable inferior outcome.

The aim of this clinical study was to provide data on clinical outcome described as progression-free interval (PFI) and overall survival (OS), as well as clinical performance and the occurrence of adverse events in dogs with intracranial tumors irradiated with either 10 × 4 Gy or the traditional protocol of 20 × 2.5 Gy. We hypothesized that a clinically detectable difference of outcome for PFI, OS time or both between the 2 treatment groups should occur, because of differences in the BED given. The resulting data will be used for the future decision, whether clinical escalation of dose per fraction for the irradiation in 10 fractions can be safely attempted.

2 | MATERIAL AND METHODS

2.1 | Study design

Retrospective observational study.

2.2 | Dog and tumor characteristics

Client-owned dogs diagnosed with symptomatic primary intracranial tumors presented for radiotherapy at the Division of Radiation Oncology, Vetsuisse Faculty, University Zurich, Switzerland, were enrolled in the study. The intracranial tumors were diagnosed based on neurologic examination including examination of cerebrospinal fluid (CSF) and magnet resonance imaging (MRI) or computed tomography (CT).[10,11,14–17] Clinical data including signalment, tumor type based on diagnostic imaging, tumor size and location, staging work-up, treatment modality, treatment schedule and response, time to last follow-up, time to progression, time to death, and cause of death were collected. All symptomatic primary intracranial tumors were enrolled, including pituitary tumors and no difference was made in terms of workup and treatment recommendations. Workup included clinical and neurological examination, complete blood count (CBC), biochemical profile, thoracic radiographs or CT and further exams such as CSF analysis, if indicated for the specific findings. Dogs with signs of neurologic disease at presentation were categorized into showing mild, moderate, or severe signs.[3] Seizures as a neurologic abnormality were recorded separately as they were not included in this classification system.

2.3 | Treatment

Protocol choice was left to owner's decision and made by owner's informed verbal or signed consent. Dogs were treated with either 20 × 2.5 Gy (group A) or 10 × 4 Gy (group B). However, most dogs before 2015 were treated with a 20-fraction protocol, and the switch to more 10-fraction treatments was made in May 2015. As similar protocols have been published in the past and a risk estimate existed,[7,13] no formal ethics approval from the Animal Ethics Council of the Canton of Zurich, Switzerland, was needed.

Radiation was delivered with a 6MV linear accelerator (Clinac iX, Varian, Palo Alto, California) equipped with a 5-mm leaf-width multi-leaf-collimator, using photons and 3-dimensional (3D) conformal radiation therapy (3DCRT) or intensity-modulated radiation therapy (IMRT).

Treatment planning was performed using Eclipse External Beam planning software (Eclipse treatment planning software, Varian Oncology Systems, Palo Alto, California), applying AAA-algorithm (10.0.28). Radiation was planned isocentrically, with heterogeneity correction, by a board-certified radiation oncologist (CRB or VM). Planning-CT and daily treatments were performed under general anesthesia in sternal recumbency. Reproducible positioning was accomplished with both an individually shaped vacuum cushion (BlueBag BodyFix, Elekta AB, Stockholm, Sweden) and a custom-made bite block.[18] Target volumes and organs at risk (OAR) were contoured in a facility internal standardized manner as previously published by our research team.[13] In brief, the gross tumor volume (GTV) was delineated using coregistered contrast-enhanced CT images or CT and MRI images, in tumors with no contrast uptake T2 sequences were used for delineation of GTV. Clinical target volume (CTV), accounting for subclinical microscopic disease extension of 2-8 mm (presumed local infiltration, according to tumor type) was defined. The CTV-margin was then extended 3 dimensionally by 2 mm to define the planning target volume (PTV), accounting for setup uncertainties in daily image-guided photon treatment. OAR were segmented as described previously.[13] Additionally, for the assessment of radiation toxicosis, a volume PTV_{brain} was computed, representing the portion of the PTV inside the calvarium. Furthermore, the ratio of the target volume to the entire brain volume (BV) was computed for each target volume.

Accuracy of positioning in daily treatments was provided with on-board imaging and daily orthogonal kilovolt-images. The recommendations for specifying dose and volumes were adhered to as proposed by Keyerleber et al.,[19] and in the ICRU reports 50 and 62 for 3DCRT and ICRU report 83 for IMRT plans.[20–22] The dose was prescribed at the ICRU reference point, delivered in a protocol of either 10 × 4 Gy (40 Gy total dose) or 20 × 2.5 Gy (50 Gy total dose). According to the Swiss law and routine procedure in our clinic, a medical physicist approved all treatment plans and the IMRT treatment plans were dosimetrically verified before treatment using a phantom (Octavius-Phantom, PTW Freiburg, Germany).

Treatment was delivered with definitive-intent, on a Monday to Friday schedule.

Additional medical treatment before and after radiotherapy was not standardized and adapted to the individual needs of the dogs. Medication was usually started at the day of diagnosis or beginning of signs of neurologic disease and adapted according to the improvement clinical signs and consisted mostly of antiepileptic drugs and corticosteroids.

