

Case report

SIMULATIONS OF PHOTON VERSUS PARTICLE THERAPY FOR TREATING CANCER IN CANINES USING MATRAD: CASE STUDY OF A BEAGLE WITH PITUITARY MACROADENOMA

Mimoza RISTOVA^{1,4*}, Andrijana GJORESKA¹, Marija SIMONOVSKA²,
Dushko LUKARSKI^{2,3}, Irena CELESKA⁵

¹University Ss Cyril and Methodius in Skopje, Faculty of Natural Sciences and Mathematics, Institute of Physics, Arhimedova St. 3, Skopje, Republic of North Macedonia; ²University Clinic for Radiotherapy and Oncology, Mother Theresa St. 17, Skopje, Republic of North Macedonia; ³University Ss Cyril and Methodius in Skopje, Faculty of Medicine, , Skopje, Republic of North Macedonia; ⁴SEIIST, Geneva, Switzerland; ⁵University Ss Cyril and Methodius in Skopje, Faculty of Veterinary Medicine, Lazar Pop Trajkov St. 7, Skopje, Republic of North Macedonia.

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In this study, we propose that dogs diagnosed with tumors exhibiting a similar pathology to those in humans could play a crucial role in trials for novel radiation therapy modalities, such as particle therapy (beyond protons and carbon ions) or FLASH therapy. A multidisciplinary team including a veterinary oncology scientist, a human radiation oncologist, and medical physicists, conducted a simulation of a comparative treatment planning using matRad software to compare the benefits of three treatment modalities: (1) X-rays, (2) protons, and (3) carbon ions. Diagnostic results from a Beagle dog with a pituitary macroadenoma were utilized for this study. The dog was euthanized due to severe deterioration in basic physiological functions, including eating, swallowing, breathing, head tilt, and movement, over a period of several days. The dog's owner, who is closely related to one of the coauthors, provided oral consent for the use of all available clinical data from the deceased dog. These results were used as a hypothetical case to simulate and compare the effectiveness of three radiation treatment modalities. This pioneering approach opens an avenue to the potential of involving living companion animals already diagnosed with cancer in treatment research, advancing both veterinary and human oncology. The results suggested that if treated with radiation, the dog would have benefited most from particle therapy, which delivers a maximum dose to the tumor while considerably minimizing exposure of the surrounding critical organs – an advantage not achieved with conventional X-rays.

This collaboration emphasizes the importance of integrating veterinary and human radiation oncology. This work paves the way for developing initial protocols to treat pets with cancer, serving as a preclinical foundation before clinical studies are conducted on humans.

Keywords: Macroadenoma in canine, matRad, particle therapy, protons and C-ions, radiation therapy, translation from veterinary to clinical trial.

*Corresponding author: e-mail: mima.ristova@gmail.com

INTRODUCTION

Companion animals have been used for translating radiation therapy (RT) research into clinic. It has been reported that proton pencil-beam radiotherapy has been applied in clinical practice to spontaneously developed brain tumors in canines [1]. Canine brain tumors often exhibit pathophysiological characteristics similar to those observed in humans. The location, size, and type of the brain tumor play a key role in the clinical condition of affected dogs. The prevalence of these diseases is approximately 2.8% – 4.5% of all neoplasms in canine oncology [2].

Anamnestic data from the dog owner, clinical examination, and additional laboratory results can aid in making a presumptive diagnosis for deep-seated brain tumors, in the case when biopsy and histopathology tests are not feasible anti-mortem.

Clinical appearance of diverse brain tumors can be used as animal models for simulating human radiological treatment of surgically inaccessible tumor proliferations [3]. Radiobiological investigations and cancer research focused on the Radio-Biological Effectiveness (RBE) of particle therapy with protons and carbon ions for oncological treatment in so far employed small animal models (mice) [4]. In isolated cases, dogs (pets) have been used for testing new concepts in radiation therapy with photons [5], protons [6], and electrons [7]. However, small animal models entail the implantation of cancer cells into specific tissues of otherwise healthy laboratory animals, subsequently inducing cancer growth [8] and subjecting the animals to various therapeutic interventions, such as drug regimens or exposure to various radiation modalities. These methodologies have spurred ethical challenges within the scientific community [9] and among organizations advocating for humane animal treatment [10].

During the technical development phase of the South East European International Institute for Sustainable Technologies (SEEIIST) [11] in the Yellow Report issued by CERN [12] Ugo Amaldi highlighted the need of conducting hadron therapy experiments on companion animals, particularly dogs already diagnosed with malignant neoplasms, diseases especially those that are notably prevalent in humans, has initiated contemplation within the scientific community. This innovative proposition aims to include pets as test subjects for evaluating the efficacy of ion-based therapies. Notably, the forthcoming hadron therapy and research center, SEEIIST, intended to fill the regional lack of particle therapy technology [13] for patients and scientists from the Balkan region [14], is exploring the possibility of utilization of pet dogs with naturally occurring tumors for investigating ion therapy effectiveness. This approach will provide a tripartite benefit: (i) it delivers advanced hadron therapy to the animal patient improving their survival time, (ii) instills optimism in the owner regarding potential remission and improved quality of life and well-being, and (iii) generates valuable insights prior to the clinical studies for radiation treatment of analogous tumors in human patients.

In this case study, we simulate alleged radiation therapy using photons, protons, and carbon ions to treat a pituitary macroadenoma in a dog. We would like to emphasize that the simulations were exercised on the post-mortem pet, while the diagnostics were done while alive. The objective of this study is to initiate identification on the optimal treatment modality in future treatment of pets already affected by cancer. With this we would like to demonstrate initial unison of the efforts of a veterinary oncologist, a human radiation oncology specialist, a medical physicist, and a physicist specializing in particle therapy research.

