Definitive-intent uniform megavoltage fractioned radiotherapy protocol for presumed canine intracranial gliomas: retrospective analysis of survival and prognostic factors in 38 cases (2013-2019).

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Abstract

Background: Radiotherapy (RT) is currently considered the treatment of choice for presumed canine intracranial gliomas. However, variable therapeutic responses are described, due to heterogeneous populations and different radiation methods or protocols. Only one study dedicated to intracranial suspected glioma highlighted prognostic criteria. Determination or confirmation of specific clinical and imaging prognostic factors may guide the therapeutic management of these tumors. The objectives were to provide data on long-term clinical outcome (including quality of life, QoL) and to determine specific prognostic factors associated with survival time. We report a single-institution retrospective study, including all dogs with suspected symptomatic primary solitary intracranial glioma, treated with a complete uniform fractionated megavoltage radiation protocol of 15x3Gy over 5 weeks, between January 2013 and February 2019. Thirty-eight client-owned dogs were included. Medical records were retrospectively evaluated for median overall survival time (MST), clinical and imaging responses. Prognostic factors on survival were researched in terms of signalment, clinical presentation, tumor imaging characteristics and response following RT. Finally, the RT’s impact on the dogs’ clinical signs and QoL were evaluated by the owners.

Results: The MST was 698 days (95% CI: 598-1135). Survival at 1 and 2 years were respectively 74.2±7.4% and 49.0±9.8%. Initial clinical signs were related to survival, as well as tumor characteristics such as cystic-pattern, mass effect and Tumour/Brain volume ratio. No significant adverse effect or radiotoxicity was observed.

Conclusions: RT appears as a safe and effective treatment for canine intracranial gliomas, allowing long-term tumor control, improvement of life’s quality and management of associated clinical signs. The initial clinical signs and MRI descriptions (Tumour/Brain volume ratio, cyst-like lesion and mass effect) may help predict the prognosis.
Keywords: brain tumor, glioma, MRI, IMRT, 3D-Conformal radiotherapy, fractionated radiotherapy, megavoltage, outcome, prognosis, quality of life.

Background

Gliomas are the second most frequent primary brain neoplasm in dogs, accounting for approximately 35% of all the central nervous system (CNS) primary tumours [1, 2]. It represents a pleomorphic group arising from glial cells and mainly includes astrocytomas and oligodendrogliomas [3, 4]. Most gliomas occur in adult dogs with median age of 8 years [1, 2]. Brachycephalic breeds as Boxer, Boston terriers, French and English Bulldogs seem to be at risk [1, 2]. Histology is the gold standard for definitive diagnosis of tumour’s type and grade, but remains rare because of practical, financial and safety considerations. Routinely, the presumptive antemortem diagnosis of intracranial tumour is based on signalment data and compatible magnetic resonance imaging (MRI) (imaging modality of choice), or Computed Tomography (CT) characteristics.

Several treatments options exist: symptomatic treatment (glucocorticoids and anticonvulsants), cytotoxic chemotherapy, surgery, radiotherapy (RT) and more recently immunotherapy [5, 6] or even entotherapy [7] (image-guided intratumoural chemotherapy treatment). Currently, RT is considered the treatment of choice for intracranial tumours in dogs [8-11]. Its objective is to induce tumour cells’ death or inhibit its further reproductions, while minimizing damage to any normal tissue surrounding or in the irradiated volume. The majority of studies on irradiation of brain neoplasms concerns all types of tumours, most cases being meningiomas [9, 12-20] and only one recent case study is exclusively dedicated to gliomas [10].

As reported in the largest studies on external fractionated megavoltage RT for animals with intracranial gliomas, the median overall survival time (MST) variates from 226 to 430 days [9-11, 13] and disease-specific survival reaches 772 days [11]. These discrepancies may be due to heterogeneous population dogs and tumour types/grade, multiple radiation protocols and various evaluation criteria. According to recent publications, only initial clinical signs and relative tumour volume appear to be prognostic criteria.
Hence, dogs with severe neurological signs (non-ambulatory state, dysphagia) [13] or depressed mentation [10, 13] have significantly lower survival time than dogs with no or mild clinical signs, and dogs with relative tumour volume under 5% of the total calvarial volume, live significantly longer [10]. However, these results are not systematically observed, and controversies persist on statistical significant criteria dedicated to gliomas [11, 14, 19, 20]. Furthermore, studies failed to demonstrate the prognostic significance of tumoral MRI features (pre-radiation MRI characteristics or tumour progression after RT) [14, 19, 20].

The aim of the present study was to provide data on long-term clinical outcome (including quality of life, QoL) in dogs with suspected primary solitary intracranial gliomas, solely treated with uniform fractionated megavoltage radiation protocol. The other objective was to determine glioma-specific prognostic factors (epidemiological, clinical and image-based) associated with survival time.

