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RESEARCH ARTICLE

STEREOTACTIC VOLUME MODULATED ARC RADIOTHERAPY PROTOCOL FOR CANINE INTRACRANIAL MENINGIOMA.

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Abstract

Objective: to assess High Dose Hypofractionated Volume Modulated Arc Radiotherapy (HDH-VMAT) feasibility and clinical efficacy in canine meningiomas.
Design: a prospective study was conducted on thirty-three patients with a presumptive diagnosis of encephalic meningiomas assumed from Magnetic Resonance Imaging (MRI) findings.
Methods: all dogs, whose neurological status was scored through the use of an innovative evaluation scale (Romanengo Veterinary Neurological Scale – RVNS), received HDH-VMAT by a Linear Accelerator (LINAC) equipped with an external beam modulator micro-multileaf collimator and an XVI Cone Beam Computed Tomography system (CBCT). The prescribed mean dose was 33 Gy delivered in 5 fractions. The treatment feasibility was tested through planned and delivered dose agreement checks. Regular clinical examinations were performed during and after irradiation time with regard to mentation, deambulation, cranial nerve dysfunction and seizures. Serial MRI exams were done 60 days after irradiation and after 4, 6, 12, 18, 24 months. Volumetric disease reduction criteria implemented with clinical neurological systematic evaluation were adopted to assess the course and to categorize patients' response.
Results: complete and partial responses were observed on the whole in 65,5% of alive patients 24 months after irradiation. Two-year overall and disease-specific survival rates were 74.3% and 97.4%, respectively, and the putative radiotoxic effects were found to be few and slight.
Conclusions: HDH-VMAT is a valid therapeutic option for encephalic canine meningioma. Volumetric MRI evaluation together with the hereby proposed RVNS should be considered for the evaluation of the post-treatment response.

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Introduction:-

Meningiomas represent about 50% of encephalic tumors in dogs and are the most common primary brain tumor in canine medicine.[1,2] They consist in extra-axial central nervous system (CNS) masses growing outside brain parenchyma and within the dura mater,[3] localized predominantly adjacent to calvarium, in the frontal or olfactory region, in the floor of the cranial cavity, in the optic chasm or in the suprasellar or parasellar regions.[3,4] On average dogs affected are over five years of age and belong to dolichocephalic breeds, whereas Boxers show an increased prevalence.[1,2] At the clinical presentation the chief concerns depend on the neuroanatomical region affected and the most common forebrain localization is usually associated with an altered consciousness, behavioral changes, seizures, circling, head pressing and visual deficits.[2,3,5] An accurate presumptive diagnosis of canine meningioma can be formulated through the use of CT and MRI techniques, as a high correlation between CT-MRI and histopathology findings has been recently demonstrated.[6] Conversely cerebro-spinal fluid (CSF) analysis presents insufficient test sensitivity or specificity to be considered as a valid option.[7] Surgery is presently considered the elective treatment for these tumors,[8] although radiotherapy and chemotherapy are used for tumors considered unresectable due to their localization or to co-morbidity related risks.[3] Radiation therapy (RT) has also been studied as a definitive or as adjuvant setting after surgery.[5,8-13] Conventional radiotherapy consists of fractionated irradiation of the tumor and a 5- to 10-mm margin of surrounding tissue at approximately 3 Gy per session. In dogs and cats, the total dose is usually 46 to 48 Gy given over several weeks.[15] Irradiation of canine and feline brain tumors is becoming common in veterinary medicine. Published studies include case series describing the use of radiation therapy after subtotal resection and some reports of different RT techniques and protocols proposed as the sole treatment for intracranial masses.[5,8-13] Since these works are essentially retrospective, there are no reliable data about the history of the meningiomas once they have been irradiated to allow the definition of important parameters, such as specific disease survival, progression free survival, response, and post-treatment imaging-based volumetric evaluation.[15,16] The initial hypothesis was that a hypofractionated stereotactic RT could be applied to these tumors for curative purpose, therefore the aim of this work was first to evaluate the clinical efficacy of primary curative frameless radiotherapy in canine meningiomas using a high dose level with Volume Modulated Arc Radiotherapy (VMAT) technique, and secondly to introduce the use of an innovative neurological evaluation scale to score meningioma affected patients from the first visit to all follow-up controls and to objectively assess the clinical response.

Materials and methods:-

Study Design:-

A prospective single institution clinical research study was conducted from January 2010 to January 2012 on client owned dogs suffering from intracranial meningiomas treated with High Dose Hypofractionated Volume Modulated Arc Radiotherapy (HDH-VMAT).

Inclusion Criteria:-

Inclusion criteria to be admitted to the study were: normal minimum diagnostic tests including complete blood cell count (CBC) and biochemistry panel and a presumptive, imaging-based, diagnosis of meningioma. Both the severity of neurological signs and the potential administration of symptomatic medical therapy before diagnosis were not considered as exclusion conditions. Patients were referred to our centre for advanced imaging and informed consent was obtained by the owners of each dog.

Patients Information:-

Medical information were recorded with regard to age, sex, breed, clinical presentation, physical examination, body condition score, hematology, biochemistry and other diagnostic exams available. The clinical neurological status was assessed by our clinical team using an evaluation scale (Romanengo veterinary neurological scale, RVNS), specifically defined to score the presenting complaints both at the first evaluation and at every follow-up control. The RVNS focuses on central neurological signs and evaluates the clinical status with regard to mentation and state of consciousness, posture and gait, cranial nerves function, proprioception, trophism of the head musculature and seizures activity (Table 1). We graded any alteration according to its severity: absence of alteration corresponds to score 0, mild alterations are scored 1, moderate alterations grade 2, and severe ones grade 3.

In order to provide a final score for each patient, dogs were graded according to the highest score received during the evaluation of the six criteria taken into account. In particular, score 3 characterized dogs that were comatose, concerning mentation state, and the ones showing hemi- or tetraparesis.

The diagnosis of meningioma was posed on the basis of brain MRI examination, as reported in literature.[17-21] According to most recent studies, the Magnetic Resonance Imaging (MRI) criteria for presumptive diagnosis of meningioma were: the occurrence of a single solid broad dural based extra-axial mass with distinct margins and the presence of intense and uniform enhancement with a dural tail sign.[17-20]

Drug protocols:-
Dogs were premedicated with a combined protocol of dexmedetomidine[a] (3 µg/kg) and methadone[b] (100 µg/kg). Anesthesia was induced using propofol[c] dosed to effect and, after endotracheal intubation, anesthesia was maintained by isoflurane[d] in oxygen administered by volume-controlled ventilation. Perioperative analgesia was provided using methadone (0.2 mg/kg).

