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THREE-DIMENSIONAL RADIOTHERAPY PLANNING IN THE PELVIC REGION OF WILD ANIMALS

(Planejamento radioterápico tridimensional em região pélvica de animais selvagens)

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ABSTRACT - Radiotherapy is a medical modality that has been constantly revolutionizing with the offer of three-dimensional computational for treatment planning systems (TPS), providing greater security in the release of the radiation dose in the target volume, improving the therapeutic response and minimizing the radiobiological effects unwanted. The incorporation of modern radiotherapy techniques, along with studies that contribute to the development of radiotherapy protocols in veterinary medicine, may contribute to improve the quality of treatments and survival of animals affected by cancer. A TPS applied in a human radiotherapy clinic was used and the radiometric, clinical and anatomical parameters were adequate for the feasibility of use in veterinary radiotherapy. Tomographic images of the pelvic region of wild animals assisted by the School of Veterinary Medicine and Animal Science (FMVZ/UNESP) were used to perform them. The simulations were made with institutional images and in vivo animals were not used. Protocols for the implementation of computational planning in veterinary medicine were verified by analyzing the homogeneity of the radiation dose distribution in the planned treatment volume (PTV) and ensuring the protection of the organs surrounding the PTV. The methodology applied for the use of TPS Eclipse in veterinary radiotherapy planning proved to be feasible and can present itself as an important tool to improve veterinary oncological therapeutic approaches.

Key words - conformational radiotherapy; neoplasms; veterinary medicine.

RESUMO - A radioterapia é uma modalidade médica que tem se revolucionado constantemente com a oferta de sistemas computacionais tridimensionais para planejamentos de tratamento (TPS), proporcionando maior segurança na liberação da dose de radiação no volume alvo, melhorando a resposta terapêutica e minimizando os efeitos radiobiológicos indesejados. A incorporação de modernas técnicas radioterápicas, juntamente com estudos que contribuam para o desenvolvimento de protocolos de radioterapia em medicina veterinária, pode contribuir para a melhoria da qualidade dos tratamentos e sobrevida dos animais acometidos de câncer. Foi utilizado um TPS aplicado em clínica de radioterapia humana e adequado os parâmetros radiométricos, clínicos e anatômicos para a viabilidade do uso na radioterapia veterinária. Para a

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realização foram usadas imagens tomográficas da região pélvica de animais selvagens assistidos pela Faculdade de Medicina Veterinária e Zootecnia (FMVZ/UNESP). As simulações foram feitas com imagens institucionais e não foram utilizados animais in vivo. Foram verificados protocolos para a implantação dos planejamentos computacionais em veterinária mediante a análise da homogeneidade da distribuição de dose de radiação no volume de tratamento planejado (PTV) e a garantia da proteção dos órgãos circunvizinhos ao PTV. A metodologia aplicada para uso do TPS Eclipse em planejamentos de radioterapia veterinária se mostrou exequível, e pode se apresentar como uma importante ferramenta para melhorar as condutas terapêuticas oncológicas veterinárias.

Palavras-chave - radioterapia conformacional; neoplasias; medicina veterinária.

INTRODUCTION

Cancer is a disease that affects both humans and animals, being responsible for a high mortality (Gordon e Kent, 2008; Moreto e Correa, 2013). Cancer represents the main cause of death in dogs in developed countries (Craig, 2001; Proschowsky et al., 2003; Siegel et al., 2013). In Brazil, studies indicate cancer as the second leading cause of death in pets and as the first, in elderly animals (Bentubo et al., 2007; Fukumasu et al., 2015).

Cancer is a recurring problem in zoo animals. Captive animals tend to live longer than in the wild and, as a result, there is an increase in animals with neoplasms. In an informal survey at a large zoo, it was observed that almost half of all mammals undergoing necropsy had some type of cancer. This event motivated specialists to research and develop therapeutic approaches (curative and palliative) for many types of cancer over the years, including the application of radiotherapy (Stoskopf et al., 2012; Kent, 2017; Vettorato et al., 2017a).