MATERIALS AND METHODS

The 10-year-old male Beagle dog was admitted to the clinic with an obese body condition and marked neurological signs. Clinical examination revealed a body temperature of 38.1 °C. Cardio-thoracic auscultation detected weakened systolic and diastolic heart sounds, while normal vesicular breath sounds were observed.

According to the anamnesis provided by the owner, the dog began exhibiting cranial neurological signs nine months prior, initially presenting with difficulty chewing and swallowing. The condition progressively worsened, manifesting as mental dullness, periodic blindness, a “tragic” facial expression, discoordination during urination and defecation, a vacant stare, loss of movement control, head tilt, subtle behavioral changes, apathy, lethargy, and excessive salivation. The dog often sought dark, quiet places to avoid sound and light stimuli.

Other clinical features consistent with severe hypothyroidism in Beagles were also observed, including weight gain attributed to myxedema, reduced physical activity, hyperpigmentation (skin darkening), non-inflammatory and non-pruritic hypotrichosis, and a “rat-tail” appearance.

Neurological testing revealed moderate deficiencies in auricular and palpebral sensation, with delayed and diminished responses from the facial nerve (cranial nerve VII) and the ophthalmic branch of the trigeminal nerve (cranial nerve V). The pupillary light reflex test indicated complete unresponsiveness of the optic nerve (cranial nerve II). Postural deficits were evident in all limbs, and prolonged proprioceptive responses were noted in the right forelimb.

A complete blood count (CBC) was performed using the Exigo Boule veterinary hematology analyzer (Sweden). Routine hematology tests revealed mild normocytic normochromic anemia, with erythrocyte count (RBC) at $4.24 \times 10^{12}/L$ (reference range: $5.5\text{--}8.5 \times 10^{12}/L$), packed cell volume (PCV) at 31.5% (37–55%), and hemoglobin (HGB) at 11 g/dL (12–18 g/dL).

Biochemical parameters were analyzed using the automated spectrophotometer ChemWell (Awareness Technology Inc., USA), following the manufacturer's instructions for Human reagent kits (Germany). The results indicated hyperlipidemia, including hypercholesterolemia (14.90 mmol/L; reference range: 3.1–6.5 mmol/L)

and hypertriglyceridemia (3.17 mmol/L; reference range: <1.14 mmol/L). Elevated serum liver enzyme levels were also observed, including alanine aminotransferase (ALT) at 126.40 U/L (8.2–57.3 U/L), aspartate aminotransferase (AST) at 70.25 U/L (8.9–48.5 U/L), and alkaline phosphatase (ALKP) at 236.5 U/L (10.6–100.7 U/L).

Thyroid function tests were conducted using the IMMULITE 1000 Immunoassay System (Siemens, USA). Serum concentrations of free thyroxine (fT4) at 0.15 ng/dL and total thyroxine (TT4) at 0.20 µg/dL were found to be extremely low. After establishing and confirming the diagnosis of pituitary dependent hypothyroidism in the pet beagle dog, therapy with levothyroxine tablets was started in a maximum dose of 22 µcg/kg twice a day. Following the start of treatment, the dog's general clinical condition improved significantly, with better physical tolerance, a normalized heart rate, reduction in myxedema, and noticeable improvement in apathy and lethargy. While the resolution of most clinical signs showed a marked improvement, the neurological symptoms only moderately improved over a period of nine months. Unfortunately, the progression of the pituitary macroadenoma further deteriorated the Beagle's quality of life, resulting in an unfavorable (infausta) prognosis.

Based on clinical, anamnestic, and laboratory findings, a hormone-related brain tumor was strongly suspected. Computerized Tomography (CT) imaging, performed under total intravenous anesthesia (TIVA), a pituitary macroadenoma was suggested [16], visualized as a round mass. Radiation Therapy (RT) was recommended as the treatment of choice to reduce the tumor's size. However, access to RT facilities for pets was not available in North Macedonia.

After the dog was euthanized, the particular canine brain tumor model was used to simulate RT with three modalities, the conventional X-ray photons and particle therapy with either protons or carbon ions. Radiation treatment of the already deceased dog were only simulated using the Digital Imaging and Communications in Medicine (DICOM) data from the CT scan on matRad software, an open-source tool for designing radiation therapy plans with modulated beams of photons, protons, and carbon ions. The benefits versus the damage was evaluated through comparative simulations made under assumption that the density and atomic composition of all relevant organs and tissues in the canine's head were equivalent to those of humans. This approach leveraged existing human tissue data integrated into the matRad software for our planning purposes.

The contouring and planning software Varian Eclipse (version 16.1) [17] was utilized for the veterinary patient (Beagle dog). The gross tumor volume (GTV) was delineated and subsequently expanded by a 2 mm margin to create the clinical target volume (CTV), ensuring coverage of subclinical disease not detectable on imaging modalities. To account for geometric uncertainties during irradiation, the CTV was further expanded by an additional 3 mm margin, resulting in the planning target volume (PTV).

Organs at risk (OARs), including whole brain, brain stem, spinal cord, distal brain structures such as the medulla oblongata, left and right eyes, and left and right

lenses, were also contoured. This contouring process was conducted collaboratively by a multidisciplinary team comprising a radiation oncologist, veterinary scientist, and medical physicist. Additionally, the dose to the entire body was recorded for comparative analysis.

RESULTS AND DISCUSSION

CAT scan and Contouring

MatRad features a DICOM import module which allowed the conversion of DICOM data (from CT scan of dog's head) into matRad compatible data format. The contouring was performed using the anti-mortem CT scan of the dead Beagle dog. Figure 1 shows the contoured irradiation regions. In the top part of the figure, three axial cross sections are shown, and the bottom left shows the coronal, the bottom right sagittal cross section.