Steroid protocol consisted of oral administration of 0.3 mg/kg of prednisolone[e] twice daily starting from the diagnosis; the dose was tapered off over the first months by decreasing the dose or the frequency of administration according to the evolution of the clinical concerns.

MRI protocol:-
The MRI examinations were conducted using a 1.5 T superconductive whole body MRI[f] scanner with gradients of 70 milliTesla/meter. A quadrature knee and a quadrature spine coil were used. A standardized patient positioning technique was developed: dogs under sedation were positioned in sternal recumbency for brain lesions and dorsal recumbency for spinal lesions, with head first. The MRI protocol provided the following scan sequences: a pulse sequence Turbo Spin Echo (TSE) T2-weighted with repetition time (TR) 3500 ms, echo time (TE) 130 ms, 2 acquisitions (NEX), 512x512 matrix; a Fluid Attenuated Inversion Recovery with TR 3000 ms, TE 150 ms, inversion time (TI) 50 ms, 2 NEX, 512x512 matrix; a Spin Echo (SE) T1-weighted with TR 450 ms, TE 5 ms, 2 NEX, 512x512 matrix; a Fast Field Echo (FFE) T1- weighted with TR 450 ms, TE 5 ms, 2 NEX, 512x512 matrix, either under basal conditions or after contrast medium intravenous injection. Sequences were oriented in the sagittal, dorsal and axial plan and slice thickness was set at 2 mm without intersection gap. For post-contrast images Gadodiamide[g] 0.5 mmol/ml was administered at the dose of 0.2 ml/kg in the cephalic vein; the injection was performed with a high pressure injection system[h] with standardized infusion rate of 3 ml/s and time of acquisition at 5 minutes post injection.

The CT simulations were performed within one week after the MRI examination using a multidetector CT scanner.[i] For all the dogs a wooden cradle containing a vacuum mattress with a plastic bite block to fit the upper dentition was provided (Figure 1). The provisional isocenter was marked with three radiopaque fiducials on the wooden cradle. The parameters used for the CT simulation were: 200 mAs, 120 Kv, pitch 0.6, rotation 1 second, slice thickness 1.5 mm. For post-contrast images Iomeprol[j] 350mg/ml was administered at the dose of 2 ml/kg in the cephalic vein; the injection was performed with a high pressure injection system with standardized infusion rate of 3 ml/s and time of acquisition 5 seconds post injection.

The imaging-based diagnosis on both MRI and CT cross-sectional images was assessed by the head master radiologist (MD).

RT protocol:-
The dogs received a radiotherapy treatment by an Elekta SynergyS LINAC[k] equipped with an external beam modulator micro-multileaf collimator and an XVI Cone Beam Computed Tomography system (CBCT). HDH-VMAT treatments were planned using a Monte Carlo statistical algorithm and the CMS Monaco 3.0 treatment planning system (TPS). MRI and Computed Tomography (CT) images fusion was routinely performed during the planning.

The gross tumor volume (GTV) was defined as the contrast enhanced lesion on fused CT and MRI images; the clinical target volume encompassed the GTV with supplementary contouring of the dural tail if present. The planning target volume (PTV) was realized by expanding the clinical target volume by 1 mm in all directions. The considered organs at risk (OARs) were eyes, optic nerve, chiasma, brain, brain stem, spinal cord, ears-cochlea,

larynx, trachea, oesophagus (Table 2). PTV and OARs were contoured on an interactive pen display[l] graphic tablet. The high dose hypofractionated protocol consisted of 33 Gy in 5 fractions delivered in 5 continuous days. The OARs dose constraints were derived from the human ones described by the American Association of Physicists in Medicine Task Group 101 (Table 2).[21] For all patients a specific plan setup was elaborated with a single 360° arc optimized over continuous dose rate variation, leaf position and gantry rotational speed for obtaining target coverage and optimized for OARs sparing. Plan effectiveness evaluation was performed by means of standard dose volume histograms (DVHs) and the Conformity Index (CI) value defined as: $CI=V_{Prescription}/V_{olume}T_{arget}$.[22] The CI describes which way the observed isodose level conforms to the target volume shape.[22]

In detail, the degree of PTV coverage considered acceptable for the $V_{95\%}$ and $V_{107\%}$ levels (the PTV volume receiving <95% and >107% of the prescription dose) was of <4% and 2%, respectively.. For the CI, the 95% isodose level was considered as $V_{Prescription}$ and the acceptability value was $CI_{95\%} \leq 1.3$. The dose distribution detailed information for each delivered RT plan with the respective CI value are reported in Table 3.

The treatment feasibility was evaluated by checking the planned and delivered agreed dose by a "patient based" quality assurance procedure "in air" using the Elekta Iview Amorfous Silicon Electronic Portal Imager Device and the Mathresolution Dosimetric Check (DC) system software. Stating the small tumour's volume, a further absolute dose comparison was performed with the Scansidos Delta4 system. In both cases, the agreement was parameterized by the gamma (γ) function, with a dose agreement of 3% and distance to agreement of 3 mm choosing an acceptance criteria of $\gamma < 1$ in more than the 93% of comparison points.[23]

The Mean Delivery Time, defined as the approximate time needed in the LINAC "beam-on" phase, was investigated too. Correct patient setup was evaluated for each treatment session using the XVI CBCT and a 2 mm tolerance displacement level was considered acceptable.

The discrepancies between the XVI CBCT and the simulation CT were registered and were considered acceptable if the displacement did not exceed 2 mm in any direction. When discrepancies were found to be between 2 mm and 5 mm, table movements were performed in accordance with the XVI CBCT software results. When discrepancies were found to be more than 5 mm, the patient was repositioned in the cradle and XVI CBCT was repeated to check the patient setup again; if agreement was still not achieved, the whole treatment procedure was repeated starting from the CT simulation. To check the differences between the planned dose and the delivery dose during different fractions, an "on-transit" control was performed using the "in vivo" dosimetry option of the DC system.

All irradiated dogs received 0.1 mg/kg of periprocedural dexamethasone[m] and anti-inflammatory doses of oral methylprednisolone sodium succinate tapered over three weeks. Phenobarbital[n] or topiramate[o] or levetiracetam[p] were administered to dogs with seizures as presenting complaints.

Follow-up:-

Regular neurological clinical examinations were performed and score attribution according to RVNS was recorded on a daily basis during irradiation time, then weekly for the first month. The need for ancillary medications, particularly corticosteroids and anticonvulsivant drugs, were recorded.