**Results:**

Of the 46 dogs presented for radiation therapy for suspected symptomatic intracranial glioma, to the authors’ institution, 38 dogs met the inclusion criteria for the study. Two dogs were excluded because of treatment discontinuation due to neurological deterioration and MRI confirmation of tumour progression. Six dogs that underwent a second radiation protocol, because of local or metastatic recurrence, were also excluded (Figure 1).

**Dogs and tumour characteristics**

Thirty-eight symptomatic dogs were considered in the study: 14 intact males, 3 neutered males, 5 intact females and 16 neutered females, with a median age of 8.2 years (mean 8.1, range 4.5–12.5 years) and a median weight of 13.1 kg (mean 18.1, range 3.7-37 kg). All dogs were pure breeds. The cohort included 20 French bulldogs, 3 boxers, 3 English bulldogs, 2 Cane Corso dogs, 2 Maltese dogs and 1 each of 8 other breeds, which represented 27 brachycephalic dogs (71%), and 11 non-brachycephalic dogs (29%).
None of the dogs had evidence of life-compromising disease or unexpected metastases based on whole-body CT (Computed Tomography) scans. The main presenting complaints at the first clinical examination included seizures (35/38), behavioral changes (8/38), circling (6/38), altered mentation (5/38), proprioceptive deficits (3/38) and ataxia (2/38). Thirty-five dogs were presented with a history of seizures (92.1%) and 23 of them (23/35, 65.7%) showed seizures as their only sign of neurologic disease. Seizure frequency was detailed in 33 dogs, 16 dogs had clusters seizures and two had demonstrated status epilepticus. During the first neurological examination, abnormalities were graded as absent in 23 dogs (seizures only), mild/moderate in seven dogs and severe in eight of 38 dogs.

Thirty-seven tumours were supratentorial, and a single one was infratentorial. Specific localization was frontal for 15 cases, parietal/temporal for 20 cases, occipital for two cases and caudal fossa for one case (brain stem). All details are reported in Table 4.

**Treatment**

Treatment with 15x3 Gy was planned for all dogs. The first radiation session occurred in a median of 10 days after the diagnostic MRI, and five days [Range 3-10] after the planning CT simulation. Thirty of the 38 dogs (78.9%) were treated with 3D-CRT (3-dimensional conformal radiation therapy) and 8/38 (21.1%) with IMRT (Intensity-modulated radiation therapy). A median of three fields was used for 3D-CRT (Range 3-5) and five for IMRT. No treatment interruption was reported.

All irradiated dogs received between 0.5 mg and 1 mg/kg/q24 of methylprednisolone, between 1.5 and 6 months, gradually tapered after the first MRI-recheck. No direct life-threatening secondary effect have been noticed, even if some dogs showed mild polyuria-polydipsia, typical pot-belly appearance and diffuse truncal alopecia.

All the patients presented with seizures received anticonvulsant treatment. They were maintained during the entire duration of the follow-up period and adapted to the seizure frequency and anticonvulsants serum levels.
All animals were followed for at least 49 days to a maximum of 1492 days, and at least 241 days until 1492 days for alive dogs at the end of study. The median duration of follow up was 561 days. At the end of the study, 18/38 dogs (47.3%) were dead, 20 dogs (52.7%) were alive (Figure 1).

Clinical follow-up and Outcome

The majority of dogs having completed the RT, were re-evaluated (clinical and MRI control) for the first time, approximatively three months after the last session of irradiation, then every two to six months. Twenty dogs had at least a second control. Ten dogs had more than three control MRI.

A significant majority of dogs showed neurologic status improvement within the five weeks of the RT (proportion of dogs with improved neurologic status = 0.86 (95% CI: 0.76-0.97, p value <0.001). In detail, 34/38 dogs showed improved neurological status at the last RT session, 1/38 showed deterioration due to seizures and three dogs were judged as stable. Further improvement was noted after the sessions for 14 dogs, mainly due to improved behavior, and according to neurological examinations realized in the clinic (proportion=0.41 [0.26-0.55], p value=0.85). During the follow-up period, an improvement or normalization of neurological status was observed in all but one seizuring dog (see below).

Thirty-three dogs initially presented with seizures had follow-up characterization of the seizures (frequency and occurrence of clusters/status epilepticus). Thirty dogs (30/33, 90.9%) showed reduction of frequency and/or intensity (disappearance of cluster /status epilepticus) of seizure. This corresponded to a significant majority of dogs with reduced seizure (proportion=0.91 95%CI: 0.82-1.00, p value < 0.001). Seizures increased in frequency during RT for one dog, despite absence of peritumoural edema and decrease of tumour size on three consecutive repeat MRI scans over a 10 month’s period. The seizures stopped with aggressive anticonvulsant treatment and the dog was still alive 706 days after the first session without further seizure.