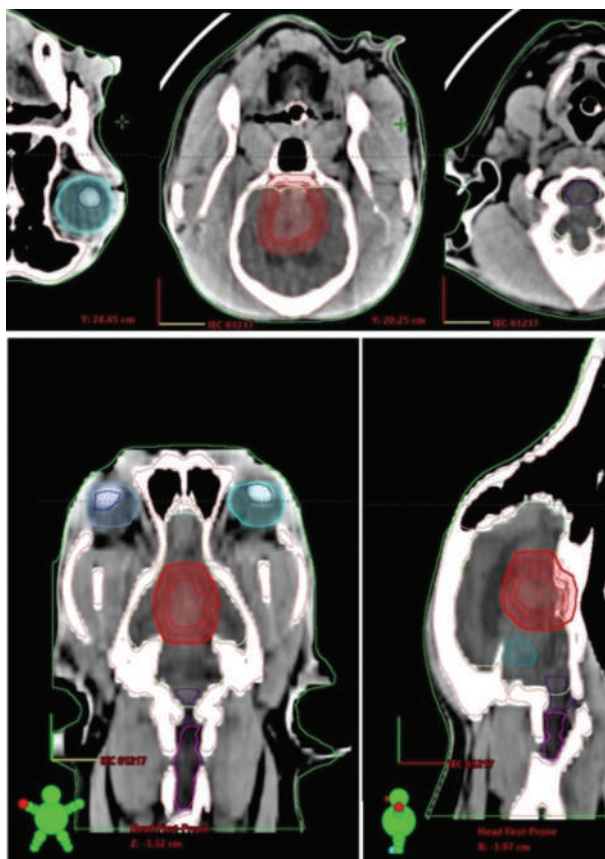


Figure 1. CT of the canine head in axial cross-section (top), coronal (bottom left) and sagittal (bottom right).

The volumes of GTV, CTV, and PTV are 4.06 cm^3 , 8.09 cm^3 , and 16.97 cm^3 , respectively. The PTV exhibits a roughly symmetrical shape with dimensions ranging between 3.5 cm and 4 cm in all three directions. Figure 2 displays the CT scan exported from Varian Eclipse with the marked contours, subsequently imported into the matRad software for treatment planning using three different irradiation modalities (X-rays, protons, and carbon ions).

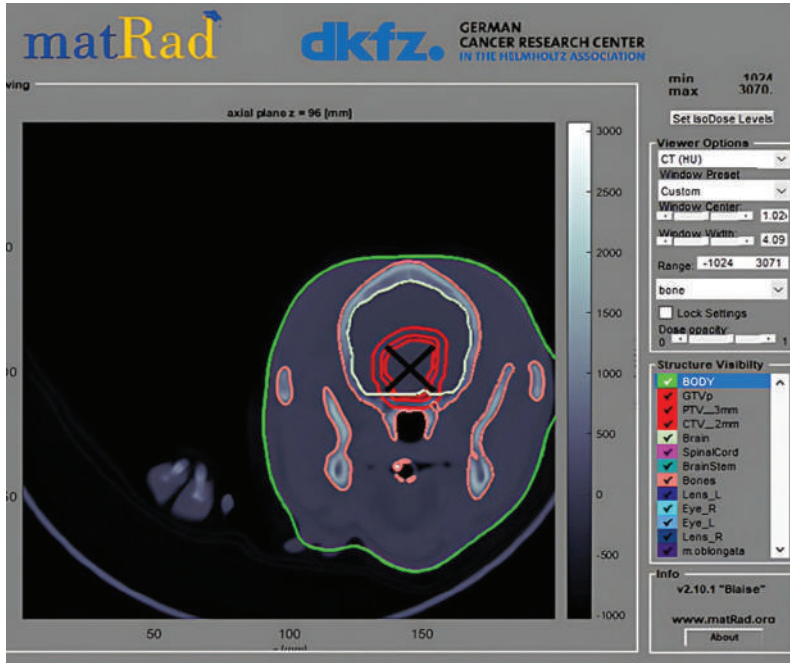


Figure 2. Axial cross section of the canine CT imported in matRad. Isocenter (cross sign) placed in the central region of the tumor volume (GTV).

Treatment planning

The isocenter, marked with the black cross-mark in Figure 2, was placed roughly in the center of the tumor lesion. As presented in Figure 3, three treatment planning models were considered for the Intensity Modulated Radiation Therapy (IMRT) with X-ray photons, each giving 70 Gy evenly distributed in twenty fractions: (a) optimized irradiation under one angle (0°), (b) three angles (0° , 30° , 330°) and (c) five angles (0° , 30° , 60° , 300° , 330°). Figures 4 and 5 show the simulated dose distributions in case protons or C-ions are used for treatment of the pituitary cancer of a dog. In both hadron treatment planning strategies two models have been considered: (a) optimized irradiation under one angle (0°), (b) under three angles (0° , 30° , 330°).

The left columns of Figures 3, 4, and 5 illustrate the isodose distributions, while the right columns present the corresponding Dose-Volume Histograms (DVHs), which show the dose received by a specific fraction of the volume of interest. Each volume

of interest is represented by a distinct color: the target volumes, including the Gross Tumor Volume of the Primary Tumor (GTVp), the Planning Target Volume with a 3 mm expansion (PTV_3mm), and the Clinical Target Volume with a 2 mm margin (CTV_2mm), are displayed in red. The critical organs considered in the analysis, such as the brain, bones, spinal cord, brain stem, eyes, lenses, and medulla oblongata, are shown in various other colors. Also the dose delivered to the body is subject to comparison.