Post-irradiation follow-up protocol consisted of clinical examination with recording of the RVNS score and serial MRI examinations performed with the subsequent periods with 5 days variance: 2, 4, 6, 12, 18, 24 months (Table 4). All the MRI scans were performed with the same scanner used for the diagnosis[a] as well the scanning parameters. Volumetric disease reduction was analysed on transverse postcontrast T1-weighted images using a CMS Monaco 5.0.3 software. Other parameters evaluated by the radiologist were the change of signal intensity of the tumor and of surrounding brain or spinal cord on TSE T2-weighted pulse sequence (TR 3500 ms, TE 130 ms, 2 NEX, 512x512 matrix), the contrast uptake of the tumor on FFE T1-weighted pulse sequence (TR 450 ms, TE 5 ms, 2 NEX, 512x512 matrix) and the presence of mass effect.

Specific response evaluation criteria were established to assess the course after irradiation. Volumetric MRI evaluation was accounted according to RECIST criteria implemented with clinical follow-up examinations.[24] The categorical assignment was determined as follows. Patients were ascribed to the Complete Response (CR) group when disappearance of all measurable enhancing tumor was observed and stable or improved clinical status was achieved without corticosteroids administration. Patients were ascribed to the Partial Response (PR) group when a

reduction in the sum of diameters of target lesions of at least 30% was found on MRI images, taking as reference the baseline sum and stable or improved clinical status was achieved with stable or decreased corticosteroids administration. Patients were ascribed to the Stable Disease (SD) group when a reduction less than 30% or an increase less than 20% in the sum of diameters of target lesions was found on MRI images, taking as reference the smallest sum of diameters of target lesions and stable or improved clinical status was achieved with stable or decreased corticosteroids administration. Patients were ascribed to the Progressive Disease (PD) group when either the appearance of one or more new lesions or at least a 20% increase in the sum of diameters of target lesions was observed during MRI scan, taking as reference the smallest sum of diameter on study. Radiation toxicities were clinically evaluated and graded according to Radiation Therapy Oncology Group (RTOG) criteria.[25]

Statistical Analysis:-

One-year and two-year overall and disease-specific survival rates were built according to the Kaplan-Meier method.

Results:-

Patients Information:-

Thirty-three dogs were enrolled (5 neutered males, 12 intact males, and 16 spayed females), with a median age of 9.8 years (mean 9.6, range 7–14 years). This cohort included 11 mixed breed, 6 Boxer, 4 German shepherd, 3 Golden retriever, 2 Dalmatian, and one each of 7 further breeds. All dogs had a single lesion. Neuro-localization included 19 encephalic supratentorial (14 frontal, 3 parietal, 2 occipital) and 14 encephalic infratentorial (12 brain stem, 2 cerebellum). Presenting complaints included seizures (19/33), cranial nerve deficits (18/33), altered mentation (3/33) and paresis (4/33); they were classified according to the Romanengo veterinary neurological scale (Table 1). At the first presentation approximately the 73% (24 cases) of the affected dogs had a final score of 2 out of 3, the 15 % (5 cases) received 1 as final score and the 12% (4 cases) represented score 3.

RT protocol:-

The mean GTV volume at the first CT simulation time measured was 3.0 ± 1.2 cm^3 (range 1–8 cm^3) and the mean PTV was 4.0 ± 1.8 cm^3 (range 1.5–9.9 cm^3). For all the irradiated patients a treatment with one 360° arc was used. Plan details were 1700 ± 200 MU, 137 ± 5 control points, 2.3 ± 0.4 modulation degrees and 2 mm of margin to target and to OARs. The dose constraints were derived by the American Association of Physicists in Medicine Task Group 101. Mean Delivery Time was 180 seconds.

All the plans fulfilled the PTV, the OARs and the CI constraints and no plan was rejected.

The obtained mean doses were 33.5 ± 0.2 Gy for the GTV and 33.3 ± 0.3 Gy for the PTV. The 95% isodose volume coverage ($V_{95\%}$) was $99.6 \pm 0.2\%$ for the GTV and $96.2 \pm 0.5\%$ for the PTV. Finally, the high 107% isodose volume coverage (V107%) was $0.9 \pm 0.15\%$ for the GTV and $0.7 \pm 0.2\%$ for the PTV. An example of dose distribution is shown in Figure 2. Similar results were obtained for all the patients.

The mean DC agreement between the planned and delivered doses showed a mean value over all the patients' data of $95 \pm 2\%$ of points with $\gamma < 1$ showing treatment feasibility. The quality assurance check by the Delta4 system resulted in a similar $97 \pm 2\%$ value, confirming a good agreement between the results of the two methods and between the delivered plan and the calculated one.

Follow-up:-

During follow-up visits, that is to say 2, 4, 6, 12, 18 and 24 months (±5 days) after the end of RT, all dogs were newly clinically evaluated and scored according to RVNS. At the same time MRI examinations were regularly performed.

After 6 months 31 dogs were still alive: one dog was euthanized because of disease recurrence, whereas the other one died after a traumatic injury. At that time clinical examinations showed reduction of frequency and/or intensity of seizures (18/33), reduction of detectable cranial nerve deficits (14/33), normalization of mentation as subjectively stated (3/33) and improvement of deambulation (4/33). Remarkable MRI changes were detected, as well: reduction of contrast enhancement, decreased mass effect and tumor volume together with decreased peritumoral edema (Fig. 3, 4).

These findings were consistent to the fact that 29/33 dogs (88%) showed no neurological alterations anymore (score 0), 4 cases (12%) reported mild alterations represented by focal epileptic seizures in one dog and decreased function

of one or more cranial nerves in the remaining three (score 1), and only one case (3%) reported moderate alteration (score 2): the dog was still suffering from generalized epileptic seizures. No dogs died from meningioma during the follow-up. The interval between the end of RT protocol and the death was considered as primary endpoint.
Survivals assessed by the Kaplan-Meier method are reported in Figure 5. The median survival time was not reached. Overall one-year and two-year survivals were 84.6% and 74.3%, respectively. A 24-months disease-specific survival rate of 97.4% was estimated.