Radiotherapy is the technique of treating diseases through ionizing radiation beams.This aims to destroy tumor cells, prevent their multiplication and save damage to the surrounding tissues. Compared to other modalities, radiotherapy provides fewer side effects than chemotherapy and makes it possible to treat inoperable tumors. The success of radiotherapy depends on several factors, including the precise elaboration of the treatment plan, ensuring that the radiation beam reaches the target with precision, or injury, of interest (Fernandes, 2000; Okuno e Yoshimura, 2010; Larue e Gordon, 2013; Foster e Smith, 2015).

With technological advances in recent decades, modern radiotherapy planning systems, called TPS (Computerized Treatment Planning Systems), have been created using computational tools that allow the three-dimensional visualization of the anatomical region to be treated, allowing a better knowledge of the dose distribution and contribute to better homogeneity of the recommended radiation dose profile. In this way, it is possible to release high doses of radiation in the lesion with greater preservation of the surrounding healthy tissues, considerably minimizing the deleterious effects of the treatment (Iaea, 2004; Forrest, 2011; Guimarães, 2013; Van Hoof et al., 2013; Larue e Custis, 2014; Feng et al., 2016).

The computational routines of the current TPS and their interfaces use radiometric, anatomical and clinical parameters stipulated for radiotherapy in human medicine. (Owadally e Staffurth, 2015). However, the indication for radiotherapy in veterinary medicine has been growing, and the therapeutic results are increasingly promising (Burg e King, 1997; Fernandes et al., 2010; Keyerleber et al., 2012; Farrely e Mcentee, 2014; Vettorato et al., 2017b).

These are complex techniques that require a lot of efficiency and involve multi-professional activities, studies should be developed aiming at adapting the radiotherapy protocols already consolidated in human medicine for their safe use in veterinary medicine (Andrade e Fernandes 2014). However, it is necessary to incorporate new forms of therapy that bring real benefits to veterinary patients, which makes it possible to increase survival, local control of the disease or even to improve the quality of life. In this sense, the university can play an important role in the development of research that offers knowledge that enables the training of specialists and professionals trained in the use of TPS in the veterinary oncology routine.

The performance of radiotherapy procedures in veterinary medicine in Brazil has been routinely performed in São Paulo and Rio de Janeiro. However, applications of radiotherapy in wild animals are limited in isolated scientific research conducted in some academic centers, without, however, constituting consolidated routine protocols (Fernandes et al., 2010; Andrade and Fernandes, 2014). In wild animals specifically, no study related to radiotherapy was conducted nationally, especially for the pelvic region. Therefore, the development of studies will contribute to a better understanding by veterinarians of the concepts and techniques of radiotherapy.

In this research, the TPS of the Eclipse System was studied, which is a 3D radiotherapy planning system used in the routine of human radiotherapy services, of the Varian Medical Systems brand. The radiotherapy planning tools of these computer systems were adapted to the specificities of veterinary radiotherapy, adjusting the radiometric, clinical and anatomical parameters of the main species of wild animals so that they can be interpreted by the pelvic region treatment plans in these animals.

MATERIALS AND METHODS

This research was approved by the Ethics Committee on Animal Use (CEUA) (Protocol n °0099/2017) School of Veterinary Medicine and Animal Science (FMVZ), Botucatu Campus, Paulista State University (UNESP).

For the realization of radiotherapy plans, the Eclipse System TPS was studied, used in the routine of human radiotherapy services, which incorporates Varian linear accelerator technologies.

Subsequently, a search was made in the computerized tomography (CT) image collection of the Veterinary Radiology sector of FMVZ de Botucatu, available in the Synapse Pacs® software. (Program System, Fujifilm, Tokyo, Japan) from the same institution for the simulation. At the end of the search, five computed tomography (CT) examinations of the pelvic region of wild animals in different species were selected, namely: a lioness (*Panthera leo*), a coati (*Nasua*), a bush dog (*Cerdocyon thous*), a maned wolf (*Chrysocyon brachyurus*) and a giant anteater (*Myrmecophaga tridactyla*). All selected exams belonged to mammalian animals, and of them, only the case of the lioness who had a diagnosis compatible with leiomyosarcoma by histopathological examination. No in vivo animals were used in the study.

In the other images, neoplastic regions were simulated. The simulated regions for the planned treatment volume (PTV) were vulva for the coati, prostate for the bush dog, left femur head for the maned wolf and straight for the giant anteater.