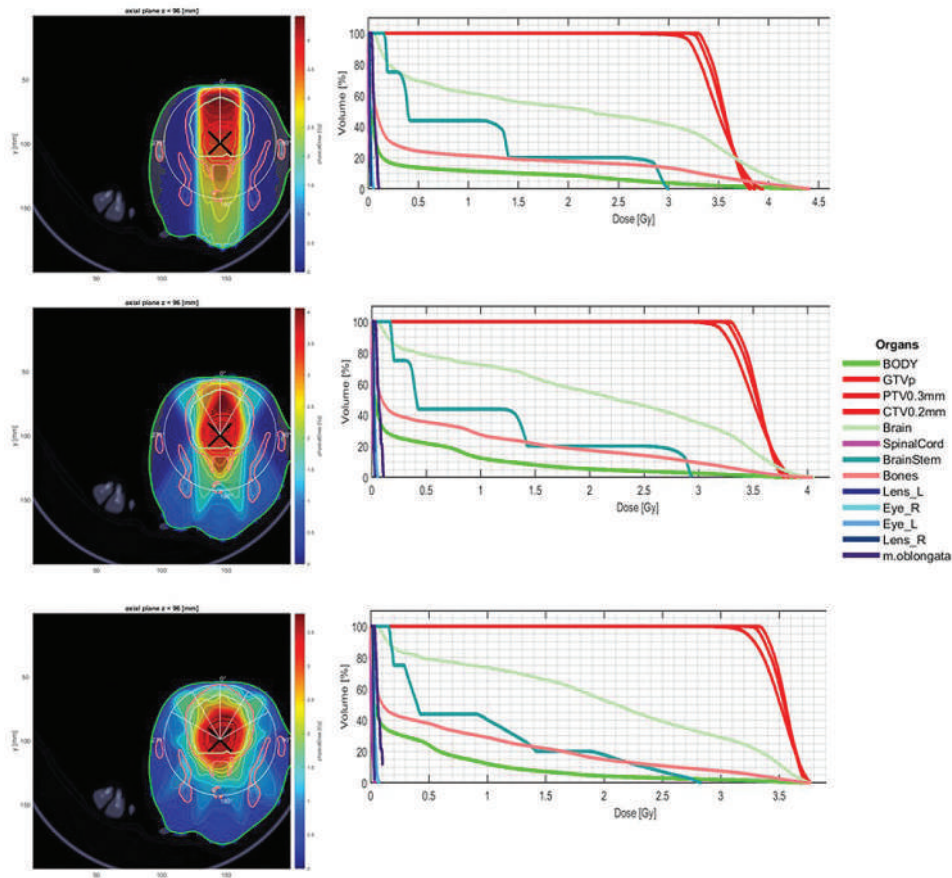


Figure 3. Treatment with X-ray photons: (Left column) Dose distribution computed with matRad in transversal slices of an Intensity Modulated Radiation Therapy (IMRT) treatment with X-photons plan using one, three and five gantry angles 0°, 30°, 60°, 300°, 330° and a couch angle at 0°; (Right column) Resulting dose volume histograms (DVH of an inversely optimized intensity-modulated photon treatment plan, using (Top row) one, (Middle) three, and (Bottom) five beam directions.

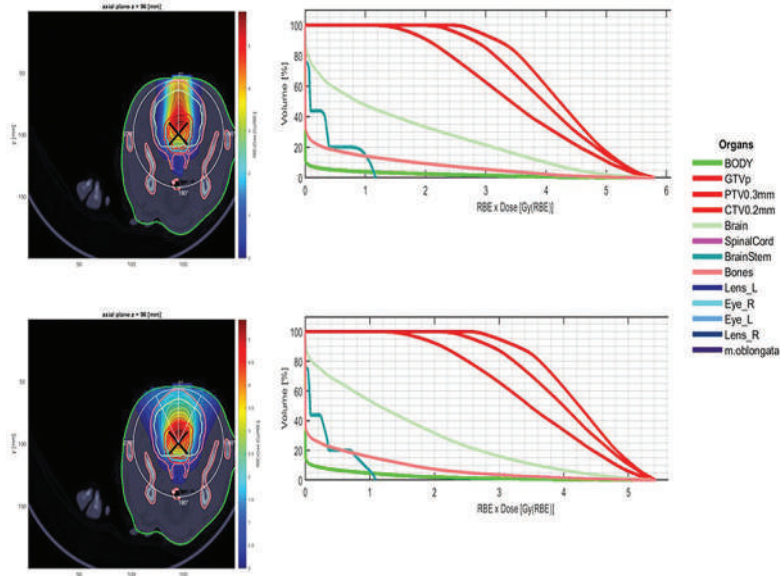


Figure 4. Treatment with protons: (Left column) Dose distribution computed with matRad in transversal slices of treatment plan using protons under one and three gantry angles 0°, 30°, 330° and a couch angle at 0°; (Right column) Resulting dose volume histograms (DVH) of an inversely optimized intensity-modulated photon treatment plan, using (Top row) one and (Bottom) three beam directions.