2.4 | Follow-up

Dogs were invited for a clinical/neurologic examination 3 weeks after radiotherapy to check for acute adverse effects and re-evaluation of initial clinical and neurological abnormalities. Follow-up examinations were recommended every 3 months for the 1st year after irradiation, the interval was then prolonged to every 6 months. Dogs underwent clinical and neurologic examination by a board-certified neurologist or an experienced resident in veterinary neurology. Diagnostic MRI was recommended at 6 and 12 months after irradiation. Further diagnostics, for example, CBC, serum biochemistry, urinalysis, thoracic radiographs, and ultrasonography examinations were not performed routinely but based on the clinician's recommendations. Suspected acute, early delayed, and late radiation toxicosis was based on the VRTOG toxicity criteria and assessed on consensus among a board-certified radiation oncologist (CRB, VM), neurologist, and radiologist (RD).[23] Suspected progressive disease was based on clinical and neurological evaluation of the dog and also assessed on consensus among a board-certified radiation oncologist (CRB, VM), neurologist, and RD. In dogs with suspected progressive disease, diagnostic imaging was recommended to confirm progressive disease.

Diagnostic imaging was mostly performed in-house in the Clinic of Diagnostic Imaging, Vetsuisse Faculty, University of Zurich, or at the referring veterinarian's diagnostic imaging institute of choice.

Settings for diagnostic imaging performed at external facilities were not standardized. Information for radiologic evaluation of dogs was obtained from the original radiology report. In cases where the radiology report did not contain all necessary information, a board-certified RD reviewed all imaging studies of the corresponding dog. Two-dimensional (2D) tumor measurements were obtained in OsiriX (OsiriX, Version 4.0 64-bit, Pixmeo Sarl, Geneva, Switzerland). For 3D tumor measurement, the control MRI studies were imported into Eclipse External Beam planning software, contoured, and the resulting tumor volumes were derived. For dogs that underwent follow-up imaging, response to treatment was assessed according to the response criteria as proposed by MacDonald.[24]

2.5 | Statistical analysis

Data were coded in excel and analyzed with SPSS (SPSS Version 24, IBM Corp., Armonk, New York). Descriptive statistics such as absolute and relative frequencies as well as mean (median) and SD (IQR) were computed. The nonparametric Mann-Whitney test investigated differences in continuous variables with respect to a binary factor. The Chi^2 test was used to disclose associations between 2 discrete variables. In case of death clearly because of other cause (without signs of disease progression), the dogs were censored at the time of death for PFI analysis. Median survival time (OS) was defined as the interval between the first radiation therapy until death. For OS, all deaths were considered events and dogs that were still alive at the time of data evaluation or lost to follow-up were censored. Both OS time and PFI were coded and analyzed with Kaplan-Meier accompanied by the log-rank and Tarone-Ware tests and Cox-Regression (HR). Survival estimates and median survival time were complemented with the corresponding 95% confidence intervals (95%CI). If not otherwise indicated, the statistical analysis was conducted under the "as treated" regime. To adjust the statistical analysis of most important outcomes for the nonrandomized study design, the "intention-to-treat" and "per-protocol" regimes were applied assuming a cut-off in May 2015 (group A = treated before cut-off, group B = treated after cut-off). Results of statistical analyses with P-value <.05 were considered statistically significant.

3 | RESULTS

3.1 | Dog and tumor characteristics

Of the 67 dogs presented for radiation therapy to the authors' institution in the relevant period between January 2012 and June 2017, 56 dogs (84%) met the inclusion criteria for the study: 30 were male (19 neutered) and 26 were female (19 spayed). A total of 35 pure (n = 24) and mixed (n = 11) breeds were represented, the most common being Boxer (n = 6), Golden Retriever (n = 5), and Labrador Retriever (n = 4). Age ranged from 1.5 to 14 years with a mean of 9.0 (±2.9) years, and weight ranged from 2.9 to 41.7 kg with a mean of 21.0 (±11.8) kg. Dogs with signs of neurologic disease at the time of presentation were judged as exhibiting mild (n = 27), moderate (n = 20), or severe signs (n = 9). Twenty-four dogs were presented with a history of seizure and 11/24 dogs showed seizure as their only sign of neurologic disease. Tumors were radiologically diagnosed as meningioma (n = 31, group A = 17, group B = 14), glioma (n = 12, group A = 6, group B = 6), pituitary gland tumor (n = 10, group A = 1, group B = 9), peripheral nerve sheath tumor (n = 2, group A only) and choroid plexus tumor (n = 1, group B only). Distribution of tumor types was significantly different between the groups when comparing all tumor types (P = .021). The analysis was repeated with tumor types occurring in both treatment groups only, however, group distribution was still different (P = .028). Mean GTV was 2.76 cm^3 (95%CI: 2.17;3.34) corresponding to a mean GTV/BV-ratio of 3.32% (95%CI:

2.60;4.03). Mean CTV was 5.67 cm^3 (95%CI: 4.40;6.54) corresponding to a mean a CTV/BV-ratio of 6.54% (95%CI: 5.26;7.83). Mean PTV_{brain} was 7.01 cm^3 (95%CI: 5.80;8.23), corresponding to a mean PTV_{brain}/BV-ratio of 8.47% (95%CI: 6.93;10.00). A significant difference in sizes between the 2 treatment groups was noted only in CTV (P = .010) but not in CTV/BV-ratio or any other target volume characteristics. Twenty-seven tumors were located in the rostral cranial fossa, 19 in the middle fossa, and 10 in the caudal fossa and there was no significant difference between the 2 treatment groups. In 9 dogs, only CT images were available for diagnosis and delineation of target volumes and OAR. Of these dogs, 4/9 (44%) were diagnosed with meningioma, 1/9 (11%) with a glioma and 4/9 (44%) with pituitary gland tumors.

Three dogs had a surgical biopsy/debulking surgery before radiotherapy, all 3 dogs were diagnosed with a meningioma and surgery (leaving macroscopic tumor behind) was performed 23, 29, and 70 days before radiotherapy.

3.2 | Treatment

Of the 56 dogs, 26 (46%) were treated with 20 × 2.5 Gy (group A), 20/26 (77%) were treated before the cut-off of May 2015, 6/26 (23%) were treated thereafter and 30 (54%) were treated with 10 × 4 Gy (group B), 2/30 (7%) were treated before the cut-off of May 2015, 28/30 (93%) were treated thereafter. Forty of 56 dogs (71%) were treated with a conformal photon plan (3DCRT) and 16/56 (29%) with an IMRT (sliding window). A median of 3 fields was used (range 2-5, 2-4 for 3D-CRT, and 5 for IMRT). Of all treated dogs, 43/56 (77%) received corticosteroids at the first fraction with the mean dose being 0.70 mg/kg (95%CI: 0.62;0.78). Corticosteroids were reduced in 84% (36/43) dogs during radiotherapy by a mean of 54% (95%CI: 47;62) and could be stopped in 10 dogs after 3 weeks, in 7 dogs after 3 months, in 7 dogs after 6 months, in 1 dog after 9 months, and in 1 dog after 12 months, 13/56 (23%) dogs did not receive corticosteroids. In 1 dog, steroid dose had to be increased during radiation therapy because of insufficient improvement of signs of neurologic disease. Corticosteroid doses and dose reductions were not significantly different between the 2 treatment groups. Twenty-seven of the dogs (48%) received antiepileptic treatment consisting of either phenobarbital (n = 18) in a dose range of 1.4-3.1 mg/kg q12h with a mean of 2.28 mg/kg (95%CI: 2.02;2.56) or levetiracetam (n = 8) in a dose range of 13.2-33 mg/kg q8h with a mean of 21.25 mg/kg (95%CI: 17.23;25.27). In general, phenobarbital dose was titrated to the upper level of the recommended range (25-30 mg/L)[25] and levetiracetam was added if seizure control was not complete, or if dogs had adverse effects from phenobarbital. Thirty-four dogs (61%) received other supportive medication as follows: gastric acid inhibitors (n = 14), antiemetics (n = 6), antibiotics (n = 9), pain killers (n = 3), antiarrhythmic drugs (n = 2), levothyroxine (n = 2) diphenhydramine (n = 1), oclacitinib (n = 1), and different topical eye medication (n = 9).

Acute radiation toxicosis was assessed in all 56 dogs, 54/56 dogs (96%) were assessed for early delayed and 47/56 dogs (84%) for late radiation toxicosis. The dogs not assessed for early delayed or late radiation toxicosis did not live long enough for assessment. None of the dogs showed acute radiation toxicosis. In 1 dog, each (1/54, 1.9% and 1/47, 2.1%) early delayed (steroid responsive and self-limiting) and late radiation toxicosis was suspected.

3.3 | Follow-up and outcome

Clinical and neurological response at 6 months after radiotherapy was assessed in 45/56 cases (80%; 21/26 from group A and 24/30 from group B) and not significantly different between the groups (P = .67): In group A, 19/21 showed improvement in clinical and neurological response, and in group B, an improvement in clinical and neurological response was documented in 20/24 dogs. The other 11 dogs (20%) had died before they reached 6 months follow-up (5/11 from group A and 6/11 from group B). Of these 11 dogs, death was attributed to the brain tumor in 10 cases, 1/11 dogs (group A) died of tumor unrelated causes. Of the dogs that died before they reached 6 months follow-up, 4/11 showed improvement of signs of neurologic disease by the first control examination after radiotherapy, 5/11 showed stable signs of neurologic disease, and only 2/11 did not show improvement of signs of neurologic disease. Eight dogs in group A and 5 dogs in group B had seizures as their only presenting sign. About 7/8 dogs (88%) in group A and 4/5 (80%) in group B had improved seizure control with no or only sporadic (<1/month) seizures after therapy, but it is not possible to determine, whether seizure control was because of tumor reduction or antiepileptic medication.