None of the dogs showed apparent late radiation toxicosis characterized by slow progressive neurologic signs occurring more than six months after the RT. For all dogs, subacute worsening or recurrence of neurologic signs, identical to initial presentation, were the cause of death or euthanasia.
**Image-based Follow-up**

On the first control, 34 diagnostic control MRI examinations were available for assessment according to the RECIST categorization: 22 with initial enhancing tumour (22/34, 64.7%) and 12 without enhancing tumour or presenting non-measurable enhancement (12/34, 35.3%). For dogs with enhancing tumour, response to treatment was Complete Remission (CR) in 13/22 (59%), Partial Remission (PR) in 5/22 (22.7%), and Stable Disease (SD) in 4/22 (18.1%). Progressive disease was not observed. The mean decrease of tumour size was 75% between the diagnosis and the first control (decrease of T1-WI+ LD).

Taking into account the 12 others non-enhancing tumours, 15 cases were classified as CR (15/34, 44.1%) and 19 cases were classified as PR/SD (19/34, 55.9%). All dogs had minimal to marked shrinkage of the mass and a reduction of the mass effect. Additional images show different responses to radiotherapy in an additional file (Additional file 6).

During follow-up, seven dogs that had completed the RT and had normalization of initial clinical signs, presented with clinical signs consistent with brain and/or cervical spinal cord disease, by a median of 229 days after the last session. Local tumour progression and new lesions localized in the brain or in the cervical spinal cord were observed on control MRI in two dogs and five dogs respectively. In those five cases, the initial lesion was stable (1/5), or had shown complete (2/5) or partial (2/5) remission. These new lesions were considered as metastatic disease. In one dog, neoplastic cells were found on CSF analysis and necropsy revealed metastases of an anaplastic oligodendroglioma in another dog. This dog was the only confirmed histologic diagnosis in our study.

**Survival analysis and prognostic factors**

The median overall survival time (MST) was 698 days (95% CI: 598-1135) (Figure 2). The estimated survival probability at 1 and 2 years were 74.2±7.4% and 49.0±9.8%, respectively.
Univariate analysis

Based on univariate analysis, initial neurological signs, MRI-cystic pattern and mass effect showed a significant influence on survival at the level of 5% (Table 3 and 4). Statistical survival at 1 year and 2 years according to these significant prognostic factors are summarized in Table 5 and KM survival curves are provided in Figure 3.

Dogs without neurological deficit observed at diagnostic consultation, or only presenting seizures, had a MST of 1135 days (95%CI: 984-inf), a 2-years probability of survival (S2y) equal to 71.0±11.7% compared to a MST of 494 days (95%CI :310-inf) and S2y =18.6±11.6% for dogs having initial neurological signs whatever their severity.

Considering significant MRI characteristics, dogs without cystic tumour had a MST of 984 days (95%CI: 666-inf) and a S2y equal to 59.2±11.6% compared to MST of 494 days (95%CI: 309-inf) and a S2y equal to 21.0%±17.0% for dogs with cystic tumour. Considering mass effect, dogs with moderate mass effect will present a better S2y and a better survival compared with dogs with severe mass effect: 61.4±11.9 versus 26.9±15.1%, and 984 days (95%CI : 620-inf) versus 666 (95%CI : 310-inf) respectively

Multivariate analysis

Additional significant variables in the univariate analysis at the level of 20% included in the multivariate Cox model were the cortical sulci disappearance, location tumour, edema, T2 hyperintensity homogeneity, tumour volume and Tumour/Brain Volume ratio. After step by step variables selection, neurologic deficits-based scale and Tumour/Brain Volume ratio were the only variables remaining significantly associated with survival (Figure 4). The regression coefficient estimated for neurologic deficit based scale was 1.89±0.58 (p value Wald test=0.001) corresponding to a Hazard ratio of 6.6, while the regression coefficient estimated for the Tumour/Brain Volume ratio was 0.13±0.05 (p value Wald test=0.02) indicating that a 1% increase in the tumour/Brain Volume ratio is associated with an increase of risk of death by 14%.
**Evaluation of dogs QoL based on owner’s opinion**

Owner questionnaire was available for 24 owners. Four owners reported a mild weakness of their dog during the first week of radiation, which disappeared at the second week of treatment. Owners’ perception of QoL was assessed with a Likert 10-value scale (1-Could not be worse and 10-could not be better). The median QoL score before diagnosis was 6 (range 3 to 7). After the radiation therapy, the median QoL was 9 (range 5 to 10). Twenty-three responders stated that the QoL of their dog was stable or had improved with the radiation therapy, which corresponded to a significant improvement of QoL score after radiation therapy (one sided Wilcoxon signed rank test z=-7.96, p value<0.001). Improvement was observed within the first three weeks of radiation for the majority of cases (21/24). Among those 21 dogs, 11 (52.3%) were classified as PR (4/11) or SD (7/11) and 19 had ongoing corticosteroids treatment for at least one week.