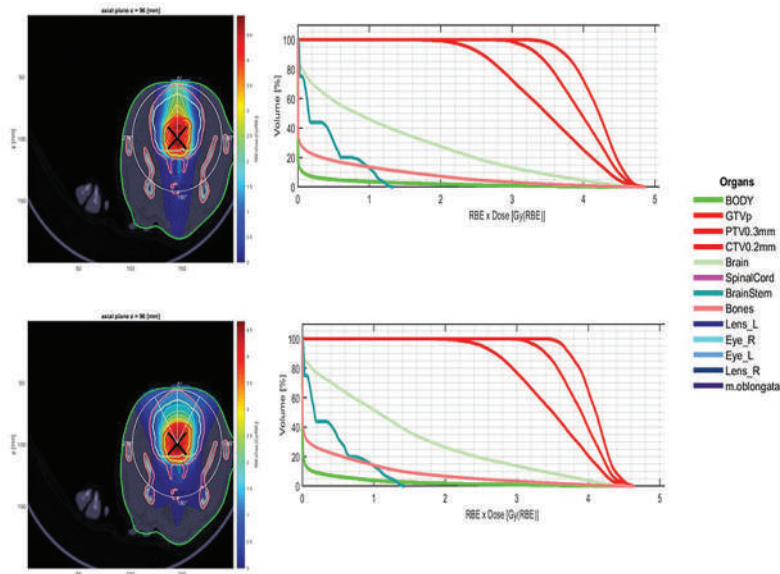


Figure 5. Treatment with C-ions: (Left column) Simulated dose distribution computed with matRad in transversal slices of treatment plan with protons using one and three beams with gantry angles 0°, 30°, 330° and a couch angle at 0°. (Right column) Resulting dose volume histograms (DVH) of an inversely optimized intensity-modulated photon treatment plan, using (Top row) one, and (Bottom) three beam directions.

From the DVHs, specific representative dose values were extracted and summarized in Table 1 for target volumes and Table 2 for organs at risk. The values in Table 1 correspond to a single fraction, whereas the values in Table 2 are cumulative across all 20 fractions.

Table 1. Comparison of dose delivered to target volume due to treatment plans with different RT modalities (photons, protons and C-ions). The doses presented refer to the dose per fraction for the corresponding treatment plan.

RT type		X-Photons (Gy)			Protons (Gy*RBE)		C-ions (Gy*RBE)	
		1	3	5	1	3	1	3
Irradiation angles		(0°)	(0°,30°,330°)	(0°, 30°,60°, 300°, 330°)	(0°)	(0°, 30°, 330°)	(0°)	(0°, 30°, 330°)
Mean	GTVp	3.55	3.55	3.55	4.22	4.20	4.18	4.08
	PTV_3mm	3.49	3.50	3.49	3.47	3.47	3.47	3.47
	CTV_2mm	3.54	3.53	3.53	3.97	3.96	3.94	3.88
STD	GTVp	0.12	0.11	0.09	0.75	0.66	0.31	0.24
	PTV_3mm	0.20	0.18	0.15	1.10	1.00	0.66	0.56
	CTV_2mm	0.15	0.14	0.11	0.88	0.79	0.43	0.34
Max	GTVp	3.83	3.80	3.74	5.79	5.42	4.88	4.66
	PTV_3mm	3.95	3.90	3.78	5.81	5.43	4.88	4.66
	CTV_2mm	3.88	3.84	3.76	5.81	5.43	4.88	4.66
Min	GTVp	3.28	3.28	3.31	2.36	2.53	3.18	3.39
	PTV_3mm	2.53	2.87	2.83	1.06	1.10	1.55	1.62
	CTV_2mm	3.18	3.20	3.21	1.87	2.04	2.57	2.76
D_2	GTVp	3.78	3.75	3.71	5.59	5.34	4.71	4.53
	PTV_3mm	3.87	3.83	3.74	5.53	5.22	4.61	4.41
	CTV_2mm	3.81	3.78	3.73	5.61	5.31	4.67	4.49
D_5	GTVp	3.75	3.73	3.69	5.44	5.22	4.65	4.46
	PTV_3mm	3.82	3.79	3.72	5.34	5.06	4.48	4.30
	CTV_2mm	3.78	3.75	3.71	5.42	5.19	4.59	4.38
D_50	GTVp	3.56	3.55	3.55	4.22	4.24	4.22	4.11
	PTV_3mm	3.49	3.50	3.51	3.41	3.47	3.48	3.51
	CTV_2mm	3.54	3.54	3.54	3.96	3.99	3.96	3.91
D_95	GTVp	3.35	3.35	3.38	2.91	2.99	3.61	3.66
	PTV_3mm	3.20	3.21	3.23	1.77	1.83	2.38	2.52
	CTV_2mm	3.31	3.30	3.34	2.52	2.59	3.21	3.28
D_98	GTVp	3.33	3.32	3.36	2.71	2.80	3.48	3.58
	PTV_3mm	3.12	3.14	3.15	1.54	1.58	2.17	2.30
	CTV_2mm	3.28	3.28	3.31	2.32	2.39	3.05	3.16

Table 2. Comparison of dose delivered to organs at risk due to treatment plans with the different RT modalities (photons, protons and C-ions). The doses presented refer to the cumulative dose from all the 20 fractions of the corresponding treatment plan.