Repeated MRI examinations showed variations of irradiated lesions (Figures 3, 4).
MRI data from subsequent examinations are listed in Table 1; volumetric criteria were considered together with T2-weighted and T1-weighted signal intensity, contrast enhancement, surrounding T2-hyperintensity and mass effect.
The categorical assignment to the CR, PR, SD and PD groups, resulted from the RECIST criteria implemented with clinical examinations during the 24-months follow-up, are reported in Table 2. No one of the 21 patients affected by seizures at presentation and receiving Phenobarbital[h] or topiramate[i] or levetiracetam[l] as anticonvulsants interrupted the therapy. Oral administration of prednisolone[e] was prescribed to all the patients. Corticosteroid dose has been increased only for the patient dead for meningioma recurrence whereas five patients received stable steroid dose during the follow-up and the remaining patients received gradually reduced doses. All dogs completed the prescribed dose and none of our patients needed a suspension of the protocol.
According to Veterinary Radiation Therapy Oncology Group toxicity criteria, adverse events potentially related to HDH-VMAT were limited to grade I in one dog, that developed a vestibular syndrome secondary to cerebellar inflammation after the end of RT and it was successfully treated with corticosteroids (0.2 mg/kg of prednisolone[e]).

Figure legends:-
Figure 1:- Immobilisation system used during CT simulation. Please note the wooden cradle (A) and the dog positioned inside it on a vacuum mattress (B), a bite block fitting the upper dentition was provided (C, D).
Figure 2:-Isodose distribution and DVH computed by Monaco TPS system of the same dog as in Figure 1.
Figure 3:- Dog #13, male, 8 years, Boxer. Pre-treatment (A), 6-months (B) and 18-months post-treatment TSE T2-W sequences (C). It was observed a complete response (CR) with progressive reduction of the mass effect and tumor volume.
Figure 4:- Dog #1, female, 12 years, small mixed breed. TSE T2-W images at the diagnosis time (A) and 18 months after RT (B). T1-W post-contrast sequences of the brain at the diagnosis time (C) and 18 months after RT (D). Although the tumor volume is constant, the reduction of contrast enhancement and decreased mass effect are evident.
Figure 5:- Kaplan-Meier survival analysis: the black line represents the disease-specific survival rate and the red line the overall survivals during the 24 months follow-up.

Table 1:-The neurological evaluation scale proposed to score meningioma affected patients from the first visit to all follow-up controls.

	0 – Normal	**1 – Mild**	**2 – Moderate**	**3 – Severe**
MENTATION, STATE OF CONSCIOUSNESS	Alert, mentation unaltered	Depressed, lethargic	stuporous	comatose
POSTURE and GAIT	No abnormalities	Altered posture with normal gait or altered gait with normal posture	Both posture and gait altered	Hemiparesis, Tetraparesis
CRANIAL NERVES FUNCTIONS	Normal brain stem reflexes	Decreased function of one or more cranial nerves	Absent function of one or more cranial nerves	-
PROPRIOCEPTION	Unaltered propioception	1-2 seconds delayed limb positioning	Absent limb positioning	-

MUSCLE TROPISM	Normal muscle tropism	Sarcopenia of masticatory muscles	Atrophy of masticatory muscles	-
SEIZURES ACTIVITY	Absent	Focal epileptic seizures	Generalized epileptic seizures	-

Table 2:-Dose Constraints for the Organs at Risk (OARs) taken into consideration for the treatment planning, derived by the TG101 Report.

Organs	Vol. %	Vol. Limit Gy	Max. Limit Gy	Refs.
Brain	100	20	-	18
Brainstem	100 1	20 26	31	18,19
Chiasma	100	20	25	18,19,20,21,22
Cranial Nerves	-	-	20	23
Ears-Cochlea	-	-	27.5	19
Esophagus	1 5 10	25 27.5 19.5	35	19,24,25,26
Eyes (Lens)	-	-	7	27
Eyes (Retina)	-	-	15	27
Larynx	-	-	20	27
Optic nerve	0.05 0.5	20 12.5	25-30	19,20,21,22,29
Spinal cord	0.25 0.5 1 8	22.5 13.5 25 20	10-30	19,24,25,26,30,31,32,33,34
Trachea	4	18	38-52	19,25

Table 3:-Dose distribution detailed information for each delivered RT plan.

Dog	PTV (cc)	Planned Dose (Gy)	Mean Dose (Gy)	Max. Dose (Gy)	Conformity Index (CI)	Obtained $V_{95\%}$ (Gy)	Obtained $V_{107\%}$ (Gy)
1	1,51	33	33,54	35,61	1,09	96,15	1,15
2	3,56	33	33,19	35,13	1,02	95,15	0,85
3	9,9	33	33,37	35,34	1,02	95,44	0,93
4	4,67	33	33,29	34,84	1,07	96,81	1,18
5	3,53	33	33,53	35,05	1,06	96,72	0,51

6	6,42	33	33,15	35,79	1,09	96,12	0,51
7	3,26	33	33,2	35,44	1,03	95,31	0,69
8	3,81	33	33,4	35,59	0,99	95,1	0,58
9	3,57	33	33,45	35,81	1,03	96,13	0,49
10	1,58	33	33,43	35,47	1,03	96,35	0,58
11	2,25	33	33,55	35,44	1,02	96,5	1,21
12	6,01	33	33,55	35,31	0,98	95,1	0,94
13	2,47	33	32,4	35,21	0,97	95,78	0,73
14	3,96	33	33,63	35,91	1,01	96,4	0,61
15	2,62	33	33,27	35,71	1,03	96,52	0,95
16	6,14	33	33,56	35,44	1,02	96,51	0,52
17	4,94	33	33,51	35,38	1,01	96,03	0,35
18	3,14	33	33,31	35,22	1,03	96,03	0,7
19	2,58	33	33,57	35,77	1,03	96,47	0,65
20	4,81	33	33,85	35,92	0,98	95,64	0,81
21	2,67	33	33,56	35,87	1,03	96,82	0,64
22	6,56	33	33,22	35,31	1,01	96,15	0,46
23	2,95	33	33,29	35,37	1,03	96,51	0,85
24	5,94	33	33,15	35,4	1,06	96,41	0,38
25	5,12	33	33,23	35,28	1,12	96,75	0,56
26	2,96	33	33,35	34,98	1,09	96,92	0,56
27	6,15	33	33,5	35,59	1,04	96,96	0,42
28	3,46	33	33,5	35,36	0,99	95,95	0,58
29	3,14	33	33,2	36	1,09	96,68	0,86
30	2,02	33	33,25	35,42	1,07	96,82	0,39
31	3,99	33	33,5	35,29	1,05	96,59	0,41
32	3,35	33	32,5	35,99	1,08	96,47	0,68
33	4,45	33	33,49	35,31	1,07	96,12	0,42

Table 4:-Categorization of the course in the follow-up period by the use of MRI volumetric assessment implemented with clinical evaluation criterion.