**Discussion:**

The present study retrospectively described the outcome in 38 dogs treated with a complete uniform fractionated megavoltage radiation protocol of 15x3Gy. To the author’s knowledge, it belongs to the largest studies on external RT as the sole treatment of presumed canine symptomatic intracranial glioma. MST was 698 days for dogs that underwent the entire protocol, with 74.2% of animals surviving more than one year and 49.0% more than two years. Previous evaluating intra-axial tumours studies, have determined MST following several treatments. In symptomatic protocols (corticosteroids and anticonvulsants) MST doesn’t exceed 3.5 months (35-94 days)[10, 37-39] and surgery doesn't offer a significant gain in terms of survival[40] compared to symptomatic treatment. Although chemotherapy is often an essential part of the therapy for human patients with intracranial gliomas[41], its benefits remains unclear in veterinary medicine[10, 37, 38]. A recent meta-analysis concerning brain tumour treatment[42], reported a median overall survival time of 226 days for RT-treated intra-axial tumours (range median of 60 to 437 days), based on 127 dogs. Data analysis and interpretation were complicated
by the use of different RT methods (orthovoltage, Cobalt radiotherapy, hypo to hyperfractionated).

When considering only recent largest studies on megavoltage RT-treated canine intracranial intra-axial
tumours, MST variates between 226 and 430 days [9-11, 13]. Disease-specific survival for intracranial
intra-axial tumour is available in only one study, and reached 772 days [11]. Then, based on our results,
a protocol of 15 fractions of 3 Gy spread on five weeks, seems to offer an interesting therapeutic
alternative associated with an apparent benefit on life expectancy, compared with symptomatic
treatment, without evidence of deleterious life-threatening early/early delayed radiation toxicosis. This
protocol was also associated with significant improvement of clinical signs, better control of seizure and
lack of evident adverse reactions. This is in accordance with a recent study [43] that demonstrated a
significant benefit of external megavoltage radiotherapy on seizure freedom period, compared with
symptomatic treatment, on dogs with intracranial tumours.

Even if comparison with other publications is problematic because of RT protocols’, study designs’ and
populations’ variabilities, several particularities of our study may have influenced the survival. The
majority of actual megavoltage RT protocols applies between 10 to 20 fractions of 2 to 4 Gy, over three
to five weeks, on consecutive or alternate days, making our protocol theoretically comparable in terms
of Biologically effective dose (BED) or toxicity [44]. However, unlike previous reports [10, 11], we
applied it homogeneously to a large number of dogs (previous populations studied do not exceed 22
dogs), without changing it to the tumour characteristics (size, imaging grade or location). Moreover,
because of a long study period and because all deaths were, potentially, attributable to the
tumour/tumour’s treatment, we were able to include animals with longer follow-up and determine a
MST comparable to disease-specific survival, that may have influenced the final survival results.

Finally, the prolonged use of corticosteroids may also contribute to the results, by reducing perilesional
edema and potential secondary radiotoxicity. The impact of a prolonged corticosteroid therapy is to be
proved in large comparative prospective studies on intracranial gliomas. Based on statistical results, the
RT delivery method (3D-CRT or IMRT) did not influence survival. This result is in accordance with a
recent study evaluating IMRT on primary brain tumours [45] showing comparable survival time and
clinical toxicity compared to previously published data on 3D-CRT.
According to the owner’s perception, the QoL of the dogs was significantly improved. Improvement was usually noted during the first three weeks of the protocol for most dogs, even for dogs without significant tumour reduction at the first control MRI or those with prior symptomatic treatment. Based on these findings, despite the theoretical prominent delayed effect of radiotherapy on neoplastic cells, an early beneficial effect may exist, and clinical improvement could be expected even during the course of the protocol. This information could be crucial in the owner’s decision to treat, generally in relation with the initial clinical status of their dog. This finding has been already reported [10, 11, 14, 16], and the exact mechanism of this assumed early effect, independent of the tumour-reduction mass effect, is not clearly understood. Actions on microscopic brain infiltration or on peri-tumoural edema or inflammation may be suspected. Serial follow-up MRIs during radiation therapy may reveal early changes, supporting this theory.

In our study, initial clinical signs were statistically related to survival. Two recent publications on canine megavoltage RT, one dedicated to gliomas [10] and one concerning all types of intracranial tumours [13], are in accordance with this observation, even if this finding remains controversial [11, 14, 20] in others studies, with all types of intracranial tumours considered. After adjustment for the other factors of variation, the initial neurological sign remains significant linked with survival. Dogs only presenting seizures as first complaint, will live statistically longer than dogs presenting other signs, regardless of their severity.