A total of 23 diagnostic imaging control examinations from 19 dogs were available for assessment according to the MacDonald response criteria.[24] Fifteen studies were performed up to 6 months (mean 163 days; ±47.9 days, range 86-219 days), 6 around the recommended 1 year (mean 363 days; ±96.9 days, range 236-496 days), and 2 at a later time point (538 and 895 days). Response to treatment classified according to the MacDonalds response criteria was complete remission in 2/23, partial remission in 7/23, stable disease in 10/23 and progressive disease (PD) in 4/23. Median reduction in sum-product of longest diameters was 35% (95%CI: 28;61). Median volumetric tumor reduction was 43% (95%CI: 37;67). The differences in 2D and 3D tumor reductions were not significant between groups A and B (P = .56 for 2D, P = .88 for 3D-reductions).

Two dogs with suspected glioma had to be excluded from comparison of 2D and 3D measurements because of a lack of contrast uptake of the brain lesion.

The mean follow-up was at 491 days, median at 483 days (95% CI: 281;686 days). During this time, 27 dogs were clinically classified as progressive. The median PFI for all cases was 663 days (95%CI: 497;828). We found no significant difference between the two groups: PFI for dogs in group A vs group B was 608 (95%CI: 437;779) days and mean (median not reached) 863 (95%CI: 644;1083) days respectively (P = .89). The proportion of dogs free of progression at 1 and 2 years were 83% (95%CI: 67;99) and 34% (95%CI: 14;54) for group A and 80% (95%CI: 66;94) and 60% (95%CI: 34;86) for group B (Figure 1). Tumor type was a significant factor for outcome occurring in both groups (P = .001) and direct comparison revealed significantly shorter PFI for gliomas compared to meningiomas (P < .001) with 224 days (95%CI: 0;548) and 882 days (95%CI: 589;1175),

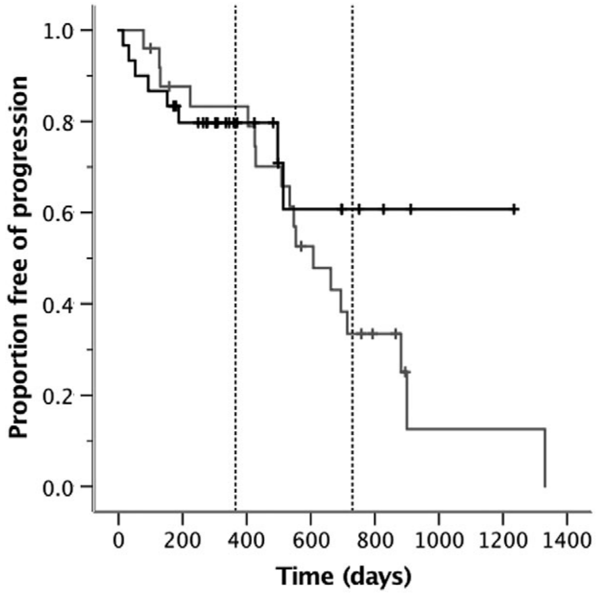

FIGURE 1 Proportion free of progression for the 2 treatment groups (black line: 10 × 4 Gy, n = 30; gray line: 20 × 2.5 Gy, n = 26). Censor marks: In case of death clearly because of other cause (without signs of disease progression), the dogs were censored at the time of death for progression-free interval analysis. The dotted lines mark 1 and 2 years. No significant difference between the 2 groups was found (P = .860)

respectively (Figure 2). Hence, for tumors radiologically diagnosed as gliomas, PFI was 658 days shorter (95%CI: 257;1059) than for meningiomas. Also, dogs with severe signs of neurologic disease had a significantly shorter PFI than dogs with mild signs (P = .008): PFI was 286 days shorter (95%CI: −107;679) in cases with severe signs of neurologic disease compared to mild signs.

Median OS was 637 days (95%CI: 403;870; Figure 3). OS in group A was 610 days (95%CI: 404;816) and was not reached in group B, (mean OS 796 [95%CI: 585;1007] days; P = .83). The proportion of dogs alive at 1 and 2 years was 77% (95%CI: 61;93) and 45% (95%CI: 25;65) for group A, and 63% (95%CI: 43;83) and 57% (95%CI: 37;77) for group B. Tumor type as well as tumor and treatment volumes in relation to the BV were significant prognostic factors for survival. Median survival time was significantly shorter (P < .001) for dogs with radiological diagnosis of glioma than meningioma, with 226 days (95%CI: 109;343) and 811 days (95%CI: 694;928). Also concerning survival time, tumors radiologically diagnosed as gliomas had a 585 days shorter OS (95%CI: 336;833) than tumors diagnosed as meningiomas.