	2 months	**4 months**	**6 months**	**12 monts**	**18 monts**	**24 months**

Complete Response Partial Response Stable Disease Progressive Disease	2 3 28 0	2 10 19 0	2 14 14 1	3 14 10 0	3 15 6 0	5 13 5 0
NUMBER OF ALIVE PATIENTS	33	31	30	27	24	23

Discussion:-

Radiation therapy plays a central role in the management of brain tumors in dogs. The ultimate goal of radiation therapy is to administer the highest possible dose to the tumor while minimizing damage to surrounding healthy tissue.[12] Radiation affects cells and their vasculature; 80% of the observed clinical effect is due to DNA damage resulting from the ionization of water and production of oxygen free radicals.[26] This effect has a latent period and can take months to occur in slow-growing meningiomas. The acute adverse effects of radiation include cerebral edema and, possibly, a temporary increase in seizure activity. Brain edema, which may be due to transient demyelination, responds to steroid therapy. Late effects of radiation can be seen months to years after therapy and are due to brain necrosis. Late effects can mimic the original clinical signs of the treated tumor and cannot be effectively treated.[12,27] In veterinary medicine, however, late effects of radiation therapy are rare because of the patients' short life span.

The technical difficulties of conformal radiation therapy of canine meningiomas, with particular regard to the shape irregularity, small size, proximity to critical neural structures as well as to markedly inhomogeneous structures, have been addressed in this work by the use of VMAT.[25,28] To the authors' knowledge, no prospective studies on VMAT RT of canine meningiomas have been published, and retrospective RT papers show a lack of homogeneity in the treatment regimens.

In the present work we have obtained overall two-year survivals of 74.3%, with an estimated disease-specific survival rate of 97.4% respectively, with putative radiotoxic effects being rare, thus showing the efficacy of the technique. In particular, high dose hypofractionation improves local tumor control probability, while VMAT permits more OARs sparing.

The agreement between the prescribed and the delivered dose was considered to be the primary step in irradiating the canine meningiomas, due to the target dimensions and the VMAT sharp dose gradients. The radiation dose of 33 Gy was derived from the literature data on meningioma sensitivity (α/β value of 3.76 Gy with 95% confidence level: 2.8–4.6 Gy) and, to compare our regimen with published data, the concept of the biologically effective dose (BED) was used.[29,30] An α/β of 3 Gy was applied for late responding tissues and late radiotoxic effects, whereas a value of 10 Gy was applied for acute responding tissues and acute radiotoxic effects.[31] The BED of a typical 3D conformal RT protocol for human meningioma (27 fractions of 2 Gy for a total dose of 54 Gy given in 6 weeks) was a Gy_3 value of 90 Gy.[32] The BED of our regimen (33 Gy given in 5 days) was 105.6 Gy (17% higher).

The use of a dedicated cradle with a vacuum mattress, a byte block, and the XVI CBCT check performed before each session, allowed to realize a frameless high precision radiotherapy in more than one fraction without any invasive device and with results comparable to surgery and better than reported results of conformal RT.[26,32,33]
The Monte Carlo statistic calculation algorithm allowed a better dose calculation at different tissue interfaces, where higher punctual doses (D_{max}) could be generated. Moreover, doses to the OARs were lower than the constraints, showing the possibility of further dose escalation to the PTV.[21]

The tumor local control probability obtained in this study proved to be better than conformal RT reported results and, more significantly, it is even better than the one obtained with gold standard surgery with resectable patients.[33,34] In fact, a recent RT study reports a 1-year and 2-year disease-specific survival of 60% and 21%, respectively, with a median of 493 days.[16] Median survival time of dogs suffering from meningiomas treated with RT alone from most published studies ranges from 5 to 12 months.[12,35,36] Standard surgery papers reported a median survival time of 7 months for dogs treated with surgery alone (range 0.5 to 22 months).[27,37] It is important to note that recent surgical works focusing on improved tumor removal by ultrasonic aspiration and neuroendoscopy

reported median survival times of 40–70 months, which appears to be better than our study results.[38-39] For a correct comparison, longer follow-up and better patient statistics are needed, but further stratification is probably necessary of both surgery and our work outcomes to better evaluate small differences.

To the best of authors' knowledge no standardized neuro-oncology volumetric response evaluation criteria have been formulated in veterinary trials. In this study volumetric assessment of the tumor was mandatory for the RT planning at the time of diagnosis, so an imaging-based volumetric post-treatment evaluation was considered particulary suitable for response evaluation.

Meningiomas are strong enhancing masses, iso/hypointense in T2-weighted sequences if compared with the normal gray matter, easily distinguished from the surrounding hyperintense oedema that may be present. They often exhibit marked mass effect, and well demarcation in respect to the surrounding brain, with infrequent cystic component in canine patients. Contrast enhancement pattern is homogeneous with clear margins. The MRI characteristics of canine meningiomas make easy to perform a volumetric standardized measurement on contrast enhanced T1-weighted pulse sequences. As a matter of fact implementation of the response assessment in neuro-oncology with clinical neurological serial examinations provides additional information that fulfills a categorical therapeutic response evaluation.

Using a combined response assessment criterion, made of volumetric measurements and clinical data assessment, 87.2% of patients showed stable disease (SD) 2 months after irradiation, 7.7% showed partial response (PR) and 5.1% complete response (CR). PR was observed in 48.3% of patients 24 months after irradiation and CR in 17.2%. Among living animals none of the patients at the 24-month follow up showed progressive disease.

Even though a considerable number of patients showed Stable Disease 2 months post-irradiation (34/39) with no volumetric reduction on MRI (Table 1), we observed variations in T2-weighted signal intensity and contrast enhancement. In particular, on MRI examinations 2-4-6 months post-treatment, the majority of encephalic meningiomas with supratentorial localization showed a reduction of T2-signal intensity whereas infratentorial meningiomas showed increased T2-weighted signal. At the same time supratentorial and infratentorial meningiomas showed a decreased contrast enhancement independently from volume variations. Considering the whole cohort two months post- irradiation contrast uptake was found reduced in 41% of patients and mass effect was decreased in 90%. Because no animal has been subject to histological examination of the irradiated lesions, only hypotheses can be advanced to explain these findings. An increase of free water, a reduction of cell density and tumor vascularization could play a role in signal intensity and contrast enhancement variations.