In accordance with the literature, among image-based MRI criteria, the relative tumour-volume [10, 13] was the strongest significant factor associated with survival. In our study, cyst-like lesions and mass effect were significantly associated with poorer outcome in the first-step univariate analysis. MRI cyst-like lesions can mainly be due to necrosis or fluid production by the tumour itself [49] and are normally suspected, based on their T1/T2 signals and margins characteristics. We decided not to differentiate necrosis areas with true cystic areas because MRI doesn’t seem to be sensitive enough to allow the specific distinction [49]. Necrosis is a typical aspect of histological high-grade glial tumour [4, 46, 47]. Therefore, MRI cystic-like lesion could reflect the histological grade tumour, then might be associated with survival. However, no statistical association had been demonstrated between MRI cystic-like
component and tumour grade [47, 48]. Moreover, to the authors’ knowledge, association between MRI
cyst-like lesions and survival has never been studied. Our results may suggest the inclusion of this MRI
criterion in future studies.

Unlike previous published data concerning RT-treated meningiomas [16] or all types of intracranial
tumours [14], severe mass effect is statistically related to a poor prognosis in our study. This may reflect
that, although the tumour size is not statistically significant, mass effect, resulting from a combination
of location, volume, edema, hemorrhage and infiltration characteristics, has to be considered. After step
by step variables adjustment, those variables were not statistically significant in the multivariable
analysis, then, cannot be considered strong statistical factors.

Contrast enhancement has been described as a significant criterion associated with high-grade gliomas
[4, 48] that can reflect neovascularization, vasodilatation or alteration of the blood-brain-barrier, all
features associated with aggressive tumours [50]. In our study, contrast enhancement (presence and
characteristics) was not associated with survival, illustrating that other factors might be important to
predict histological grade on MRI or, less probably, that histological grades might not be associated with
survival in treated dogs. As a consequence, in a context where predictability of glial tumour type or
grade is indeed considered moderate with CT, or even with high field MRI [47, 48, 51], only the
statistical significance of the objective Tumor / Brain Volume ratio may be useful improve the prognosis
without histological analysis.

Several imaging-based brain tumour response criteria have been described and used in veterinary
medicine [34], according to human literature and experience. They allow an objective evaluation of
therapeutic response and can constitute an important part in the study of clinical management of brain
tumours in veterinary patients. Nonetheless, no consensus has been established. In our study, we decided
to choose the RECIST criteria implemented by clinical assessment and taking into account the lesion’s
T2-WI hyperintensity (excluding suspected peri-tumoural edema). This can allow specific assessment
of non-enhancing tumour, that can be observed in canine glial tumours. However, according to statistical
analysis, we did not highlighted any link between RECIST criteria and survival, neither between T1LD
variation and survival, as suspected in previous study [19]. Therefore, the categorization of CR or ST
might not preclude a longest survival time. RECIST criteria may help homogenize therapeutic response
assessment in future studies, but its association with survival might not be significant. Our statistical
conclusions are limited by relatively small sample sizes in classification subgroups. Furthermore, small
numbers of non-censored dogs as time progresses are associated with larger standard errors.

In this study, seven dogs had evidence of progressive disease during the follow-up period, including two
dogs with local recurrence and five dogs with meningeal or parenchymal intracranial or spinal cord,
multifocal suspected metastasis without evidence of local recurrence. The occurrence of metastatic
intracranial glioma is not clearly defined in canine medicine, even more in irradiated animals [10]. In
our study, only two dogs had cytological or histological confirmation of the diagnosis of metastatic
disease. This finding could be of interest for further studies describing the occurrence of secondary
metastatic disease of intracranial gliomas. It might suggest that chemotherapy might be an additional
treatment to RT to limit dissemination.

Several limitations can be discussed. One is the lack of histopathological analysis to confirm glioma and
their grade. However, MRI have been demonstrated to be a sensitive and specific tool to detect
neoplastic lesions and diagnose tumour type (extra/intra-axial), particularly gliomas [30, 49], even more
when clinical information and epidemiological data are considered [23, 25, 30]. However, vascular
disease may lead to false diagnosis and cerebrovascular strokes may be misdiagnosed as gliomas [25,
30]. In order to decrease this risk of misdiagnosis, several measures have been taken:

- Clinical and epidemiological information’s of each dog were available for the reviewers.

- The presence of mass effect was an inclusion criterion, which is considered discriminant between
  ischemic infarct and neoplastic disease [21, 25, 26].

- The DWI and signal analysis on ADC Map were incorporated in the MRI characteristics. Although
definitive diagnosis cannot be done in Humans or animals based on DWI [52, 53], it may help in the
differentiation between gliomas and acute infarction with low ADC and high DWI signal [8, 25]. These
MR lesions were therefore excluded.
The retrospective nature of the study didn’t permit to obtain all the questionnaires and their homogeneous fulfilling (anonymously and at the same point during the follow-up period) and lack of necropsy didn’t allow to establish the exact death’s cause, tumour recurrence or radionecrosis, in dogs with neurologic worsening.