Of the 33 animals (59%) documented to have died, 22/26 dogs were from group A, and 12/30 dogs were from group B; 22/33 (67%) died of tumor (or potentially treatment)-related causes, all of them showed worsening signs of neurologic disease and progression of clinical signs identical to the initial presentation. Of these dogs, 11/22 (50%) did not have imaging confirmation; therefore, late radiation toxicosis could not be entirely ruled out but seemed unlikely based on the clinical assessment. Death of tumor unrelated causes occurred in 11/33 cases (33%), these animals died of development of other neoplastic diseases (n = 5), multiorgan failure (n = 4), other not tumor related neurologic conditions (n = 2).

Survival analysis and analysis of PFI for the groups split by "intention to treat" and "per protocol" did not show any relevant differences to the analyses above for groups split by "as treated" factor.

4 | DISCUSSION

In this study, we chose a conservative approach for the 1st-time application of this moderately hypofractionated 10-fraction protocol in dogs. A short protocol with 10 fractions and the same risk for late toxicosis (NTCP), based on mathematical calculations, was compared to the standard 20-fraction protocol.[13] Based on VRTOG clinical observations, no increased occurrence of toxicosis was found. The outcome, as well as the low occurrence of adverse events in dogs irradiated with this moderately hypofractionated protocol of 10 × 4 Gy for their brain tumors was not different from the standard protocol and can be summarized as favorable.

Prior protocols used for the treatment of intracranial tumors in dogs using a lower fraction number raised the suspicion that OS was compromised by fatal acute or late radiation complications in >16%.[5,8] Overall, large fraction sizes chosen and applied with older 2D or nonimage-guided 3D techniques cannot be recommended for safe future use.[6] For some tumor constellations with small tumor volumes in nonsensitive areas, a reduction in fraction size can safely be performed, given an appropriate technical radiation therapy standard.[4,26] Furthermore, a new protocol with 10 fractions of 4.35 Gy has been theoretically calculated in 64 dogs and suggested that it may be safe to treat small to intermediate sized tumors that are neither located near the optic chiasm nor at the brainstem with 10 daily fractions of 4.35 Gy.[13]

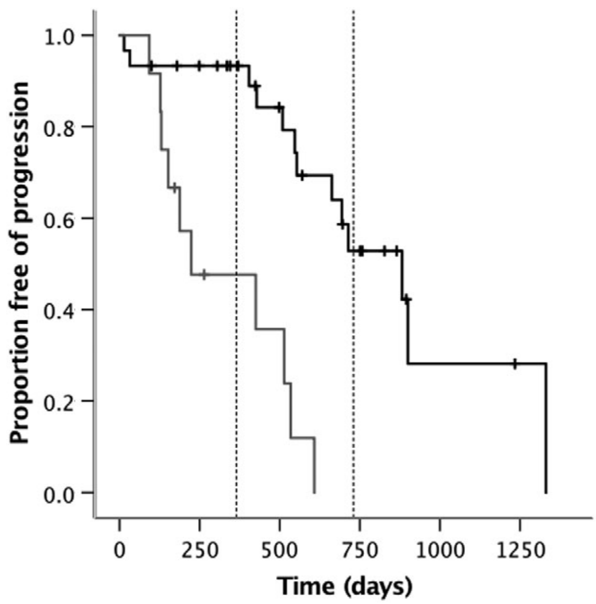

FIGURE 2 Proportion free of progression for dogs with meningiomas (black line, n = 31) and gliomas (gray line, n = 12), imaging diagnosis. Censor marks: In case of death clearly because of other cause (without signs of disease progression), the dogs were censored at the time of death for progression-free interval (PFI) analysis. The dotted lines mark 1 and 2 years. PFI was significantly shorter for dogs diagnosed with gliomas (P < .001)

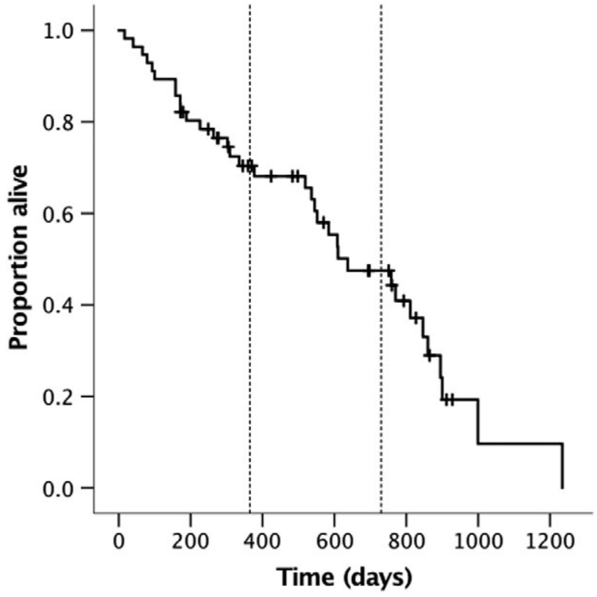

FIGURE 3 Proportion alive for all dogs. Censor marks: For OS, all deaths were considered events and dogs that were still alive at the time of data evaluation or lost to follow-up were censored. The dotted lines mark 1 and 2 years