RT type		X-Photons (Gy)			Protons (Gy*RBE)		C-ions (Gy*RBE)	
Irradiation angles		1 (0°)	3 (0°,30°,330°)	5 (0°, 30°, 60°, 300°, 330°)	1 (0°)	3 (0°, 30°, 330°)	1 (0°)	3 (0°, 30°, 330°)
Max	Body	88.3	81.3	75.6	116.2	108.6	97.6	93.2
	Brain	88.3	81.3	75.6	116.2	108.6	97.6	93.2
	Spinal Cord	0.7	0.7	0.8	0	0	0	0
	Brain Stem	60.1	58.8	56.7	23.7	21.9	26.9	28.9
	Lens_L	0.6	0.6	0.8	0	0	0	0
	Eye_R	1.3	1.3	1.6	0	0	0	0
	Eye_L	1.2	1.3	1.6	0	0	0	0
	Lens_R	0.6	0.6	0.7	0	0	0	0
	m.oblongata	2.2	2.2	2.1	0	0	0	0
	Body	69.9	63.6	59.9	49.1	39.6	38.9	36.3
D_2	Brain	84.8	77.7	73.9	100.7	95.5	86.5	83.5
	Spinal Cord	0.7	0.7	0.7	0	0	0	0
	Brain Stem	59.4	58.5	55.3	23	21.4	24.7	26.9
	Lens_L	0.6	0.6	0.7	0	0	0	0
	Eye_R	1	1	1.3	0	0	0	0
	Eye_L	1	1	1.3	0	0	0	0
	Lens_R	0.5	0.6	0.7	0	0	0	0
	m.oblongata	2.1	2.1	2.1	0	0	0	0

To facilitate comparison of the simulated outcome from the radiation therapy with photons, protons and C-ions, the values of the mean doses per fraction and the standard deviation (STD) derived from Table 1, delivered to the target volumes with each treatment modality were plotted in the histogram shown in Figure 6.

According to Figure 6, for conventional radiotherapy using X-rays, slightly lower mean dose values are observed compared to protons and C-ions. Obviously, the average dose is not influenced by the number of beam angles, but dose homogeneity improves as the number of angles increases.

In Figure 7 we show the results from Table 2 for the doses in the organs at risk, plotted as histograms. As more representative value we use the D_2 value, i.e the dose received by the hottest 2% of the corresponding organ at risk. Herein the dose to the body, brain and brain stem appeared much lower for the particle therapy plans in comparison to the photon plans.

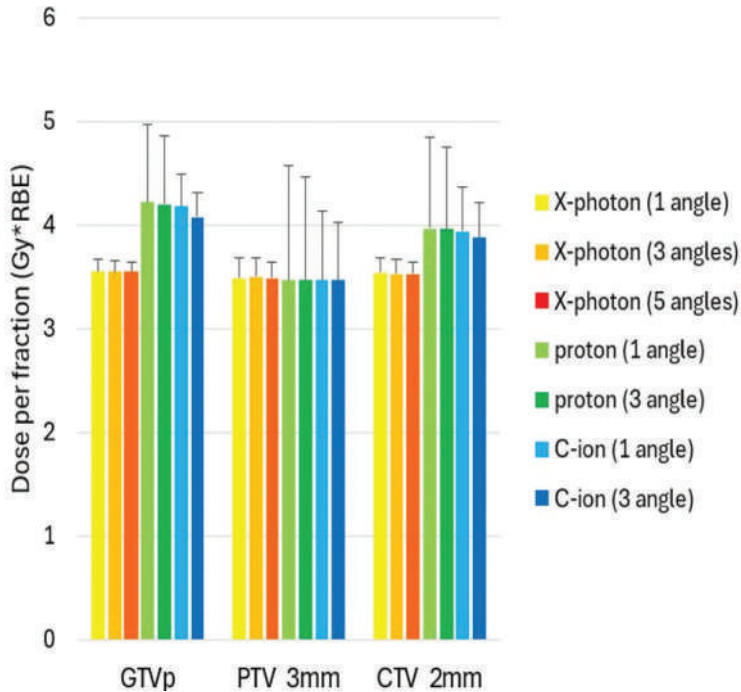


Figure 6. Mean dose and STD per fraction in Gy*RBE to the target volumes, delivered with the three different treatment modalities, whereas RBE is the Radio-Biological Effectiveness of the radiation treatment.

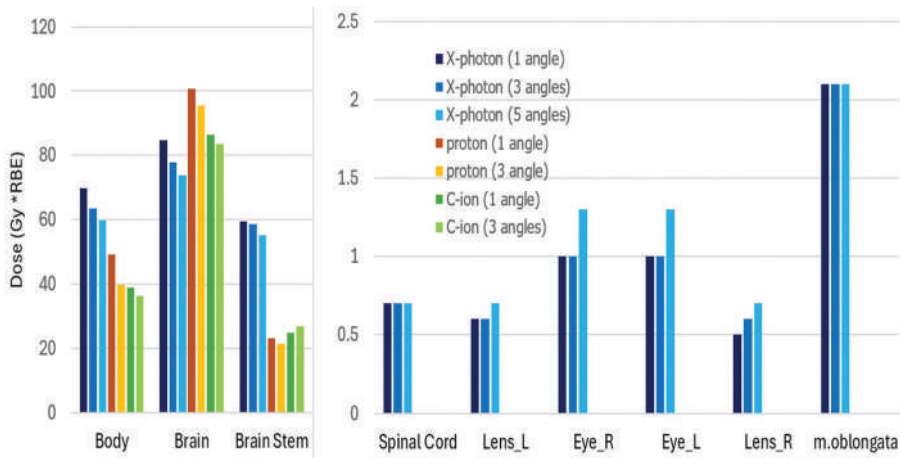


Figure 7. Cumulative dose to the hottest 2% of the organs at risk with the different treatment modalities.

Finally, as shown in Figure 7, either negligible or no dose is delivered to the organs at risk, such as the spinal cord, eyes, lenses, and medulla oblongata by using protons or carbon ions (C-ions) for radiation therapy. In contrast, conventional radiotherapy with

X-rays, despite optimizations, consistently delivers a dose to critical organs. This dose typically decreases as the number of gantry angles increases. However, this residual exposure to the surrounding tissues can lead to radiation-induced side effects, damage to organs or tissues, and an increased risk of secondary cancer development.