**Conclusion**

In conclusion, external megavoltage radiation therapy with fractionated protocol (15x3 Gy, for five weeks), for dogs with primary suspected intracranial glial tumours, provides a long-term tumour control with a reasonably low risk of symptomatic complications and a significant early and persistent improvement in the dogs’ quality of life. In our study, the initial neurologic deficits and the Tumor/Brain Volume ratio are statistically related to survival as in previous studies. Our results also suggest that MRI cyst-like lesions and mass effect may be of prognostic interest.

**Materials and Methods:**

**Study design:**

Retrospective observational study.

**Dogs and tumour characteristics**

The database of the neurology service of the authors’ institution was searched for dogs with presumptive symptomatic intra-axial brain tumours that had been treated with fractionated radiation therapy as a primary treatment modality (between January 2013 and February 2019). The protocol has to be entirely completed. All dogs had full clinical and neurologic examinations performed before the radiation protocol. The presumptive diagnosis of intracranial glioma was made on signalment, history, neurological symptoms and compatible MRI characteristics, based on veterinary neurologist and human radiologist interpretations. MRI features consistent with glial tumour included the identification of a
solitary intra-axial lesion exerting a mass effect and characterized by an altered T2 signal [8, 21-23] with variable contrast enhancement (ranging from none to variably intense, non-uniform or ring-like enhancement) and possible perilesional edema. In order to streamline our data and homogenize final information with anterior studies, we decided to consider, at least, inclusion and exclusions criteria, descriptions indices and gradings (clinical and imaging, not correlated with histological analysis) previously described.

The clinical-imaging exclusion criteria were inspired by Dolera [10], and implemented as followed:

- Previous chemotherapy or surgical treatment of the tumour;
- Lesion localization close to a vascular territory of a main cerebral artery or a perforating artery with sharp demarcation [26], strong hyperintensity in the diffusion image and hypointensity on ADC (Apparent Diffusion Coefficient) map [24-26];
- Fever/other symptoms or blood abnormalities correlated with inflammation, presence of any predisposing factor to infection, image characteristics of an abscess (T2-Weighted images (T2-WI) hypointense peripheral rim or peripheral concentric “onion skin like” hypointense rim, thick strong peripheral rim contrast enhancement [27] or a granuloma (dural contact, T2-WI hypointensity) [28] and concurrent findings of meningitis [28,29]; these aspects were considered indicative of inflammatory diseases [30];
- Well defined rounded structure, isolated or in continuity with ventricles and cisterns with thin, smooth non-enhancing walls and content resembling cerebrospinal fluid (CSF) or fat, that did not display contrast enhancement, were considered congenital intracranial cysts (arachnoid or dermoid cysts) [31].

Data from the medical records were reviewed, including breed, age, sex, weight, neurological status and seizure history at the time of presentation, additional treatments and survival time. For evaluation of prognostic factors, the initial clinical signs were classified by a board-certified neurologist, according to a neurological scale based on their severity and the presence or absence of seizures [11, 20, 32] (Table 1).
All dogs had a complete whole-body CT scan (16-row multidetector helical CT unit GE Healthcare), before and after administration in a cephalic vein of 2 mL/kg body weight of sodium and meglumine ioxotalamate IV, ventilation being manually controlled in all dogs, and scans made at the end of inspiration to evaluate potential co-morbidity, that could modify the therapeutic decision and outcome.

All MRIs were conducted using a 1.5-T MRI scanner (1.5-T GE Healthcare) and performed prior to the beginning of radiation protocol. Imaging sequences were obtained in 3mm transverse T2-WI, T2 fluid-attenuated inversion recovery (T2-FLAIR-WI), transverse diffusion-weighted echo planar pulse sequence (DWI, b-value 1000 s/mm2), T2*-weighted gradient record echo (T2*-WI) or Susceptibility Weighted images (3D gradient Echo, SWAN sequence), and 0.8 mm 3D-T1-weighted images (T1-WI), before and after intravenous injection of a contrast medium (T1-WI +). For post-contrast images, Gadoliamide (Dotarem; Guerbet, France) 0.05 mmol/mL was administered intravenously at the dose of 0.2 mL/kg.

With regard to tumour characteristics, images were reviewed and 14 description criteria were considered (Table 2). Some of them were used to determine an imaging grade previously defined by Dolera [10]. The grading system is reported in an additional file (Additional file 1). Tumour volume (GTV volume) and the Tumour/Brain volume ratio were computed for each dog and added to the tumour characteristics reported in the Table 2. Finally, the grade and all the tumour criteria were then evaluated for prognosis evaluation.