In the dogs that had imaging performed at progression of signs of neurologic disease, these signs could be attributed to tumor progression (local or locoregional) and based on diagnostic imaging, no late radiation toxicosis was suspected. As the latency to occurrence of radiation necrosis varies greatly, the low incidence might have been attributed to the only intermediate OS of the dogs compared to toxicosis outcomes observed in human patients. However, the incidence as well as the time of occurrence of radiation necrosis increases with increasing BED.[27] The incidence of radiation necrosis in the cerebrum is 4% for a BED >85-120 Gy_2 and increases to 17% for BED >155-190 Gy_2 and 22% for BED >190-225 Gy_2.[27] Calculation of BED for the protocols used in our study were on the lower end with 112.5 Gy_2 in group A and 120 Gy_2 in group B, reassuring the incidence of radiation necrosis is probably ≤4%, but might occur in some cases.

Clinical improvement as well as PFI and OS was not significantly different between the treatment groups, even if the lower BED in the 10-fraction protocol implies a lower efficacy and tumor control probability.[13] The median PFI of 22 months (95%CI: 16;27) in this study as well as the percentage of dogs free of progression at 1- and 2-years (81% and 41%) are comparable with other studies, as their 1- and 2-year proportions free of progression lie within our 95%CI range. Also, the OS with a median of 21 months in this study (95%CI: 13;29) and the proportion alive at 1- and 2-years (70% and 47%), respectively, is comparable to reported findings.[1–3] The outcomes with the new, 10-fraction protocol represent a novelty, because the relatively lower total dose of this moderately hypofractionated protocol can most likely safely be escalated (as well as the total dose of a protocol with the more finely fractionated, 20 × 2.5 Gy fractions) if applied with conformal, daily image-guided treatment.

The herein used moderately hypofractionated protocol differs from the currently increasingly used extreme hypofractionated stereotactic or radiosurgery treatments.[4,26,28] These treatments are applied in humans in situations of noninfiltrative tumors and volumes that do not exceed defined sizes. The risk for complications in radiosurgery increases rapidly when >5-10 cm^3 of brain tissue receive >12 Gy.[29] In relation, 10 cm^3 represent 0.7% of the human BV with an estimate of 1′400 cm^3. Brain tumors in dogs usually do not meet the criteria of non-invasiveness and small size, in our study all of the dogs were treated with a PTV > 2.17% of the dog's BV. Consequently, such extreme treatment protocols are feasible in only few, carefully selected dogs in veterinary medicine. Volume recommendations for high doses per fraction in veterinary medicine suggest a volume for normal brain tissue at prescribed dose <1.1cm^3 (corresponding about 1.26% under the assumption of a median BV of 87.24 cm^3 as commonly found in dogs), in dogs treated with 3 × 8 Gy, to be safe in regards of complications to radiotherapy.[4] However, the high occurrence of locally invasive variants of meningioma, as well as the lack of confirmatory biopsy verifying noninvasive nature of the tumors, limits the appropriate use of extremely hypofractionated, stereotactic radiation therapy to small-intermediate size benign trigeminal nerve sheath tumors and (small) pituitary adenomas.

MRI control examinations showed marked regression of tumor volume of 19%-100% at the primary irradiated site in all dogs. Reduction of tumor burden depended on the method of measurement. Three-dimensional measurements resulted in a "greater reduction" of tumor volume than comparing the sum product of largest diameters. This effect occurs in human glioblastoma multiforme, suggesting 3D measurements to be preferred for accurate response assessment after radiotherapy.[30,31] Furthermore, 2 dogs with suspected glioma had to be excluded from comparison of 2D and 3D measurements, because of a lack of contrast uptake of the brain lesion. MacDonald's response criteria were published in 1990 for assessment of CT studies limiting their use in MRI, which has since progressed to be modality of choice in brain diagnostics.

We acknowledge the limitations of the results presented herein: The first statistical limitation was the almost-randomized design of the study impedes interpretation of the results. For statistical analysis, the "as treated" regime was applied. In this regime, the dogs are assigned to the actual treatment groups. The chronological switch from 1 protocol (group A) to another (group B) does not represent an approximation to randomization. Therefore, 2 additional "intention to treat" and "per protocol" regimes for statistical analysis aimed at adjusting for this difficulty. The "intention to treat" regime adjusts for the time cut-off by allocating the dogs treated before the cut-off to the A and otherwise to the B group independently of their actual treatment. In contrast, the "per protocol" regime considers only dogs treated before the cut-off as truly A-dogs and those treated after the cut-off as truly B-dogs. Although, some dogs before May 2015 had been treated with 10 × 4 Gy and some dogs after May 2015 were treated with 20 × 2.5 Gy, comparison of survival analysis for "as treated" with "intention to treat" and "per protocol" regimes showed only minor discrepancy. However, under the assumption of "same risk" (probability estimates of toxicosis, eg, NTCP), one had to assume less tumor control and hence we had to leave the choice of protocol to the owners. The second statistical limitation was the relatively small sample size could limit power of statistical analyses, especially in the low frequency of occurrence of expected late toxicosis and survival analysis. The 3rd statistical limitation has a large impact on the structure of statistical models. Because of the sample size, adjusting for possible confounders was hardly possible and only univariate models were considered.