Evidence is emerging that there is a different radiobiological mechanism of tumor response to radiation between the application of a conventional fractionation (i.e. 2 Gy per day) protocol and a high dose hypofractionated one.[40-42] Conventional fractionated treatment causes re-assortment of tumor cells into more radiosensitive phases and re-oxygenation of hypoxic cells between fractions, as hypoxic cells are more radioresistant. Re-assortment and re-oxygenetion lead to an improvement of the therapeutic ratio.[40] Conversely, recent work suggests that high doses of radiotherapy activates apoptosis through acid sphingomyelinase (ASM) pathway.[41] Since ASM concentration is significant higher in endothelial cells than in epithelial and neoplastic ones, high doses are likely to provoke tumor death damaging mainly microvasculature. Therefore this could explain how subtentorial necrosis and progressive sovratentorial impregnation coexist with volumetric stability in some of the cases exposed.

Clinical neurological evaluation of post-irradiated patients deserves some observations. Patients categorized as stable disease (SD)-affected showed clinical improvement despite no significant volume reduction. Since clinical signs resulting from meningioma are essentially compressive, often complicated by inflammation and oedema in the brain or spinal cord, in these patients improvement could be due to the reduction of peri-tumoral oedema and mass effect. This finding suggests that radiation treatment not only provides for a reduction of the compression exerted by the neoplastic lesion, but it also could play a role in the inflammatory mechanisms over its own inductive normal tissues inflammation feature.

The limitations of this prospective study are the lack of hystopatological confirmation and immunohistochemical or molecular tests to determine the histological degree of meningiomas. However, presumptive diagnosis by imaging is validated by several veterinary medicine papers that have assessed 89–100% MRI sensitivity in differentiating

neoplastic from non-neoplastic intracranial lesions and 70–96% specificity in identifying tumour type.[13,18,19,35,43] Similar results are reported in human literature.[20]

Conclusion:-

In conclusion, HDH-VMAT is a valid therapeutic option for encephalic and spinal canine meningiomas. Two-year overall and disease-specific survivals are much longer than published data on conventional RT and are similar to standard surgery but with fewer and slighter adverse effects. Volumetric MRI evaluation together with the proposed RVNS should be considered for the post-treatment course evaluation of veterinary patients treated with encephalic tumor RT.

Abbreviations:-

BED, biologically effective dose; CBCT, Cone Beam Computed Tomography; CI, Conformity Index; CR, complete response; DC, Dosimetry Check; D_{max}, higher punctual doses; DVHs, dose volume histograms; FFE, Fast Field Echo; GTV, gross target volume; HDH-VMAT, High Dose Hypofractionated Volume Modulated Arc Radiotherapy; LINAC, Linear Accelerator; MRI, Magnetic Resonance Imaging; NEX, number of acquisitions; OARs, organ at risks; PD, progressive disease;
PR, partial response; PTV, planning target volume; QA, quality assurance; RT, Radiation Therapy; RVNS, Romanengo Veterinary Neurological Scale; SD, stable disease; SE, Spin Echo; TE, echo time; TR, repetition time; TSE, Turbo Spin Echo.

Footnotes:-

[a]Dexdomitor; Orion Pharma, Milan, Italy
[b]Semforta; Ati s.r.l., Ozzano Emilia, Bologna, Italy
[c]Propovet; Esteve, Milan, Italy
[d]Isovet; Piramal Healthcare, Mumbai, India
[e]Medrol; Pharmacia Italia, Milan, Italy
[f]MRI Intera 1.5T; Philips Medical Systems, Eindhoven, the Netherlands
[g]Omniscan; GE Healthcare, Milan, Italy
[h]Medrad Spectris; Volkach, Germany
[i]CT Brilliance; Philips Medical Systems, Eindhoven, the Netherlands
[j]Iomeprol; Iomeron 350, Bracco, Milano
[k]SynergyS LINAC; Elekta, Crawley, UK
[l] Cintiq; Wacom, Saitama, Japan
[m]Desashok; Fort Dodge, Milan, Italy
[n]Phenobarbital; Gardenale, Aventis Pharma, Milan, Italy
[o]Topamax; Janssen-Cilag, Milan, Italy
[p]Keppra; UCB Pharma, Milan, Ital