**Treatment**

All dogs were treated with external beam megavoltage RT. Radiation protocol for all dogs consisted of 15 sessions of 3 Gray (Gy), spread on five weeks, on a Monday-Wednesday-Friday schedule to a total dose of 45 Gy. Radiation was delivered with a 6-MV linear accelerator (Clinac iX, Varian, Palo Alto, California) equipped with a 5-mm leaf-width multi-leaf-collimator, using 3D-CRT or IMRT. Additional details on the radiotherapy protocol description are summarized in an additional file (Additional file 2).
All irradiated dogs received approximately, 0.5 mg/kg/q24, methylprednisolone sodium succinate during the RT protocol until, at least, the first follow-up. When seizures were reported, anticonvulsants treatment were recorded.

Clinical and image-based follow up
Clinical and neurological examinations were performed at least once a week during the irradiation period and at the last session of the protocol. After the treatment period, dogs were re-evaluated (clinical and MRI control) for the first time, approximatively three months after the last session, then every two to six months. Evolution of neurological signs and corticosteroid therapy were carefully recorded allowing detection of potential early/early delayed radiation toxicity between last session and first control. Neurological status’ evolution was then retrospectively evaluated as “stable”, “improvement” or “degradation” at the last radiation session and at the first post-radiation consultation, based on follow-up informations, gathered from medical records. Specific response evaluation criteria were established to assess regression after irradiation, and observed on the first control MRI. The MRI evaluation was performed according to the revised Response Evaluation Criteria in Solid Tumour (RECIST) categorization implemented with clinical status[30]. In case of enhancing lesions, it was based on a one-dimensional tumour measurement of enhancing lesions on transverse T1-WI+ or, in case of non-enhancing lesion, it was based on a two-dimensional tumour measurement on transverse T2-WI [33, 34]. The categorical assignment criteria are reported in an additional file (Additional file 3). For dogs that were not re-evaluated by ourselves, referring veterinarians and owners were interviewed by phone by one of the authors. Death was attributed to the tumour or to the RT, if intracranial neurological signs were reported.

Evaluation of dogs’ quality of life based on owner’s opinion
Information regarding owner appreciation was obtained using a standardized questionnaire (Additional file 5). The questionnaire was distributed to the owners after completion of the radiation protocol: at their first re-evaluation, sent by e-mail or fulfilled by telephone with one of the authors, between two months and four years after the radiation therapy. The goal was to determine owner’s perception of the clinical sign’s evolution and quality of life (QoL) of their dogs before, during, just after RT and during the follow-up period, and evaluate their opinion about their decision to treat.

**Statistical analysis**

To test if a majority of dogs showed improvement of their clinical status, the proportion of animal showing improvement for each of the clinical criterion was compared to 0.5 using one-side z-test. Data were encoded in Excel and analyzed with R (version 3.5.3, Vienna, Austria). Animals that didn’t complete the entire RT protocol were excluded from the statistical analysis. All deaths were considered events. Dogs lost to follow-up and dogs alive at the time of reporting were censored. Survival time or time until censoring were defined from the first session of the RT protocol.

In a first step of the analysis, population survival probabilities were calculated using Kaplan–Meier (KM) approach. Log-rank tests were also used to assess in univariate analysis the effect of each cross classified epidemiological, clinical, and imaging variables, as well as radiation therapy type (3D CRT/IMRT) on survival curve, and to recodify the factors, keeping biological meaning, by gathering classes which survival did not significantly differ. Cox proportional hazard model and likelihood ratio test were used in univariate analysis to assess the effect of continuous variables (significant $p$ value < .05). In addition, in a second step of the analysis, multivariate analysis was performed using Cox proportional hazard model. All factors with $p$ value lower than 0.2 in the first step of the analysis, were included in the saturated Cox model. Variables were then selected by step by step descending procedure using the likelihood ratio test as selection criterion to obtain the reduced Cox model. The proportional hazards assumption was checked using the Schoenfeld residuals for each variable included in Cox models. R Survival package was used for the analysis (A Package for Survival Analysis in R. R package version 3.1-12, https://CRAN.R-project.org/package=survival).
Improvement in the QoL was tested by comparing QoL during and after RT using one sided Wilcoxon signed rank test.

**Abbreviations:**

3D-CRT: 3-dimensional conformal radiation therapy

ADC: Apparent Diffusion Coefficient

BED: Biologically effective dose

CNS: Central nervous system

CR: Complete remission

CSF: Cerebrospinal fluid

CT: Computed tomography

CI: Confidence interval

DWI: Diffusion-weighted images

GTV: Gross volume tumor

Gy: Gray

IMRT: Intensity-modulated radiation therapy

IV: intravenous

KM: Kaplan-Meier

MRI: Magnetic Resonance Imaging

MST: Median overall survival time

PD: Progressive disease
PR: Partial remission

PTV: Planning target volume

QoL: Quality of life

RECIST: Response Evaluation Criteria in Solid Tumor

RT: Radiotherapy

S2y: 2-years probability of survival.