A further limitation of the study was the absence of histological confirmation of the origin of the tumor in the majority of the dogs. Diagnostic imaging represents a well-established modality for tumor diagnosis. Intracranial neoplasia can quite reliably be differentiated from non-neoplastic diseases.[10,11,14–17] Nevertheless, accuracy for distinction between different tumor types with standard magnetic resonance imaging dropped to 70% in 1 study, making it difficult to rely on statistical differences between tumor types when no histology is available.[16] In addition the presumed tumor types were not evenly distributed between the 2 groups, causing a possible bias. Some authors have hypothesized that pituitary tumors treated with radiation have a more favorable outcome compared to tumors of different histologic origin. The assumption that any of the possible histotypes in dogs with intracranial tumors and having resulting signs of neurologic disease have a different outcome upon treatment has not been shown to date.[1–3,8,32] In our study, we showed a significantly inferior outcome in terms of PFI for dogs with diagnosed glial tumors compared to meningioma (P = .001), but no superior outcome for pituitary gland tumors. Another finding was the shorter PFI for dogs with severe signs of neurologic disease (P = .005), which had not been shown in similar reports.[1–3] A further limitation of the study results from challenges encountered in measuring tumor size on CT and MRI in 2 cases. One, comparing an MRI and a CT where the high concentration of fluid surrounding the tumor made the interpretation of the measurements difficult, the other showing stable tumor volume in a dog with stable signs of neurologic disease where we therefore assumed radiation to have had a positive effect.

In conclusion, the outcome, as well as the low occurrence of adverse events in dogs irradiated with this moderately hypofractionated protocol of 10 × 4 Gy for their brain tumors can be summarized as favorable. This shorter and hence less cost intense protocol provided an improved or even normal quality of life to the vast majority of dogs for a remarkable time span. When escalating the doses with this moderately hypofractionated protocol as a future route to improve local tumor control, correct positioning of the dogs, and correct target localization with image guidance as well as uniform delineation of OAR and target volumes must continuously be adhered to. In parallel to local control, potential late toxicoses resulting from lesser-fractioned protocols must also remain an important focus for the future.

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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.

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REFERENCES

1. Keyerleber MA, McEntee MC, Farrelly J, et al. Three-dimensional conformal radiation therapy alone or in combination with surgery for treatment of canine intracranial meningiomas. *Vet Comp Oncol*. 2015;13:385-397.
2. Bley CR, Sumova A, Roos M, et al. Irradiation of brain tumors in dogs with neurologic disease. *J Vet Intern Med*. 2005;19:849-854.
3. Treggiari E, Maddox TW, Goncalves R, et al. Retrospective comparison of three-dimensional conformal radiation therapy vs. prednisolone alone in 30 cases of canine infratentorial brain tumors. *Vet Radiol Ultrasound*. 2017;58:106-116.
4. Griffin LR, Nolan MW, Selmic LE, et al. Stereotactic radiation therapy for treatment of canine intracranial meningiomas. *Vet Comp Oncol*. 2016;14:e158-e170.
5. Marcinowska A, Warland J, Brearley M, et al. Comparison of two coarse fractionated radiation protocols for the management of canine pituitary macrotumor: an observational study of 24 dogs. *Vet Radiol Ultrasound*. 2015;56:554-562.
6. Bley CR. Comparison of two coarse fractionated radiation protocols for the management of canine pituitary macrotumor: an observational study of 24 dogs. *Vet Radiol Ultrasound*. 2016;57:107-108.
7. Theon AP, Feldman EC. Megavoltage irradiation of pituitary macrotumors in dogs with neurologic signs. *J Am Vet Med Assoc*. 1998;213:225-231.
8. Brearley MJ, Jeffery ND, Phillips SM, et al. Hypofractionated radiation therapy of brain masses in dogs: a retrospective analysis of survival of 83 cases (1991-1996). *J Vet Intern Med*. 1999;13:408-412.
9. Stockham AL, Tievsky AL, Koyfman SA, et al. Conventional MRI does not reliably distinguish radiation necrosis from tumor recurrence after stereotactic radiosurgery. *J Neurooncol*. 2012;109:149-158.
10. Wolff CA, Holmes SP, Young BD, et al. Magnetic resonance imaging for the differentiation of neoplastic, inflammatory, and cerebrovascular brain disease in dogs. *J Vet Intern Med*. 2012;26:589-597.
11. Young BD, Fosgate GT, Holmes SP, et al. Evaluation of standard magnetic resonance characteristics used to differentiate neoplastic, inflammatory, and vascular brain lesions in dogs. *Vet Radiol Ultrasound*. 2014;55:399-406.
12. Rock JP, Scarpace L, Hearshen D, et al. Associations among magnetic resonance spectroscopy, apparent diffusion coefficients, and image-guided histopathology with special attention to radiation necrosis. *Neurosurgery*. 2004;54:1111-1117. discussion 1117-1119.
13. Bley CR, Meier V, Schwarz P, Roos M, Besserer J. A complication probability planning study to predict the safety of a new protocol for