CONCLUSION

In this study, we present the initial steps in unifying the professional efforts of a veterinary oncologist, a human radiation oncology specialist, a medical physicist, and a physicist specializing in particle therapy research for radiation therapy treatment planning in veterinary oncology. The team developed radiation treatment plans using photons, protons, and carbon ions for an alleged radiotherapy treatment of a deceased canine which was diagnosed with a pituitary macroadenoma through a CT scan and blood tests. This research initiative aligns with the future objectives of the particle therapy center for Balkan countries, contributing to the development of protocols for cancer treatment clinical studies and research involving already ill pets. These results present a modest contribution towards developing protocols for cancer treatment clinical studies and research involving sick pets.

Our study showed that the dog would have benefited most from radiation therapy protons or carbon ions to treat the pituitary adenoma, having in mind that a more conformal dose distribution is delivered to the tumor and a negligible dose is delivered to the organs at risk and the surrounding organs and tissues, which will reduce the potential neurocognitive damage, in case of conventional radiation therapy with X-photons, as was demonstrated in earlier medical studies [18].

These modalities deliver the maximum prescribed dose to the entire tumor volume, while the dose to critical organs is negligible or even zero, unlike in the case of conventional radiotherapy with X-rays.

As an overarching conclusion, the scientists from the Balkan countries should start gathering around multidisciplinary teams, including veterinarians, oncologists, medical physicists, and particle therapy experts. These teams will be able to create selection criteria and protocols for treating dogs with neoplasms similar to those in humans. This initiative aims to prepare a comprehensive scientific program for veterinary clinical studies involving dogs that are already ill, as collaborative projects in the future South East European International Institute for Sustainable Technologies (SEEIIST particle therapy centre).

Authors' contributions

MR has set up the concept for this research, organized the team, initiated the simulations and treatment planning, collected the results, drafted the manuscript and finalized the manuscript. AG is a master-student who has performed the computer simulations with MatRAD and plotted all the graphs. MS is an MD specialist in human

radiotherapy who has participated in treatment planning – contouring the target organs and organs at risk together with the medical physicist DL. IC has treated the dog, provided the CT image and contributed with all the clinical data for diagnostics and treatment. DL has contributed in treatment planning by contouring and analysis of the doses delivered to all relevant organs along with MS, has written the discussion pertaining to the delivered dose and comparison and drafted the conclusions. All the authors have approved the final version of the manuscript.

Declaration of conflicting interests

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


Statement of Informed Consent

The owner understood procedure and agrees that results related to investigation or treatment of their companion animals, could be published in Scientific Journal *Acta Veterinaria-Beograd*.

ORCID iDs

Mimoza Ristova  <https://orcid.org/0000-0002-8042-8087>

Dushko Lukarski  <https://orcid.org/0000-0003-4286-2330>

Irena Celeska  <https://orcid.org/0000-0001-7488-5911>

REFERENCES

1. Mayer-Stankeová S, Fidel J, Wergin MC, Hauser B, Sumová A, Goitein G, Pedroni E, Lomax AJ, Schneider U, Blattmann H, Kaser-Hotz B: Proton spot scanning radiotherapy of spontaneous canine tumors. *Vet Radiol Ultrasound* 2009, 50(3):314-318.
2. José-López R, Gutierrez-Quintana R, de la Fuente C, Manzanilla EG, Suñol A, Pi Castro D, Añor S, Sánchez-Masian D, Fernández-Flores F, Ricci E, Marioni-Henry K, Mascort J, Matiassek LA, Matiassek K, Brennan PM, Pumarola M: Clinical features, diagnosis, and survival analysis of dogs with glioma. *J Vet Intern Med* 2021, 35(4):1902-1917.
3. Schramm MWJ, Currie S, Lee MT, Livermore LJ, Solanki SP, Mathew RK, Wurdak H, Lorgier M, Twelves C, Short SC, Chakrabarty A, Chumas P: Do animal models of brain tumors replicate human peritumoral edema? A systematic literature search. *J Neurooncol* 2023, 161(3):451-467.
4. Schmid TE, Multhoff G: Preclinical mouse models for the evaluation of novel techniques in particle therapy. *Prog Tumor Res* 2017, 44:122-129.
5. Moore AS: Radiation therapy for the treatment of tumours in small companion animals. *Vet J* 2002, 164(3):176-187.
6. Vanhaezebrouck IF, Scarpelli ML: Companion animals as a key to success for translating radiation therapy research into the clinic. *Cancers (Basel)*. 2023, 15(13):3377.
7. Santoro D, Kubicek L, Lu B, Craft W, Conway J: Total skin electron therapy as treatment for epitheliotropic lymphoma in a dog. *Vet Dermatol* 2017, 28(2):246.