ST: Stable disease

T1LD: T1-WI longest diameter

T2-WI: T2 weighted images

T1-WI: T1 weighted images

T1-WI+: T1 weighted images post-contrast

T2-FLAIR-WI: T2 fluid-attenuated inversion recovery weighted images

T2*-WI: T2* weighted images

Declarations

Ethics approval and consent to participate

Authors declare no Institutional Animal Care or other approval was needed.

Consent for publication

Not applicable

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interests**

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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**Author’s contributions**

MD and JLT collected the clinical data, reviewed the MRI images and drafted the manuscript. ID performed the statistical analysis. FD, PDF and PD participated in the collection of the radiotherapy informations. MND participated in the images’ review. All authors read, corrected and approved the final manuscript.

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Legends:

**Table 1**: The neurologic deficit-based scale considers neurological abnormalities observed during the neurological examination performed at the diagnostic consultation [11, 20, 32]

**Table 2**: Pre-radiation MRI characteristics used for tumor description and statistical analysis [11, 14, 16, 19].

**Figure 1**: Diagram illustrating the study population (Orange writings: censored animals).

**Figure 2**: Kaplan-Meier cumulative survival plot for dogs with suspected symptomatic gliomas that had completed the entire RT protocol (gray zone representing 95% CI). Ticks indicate censored observations. Vertical dotted lines representing 1 and 2 years survival, dashed lines representing median survival time.
**Figure 3:** (a-c) Kaplan-Meier cumulative survival plot for dogs with suspected gliomas that had completed the entire RT protocol (a: according to tumor-mass effect; b: according to tumour-cystic pattern; c: according to neurological deficits-based scale). Ticks indicate censored observations. Initial neurological signs, MRI-cystic pattern and mass effect have a significant influence on survival ($p < .05$).

**Figure 4:** Forest plots of the Hazard ratio and their 95%CI intervals associated with neurologic deficits-based scale and Tumour/Brain Volume ratio.

**Table 3:** Epidemiological and clinical criteria used for statistical analysis on 38 dogs that had completed the entire RT protocol. Results of univariable statistical analysis on survival (Log-rank tests). Neurologic-deficit-based scale was recodified to allow significance significant effect on survival.

**Table 4:** MRI image-based criteria used for statistical analysis. Results of univariable statistical analysis (KM and Log-rank tests for cross classified variables, Cox regression model and LRT test for continuous variables). MRI-cystic pattern, tumor location and mass effect have a significant effect on survival ($p < .05$).

**Table 5:** Statistical survival according to significant criteria based on results of univariate analysis (Log-rank tests, $p < .05$; standard error: s.e)

**Additional file 1:** MRI-based tumour grade classification according to Dolera [10].

**Additional file 2:** Radiotherapy protocol description.
**Additional file 3: RECIST criteria implemented with clinical evaluation [20, 33, 34]:**

MRI enhancing lesions are designed as enhancing lesions visualized on transverse T1-WI+. MRI non-enhancing tumours are designed as well delimited T2-hyperintensity (suspected vasogenic edema, corresponding to diffuse T2 hyperintensity of the surrounding white matter, was excluded), visualized on transverse T2-WI. For enhancing tumours, the longest diameter (LD) across the contrast-enhancing lesion on transverse T1-WI+ was measured and reported as the baseline diameter (*T1-WI+ LD*). Non-enhancing tumour’ surface were calculated as the product of the longest perpendicular diameters (*T2 surface*, mm²).

**Additional file 4:** Radiation toxicities, definitions and grades of radiation toxicities used in the study (according to the Veterinary Radiation Therapy Oncology Group) [35, 36].

**Additional file 5:** Owner questionnaire.

**Additional file 6:**

**Figure a:** Right frontal MRI-grade II glioma. A, B: Pre-treatment T2-WI (A), T1-WI+ (B).

C,D: Three months post-RT. T2-WI (C), T1-WI+ (D). These images show complete response with disappearance of contrast-enhancement and residual cavitation (arrow, T2-WI hyperintensity, T1-WI and T2- FLAIR WI hypointensity, data not shown).

**Figure b:** Right piriform MRI-grade III infiltrating glioma. A,B: Pre-treatment T2-WI (A), T1-WI+ (B). Absence of contrast enhancement.

C,D: 2 months post-RT. T2-WI (C), T1-WI+ (D). These images show partial/stable disease with decreased T2-WI hyperintensity.

**Figure c:** Left piriform MRI-grade IV glioma. A,B: Pre-treatment T2-WI (A), T1-WI+ (B).
C,D: Four months post-RT. T2-WI (C), T1-WI + (D). These images show partial response with persistent diffuse contrast enhancement (dotted arrow).