intracranial tumour radiotherapy in dogs. *Vet Comp Oncol*. 2017;15:1295-1308.

14. Bentley RT. Magnetic resonance imaging diagnosis of brain tumors in dogs. *Vet J*. 2015;205:204-216.

15. Lipsitz D, Higgins RJ, Kortz GD, et al. Glioblastoma multiforme: clinical findings, magnetic resonance imaging, and pathology in five dogs. *Vet Pathol*. 2003;40:659-669.

16. Rodenas S, Pumarola M, Gaitero L, et al. Magnetic resonance imaging findings in 40 dogs with histologically confirmed intracranial tumours. *Vet J*. 2011;187:85-91.

17. Turrel JM, Fike JR, LeCouteur RA, Higgins RJ. Computed tomographic characteristics of primary brain tumors in 50 dogs. *J Am Vet Med Assoc*. 1986;188:851-856.

18. Bley CR, Blattmann H, Roos M, Sumova A, Kaser-Hotz B. Assessment of a radiotherapy patient immobilization device using single plane port radiographs and a remote computed tomography scanner. *Vet Radiol Ultrasound*. 2003;44:470-475.

19. Keyerleber MA, McEntee MC, Farrelly J, et al. Completeness of reporting of radiation therapy planning, dose, and delivery in veterinary radiation oncology manuscripts from 2005 to 2010. *Vet Radiol Ultrasound*. 2012;53:221-230.

20. International Commission on Radiation Units and Measurements. *Prescribing, Recording, and Reporting Photon Beam Therapy (Report 50)*. Bethesda, MD: International Commission on Radiation Units and Measurements; 1993.

21. International Commission on Radiation Units and Measurements. *Prescribing, Recording, and Reporting Photon Beam Therapy (Report 62, Supplement to ICRU Report 50)*. Bethesda, MD: International Commission on Radiation Units and Measurements; 1999.

22. International Commission on Radiation Units and Measurements. *Prescribing, Recording, and Reporting Photon-Beam Intensity-Modulated Radiation Therapy (IMRT) (Report 83)*. Oxford, UK: Oxford University Press; 2010.

23. Ladue T, Klein MK, Veterinary Radiation Therapy Oncology G. Toxicity criteria of the veterinary radiation therapy oncology group. *Vet Radiol Ultrasound*. 2001;42:475-476.

24. Macdonald DR, Cascino TL, Schold SC Jr, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. *J Clin Oncol*. 1990;8:1277-1280.

25. Bhatti SF, De Risio L, Munana K, et al. International veterinary epilepsy task force consensus proposal: medical treatment of canine epilepsy in Europe. *BMC Vet Res*. 2015;11:176.

26. Zwingenberger AL, Pollard RE, Taylor SL, Chen RX, Nunley J, Kent MS. Perfusion and volume response of canine brain tumors to stereotactic radiosurgery and radiotherapy. *J Vet Intern Med*. 2016;30:827-835.

27. Ruben JD, Dally M, Bailey M, Smith R, McLean CA, Fedele P. Cerebral radiation necrosis: incidence, outcomes, and risk factors with emphasis on radiation parameters and chemotherapy. *Int J Radiat Oncol Biol Phys*. 2006;65:499-508.

28. Hansen KS, Zwingenberger AL, Theon AP, et al. Treatment of MRI-diagnosed trigeminal peripheral nerve sheath tumors by stereotactic radiotherapy in dogs. *J Vet Intern Med*. 2016;30:1112-1120.

29. Lawrence YR, Li XA, el Naqa I, et al. Radiation dose-volume effects in the brain. *Int J Radiat Oncol Biol Phys*. 2010;76:S20-S27.

30. Thomson CB, Haynes KH, Pluhar GE. Comparison of visual metric and planimetry methods for brain tumor measurement in dogs. *Am J Vet Res*. 2016;77:471-477.

31. Gladwish A, Koh ES, Hoisak J, et al. Evaluation of early imaging response criteria in glioblastoma multiforme. *Radiat Oncol*. 2011;6:121.

32. Kent MS, Bommarito D, Feldman E, Theon AP. Survival, neurologic response, and prognostic factors in dogs with pituitary masses treated with radiation therapy and untreated dogs. *J Vet Intern Med*. 2007;21:1027-1033.

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