8. Li Z, Zheng W, Wang H, Cheng Y, Fang Y, Wu F, Sun G, Sun G, Lv C, Hui B: Application of animal models in cancer research: recent progress and future prospects. *Cancer Manag Res* 2021, 13:2455-2475.
9. Kiani AK, Pheby D, Henahan G, Brown R, Sieving P, Sykora P, Marks R, Falsini B, Capodicasa N, Miertus S, Lorusso L, Dondossola D, Tartaglia GM, Ergoren MC, Dundar M, Michelini S, Malacarne D, Bonetti G, Dautaj A, Donato K, Medori MC, Beccari T, Samaja M, Connelly ST, Martin D, Morresi A, Bacu A, Herbst KL, Kapustin M, Stuppia L, Lumer L, Farronato G, Bertelli M, International Bioethics Study Group: Ethical considerations regarding animal experimentation. *J Prev Med Hyg* 2022, 63(2 Suppl 3):E255-E266.
10. Workman P, Aboagye EO, Balkwill F, Balmain A, Bruder G, Chaplin DJ, Double JA, Everitt J, Farningham DA, Glennie MJ, Kelland LR, Robinson V, Stratford IJ, Tozer GM, Watson S, Wedge SR, Eccles SA; Committee of the National Cancer Research Institute: Guidelines for the welfare and use of animals in cancer research. *Br J Cancer* 2010, 102(11):1555-1577.
11. Amaldi U, Benedetto E, Damjanovic S, Dosanjh M, Durante M, Georgieva P, Haberer T, Plesko M, Ristova M, Rossi S, Sammut N, Sapinski M, Schopper H, Specht H, Voss R, Vretenar M, Wenninger H: South East European International Institute for Sustainable Technologies (SEEIIST). *Front Phys* 2021, 8:567466.
12. Amaldi U, Balosso J, Dosanjh CERN M, Overgaard SJ, Rossi S, Singers Sørensen B: A facility for tumour therapy and biomedical research in south-eastern europe [Internet]. 2019. Available from: <https://doi.org/10.23731/CYRM-2019-002>
13. Dosanjh M, Ristova M, Gershan V, Georgieva P, Balin Kovacevic M, Bregu L, Coralic I, Djurovic T, Dosieva D, Foka Y, Fröbe A, Hatzioannou K, Hourdakos CJ, Kabashi Y, Kalev D, Kurtishi I, Litov L, Mezlechiu B, Nestoroska Madjunarova S, Nikolova G, Skrk D, Smajlbegovic V, Smichkoska S, Stojkovski I, Strojani P, Tecic Z, Tešanović D, Todorovic V, Valerianova Z: Availability of technology for managing cancer patients in the Southeast European (SEE) region. *Clin Transl Radiat Oncol* 2022, 34:57-66.
14. Ristova MM, Gershan V, Schopper H, Amaldi U, Dosanjh M: Patients with cancer in the countries of South-East Europe (the Balkans) Region and prospective of the particle therapy center: South-East European International Institute for Sustainable Technologies (SEEIIST). *Adv Radiat Oncol* 2021, 6(6):100772.
15. Wieser HP, Cisternas E, Wahl N, Ulrich S, Stadler A, Mescher H, Müller LR, Klinge T, Gabrys H, Burigo L, Mairani A, Ecker S, Ackermann B, Ellerbrock M, Parodi K, Jäkel O, Bangert M: Development of the open-source dose calculation and optimization toolkit matRad. *Med Phys* 2017, 44(6):2556-2568.
16. Sanders K, Galac S, Meij BP: Pituitary tumour types in dogs and cats. *Vet J* 2021, 270:105623.
17. Varian: Veterinary Hospitals Around the World Use Varian Technology to Treat Pets [<https://www.varian.com/resources-support/blogs/veterinary-hospitals-around-world-use-varian-technology>]
18. Wattson DA, Tanguturi SK, Spiegel DY, Niemierko A, Biller BM, Nachtigall LB, Bussière MR, Swearingen B, Chapman PH, Loeffler JS, Shih HA: Outcomes of proton therapy for patients with functional pituitary adenomas. *Int J Radiat Oncol Biol Phys* 2014, 90(3):532-539.

SIMULACIJE FOTONSKE VS. ČESTIČNE TERAPIJE ZA LEČENJE KANCERA KOD PASA POMOĆU MATRAD-A: STUDIJA SLUČAJA PSA RASE BIGL SA MAKROADENOMOM HIPOFIZE

Mimoza RISTOVA, Andrijana GJORESKA, Marija SIMONOVSKA,
Dushko LUKARSKI, Irena CELESKA

U ovde opisanoj studiji predlažemo da bi psi kojima su dijagnostikovani tumori koji pokazuju sličnu patologiju kao kod ljudi mogli da igraju ključnu ulogu u ispitivanjima novih modaliteta terapije zračenjem, kao što je terapija česticama (pored protona i jona ugljenika) ili FLASH terapija.

Multidisciplinarni tim koji uključuje naučnika iz oblasti veterinarske onkologije, onkologa za primenu zračenja u humanoj medicini, kao i biofizičare, sproveo je simulaciju uporednog planiranja lečenja koristeći softver matRad kako bi uporedio prednosti tri modaliteta lečenja: (1) rendgenskih zraka, (2) protona i (3) jona ugljenika.

U studiji su korišćeni dijagnostički rezultati psa rase Bigl sa makroadenomom hipofize. Pas je eutanaziran zbog ozbiljnog pogoršanja osnovnih fizioloških funkcija, uključujući apetit, gutanje, disanje, nagnjanje glave i kretanje, u periodu od nekoliko dana. Vlasnik psa dozvolio je korišćenje svih dostupnih kliničkih podataka od uginulog psa. Ovi rezultati su korišćeni kao hipotetički slučaj za simulaciju i poređenje efikasnosti tri modaliteta tretmana zračenjem.

Ovaj pionirski pristup otvara put ka potencijalnom uključivanju živih životinja kojima je predhodno dijagnostikovao karcinom u cilju istraživanja lečenja, istovremeno unapređujući veterinarsku i humanu onkologiju.

Rezultati navode da bi, ako bi se lečio zračenjem, pas imao najviše koristi od terapije česticama, koja daje maksimalnu dozu tumoru dok značajno minimizira izlaganje okolnih kritičnih organa - prednost koja se ne postiže konvencionalnim rendgenskim zracima.

Ovakva saradnja naglašava važnost integracije veterinarske i humane radijacione onkologije. Ovaj rad predstavlja put za razvoj početnih protokola za lečenje kućnih ljubimaca sa kancerom, služeći kao pretklinička osnova za sprovođenje kliničke studije na ljudima.