Figures:-

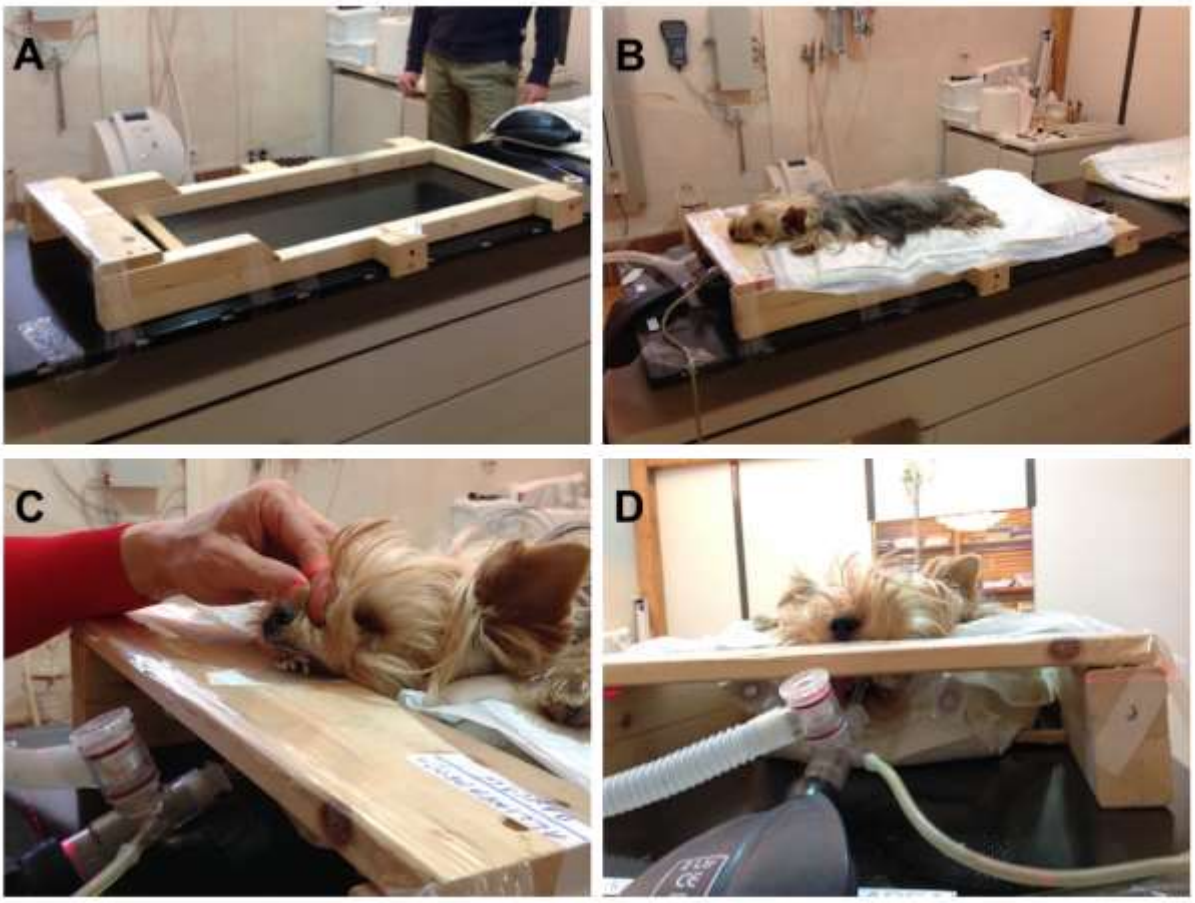
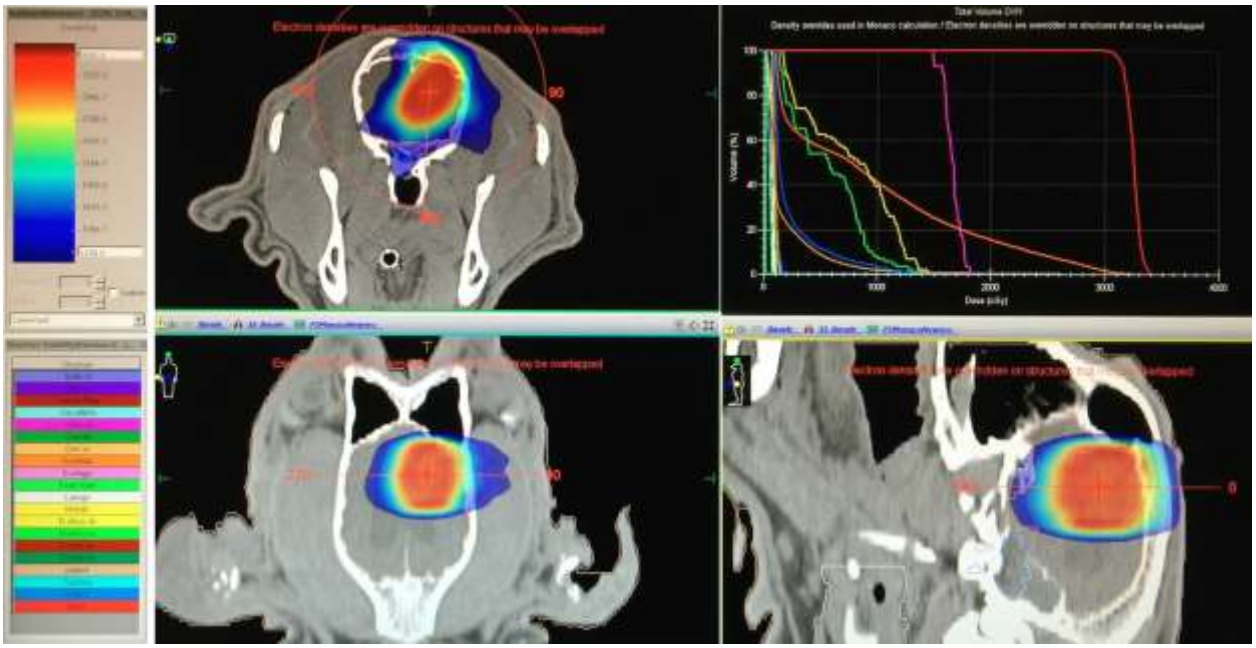


Fig.1



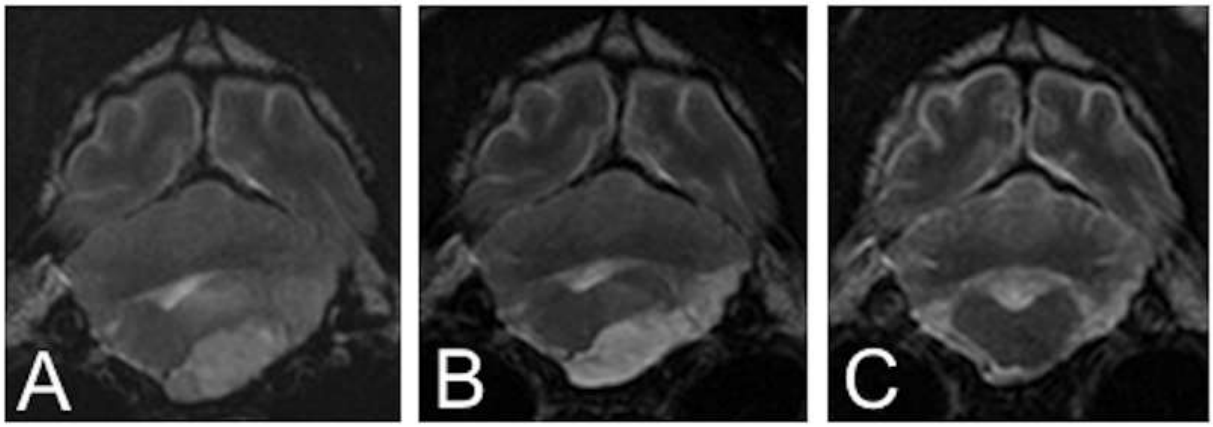


Fig.2
Fig.3

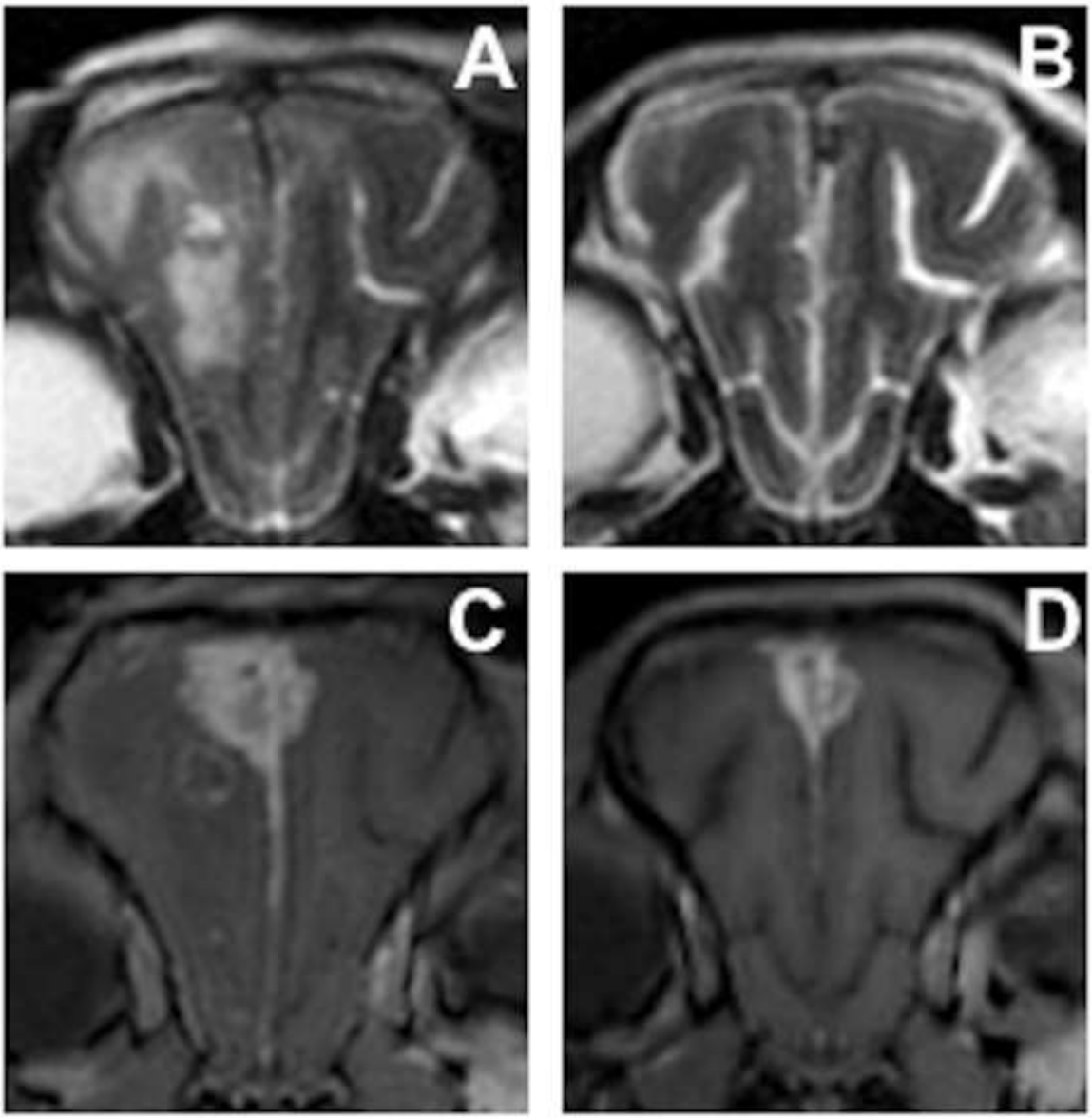


Fig.4

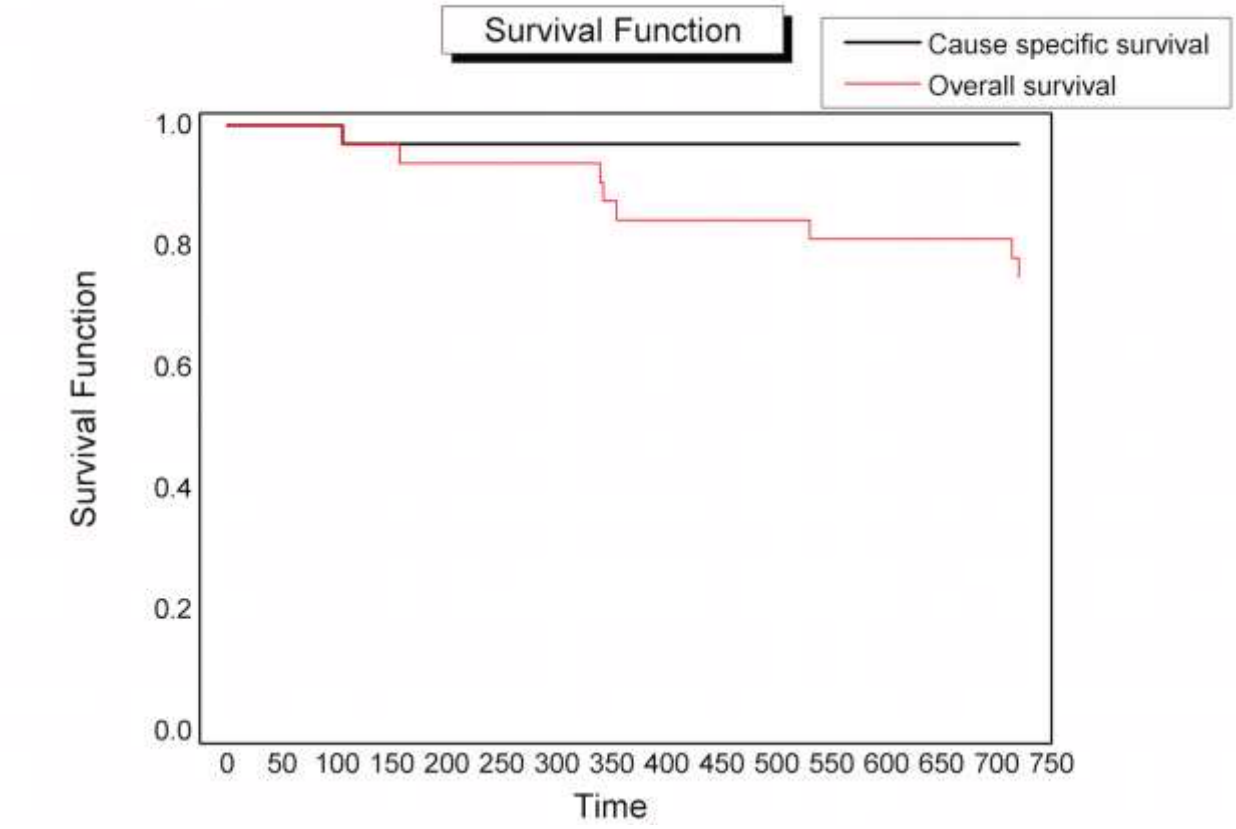


Fig.5

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