The images were taken, digitally, to the medical physics room of the radiotherapy sector of the Clinics Hospital of the Botucatu School of Medicine (HC-FMB) and inserted in the workstation for contours of the anatomical regions of interest of analysis for treatment. The computational tools of the TPS Eclipse were adjusted to perform the veterinary anatomical contours, in accordance with the respective specificities. After the outline of the risk organs (OAR) surrounding the target irradiation volume and the PTV, the images were transferred to the radiotherapy planning station for treatment simulations

At the radiotherapy planning station, the radiometric, clinical and anatomical parameters for interpretation by TPS were adjusted. The irradiation fields were designed to encompass the entire tumor volume, considering safety margins according to clinical protocols used in radiotherapy for humans. The radiation fields were simulated for different dimensions and angles of the gantry considering the isocenter positioning technique. For each of the simulations, the respective dose-volume histograms (DVH) were obtained, which were analyzed in order to evaluate the conditions of radiation dose distributions in the PTV and in the OAR, aiming to reference the quality of the radiotherapy planning. For an effective planning, it is desired that the radiation dose in the PTV is the closest to the recommended dose, and that the doses that reach the OAR are the minimum possible and below the dose limits known in human medicine for these organs, satisfying the clinical protocols.

RESULTS AND DISCUSSION

All simulations presented below were performed using previous imaging tests in the institution's archives and do not show the results in live animals.

Regarding the organs of interest analyzed, doses of 15%, 20%, 25%, 35%, 50%, 70% of their volume were evaluated in the rectum (parameters analyzed at the institution). In the bladder, doses in 15%, 25%, 35%, 50%, 55% of their volume were analyzed. The femur heads were analyzed in 10% and the maximum dose at 1%. The maximum dose values for the risk organs of the pelvic region used in HC-FMB were extracted from the literature (Fiorino et al., 2009; Michalski, 2013; Michalski et al. 2010; Viswanathan et al., 2010) and the OAR related to their respective design colors are illustrated in Table 1.

Table 1 - Dose limits for organs at risk and PTV in the pelvic region, with their respective colors.

Organ	Dose x volume		Color
Bladder	80Gy < 15%	75Gy < 25%	
Bladder	70Gy < 35 %	65 Gy < 50%	Yellow
Bladder	50Gy < 55%		
Rectum	75Gy < 15%	70Gy < 20%	
Rectum	65Gy < 25%	60Gy < 35%	Brown
Rectum	50Gy < 50%	40Gy < 70%	
Right fêmur	50Gy < 10%	Dmáx (1%) 55Gy	Purple
Left fêmur	50Gy < 10%	Dmáx (1%) 55Gy	Orange
PTV	95% (prescribed dose) ≥ 95%		Red

Gy = Gray

In the first case (lioness) two plans were made. In the first, the boxed technique was used, which consists of four parallel-opposite radiation fields (ventral, dorsal, right and left sides). In this technique, the beams of the four fields converge at a single point, where the central rays intersect, that is, at the center of the PTV.

This can be performed using isocentric fields or fields with fixed source-surface distance, beam technique in two 120° rotating arcs, combination of both or three field technique (one ventral field and two parallel and opposite right and left side fields). The treatment with rotational technique (360°) can also be used as a dose reinforcement (in a second phase), however, with this technique the dose in the ventral rectal wall is higher

For all treatment fields, the same weight was considered. For the two side fields, two wedge filters were used, as the use provides clinical advantages regarding the distribution of radiation dose to the periphery of the field. In this case, the filter was used to minimize the dose to the femur heads and also to make the dose in the PTV more homogeneous.

In the second planning, from the same lioness, six angled radiation fields were used: 0°, 45°, 90º, 180°, 270º, 315º, also with equal weights and wedge filters in fields two and six, for better homogeneity of the distribution dose in the irradiated volume.

The total dose in both plans was 4,500 centiGray (cGy), with 25 fractions of 180cGy, following the recommendations in the literature for the treatment of human tumors, (Salvajoli et al., 2013), which was also followed in the next plans, except for the maned wolf. In all plans made, the margins chosen for the adjustment of the multileaf collimator (MLC) were 0.5cm in all directions of the PTV and for all plans. Also in all plans, the isodoses were normalized to the point of maximum dose, in this case the 95% isodose was chosen, which encompasses the entire target volume (Figure 1).

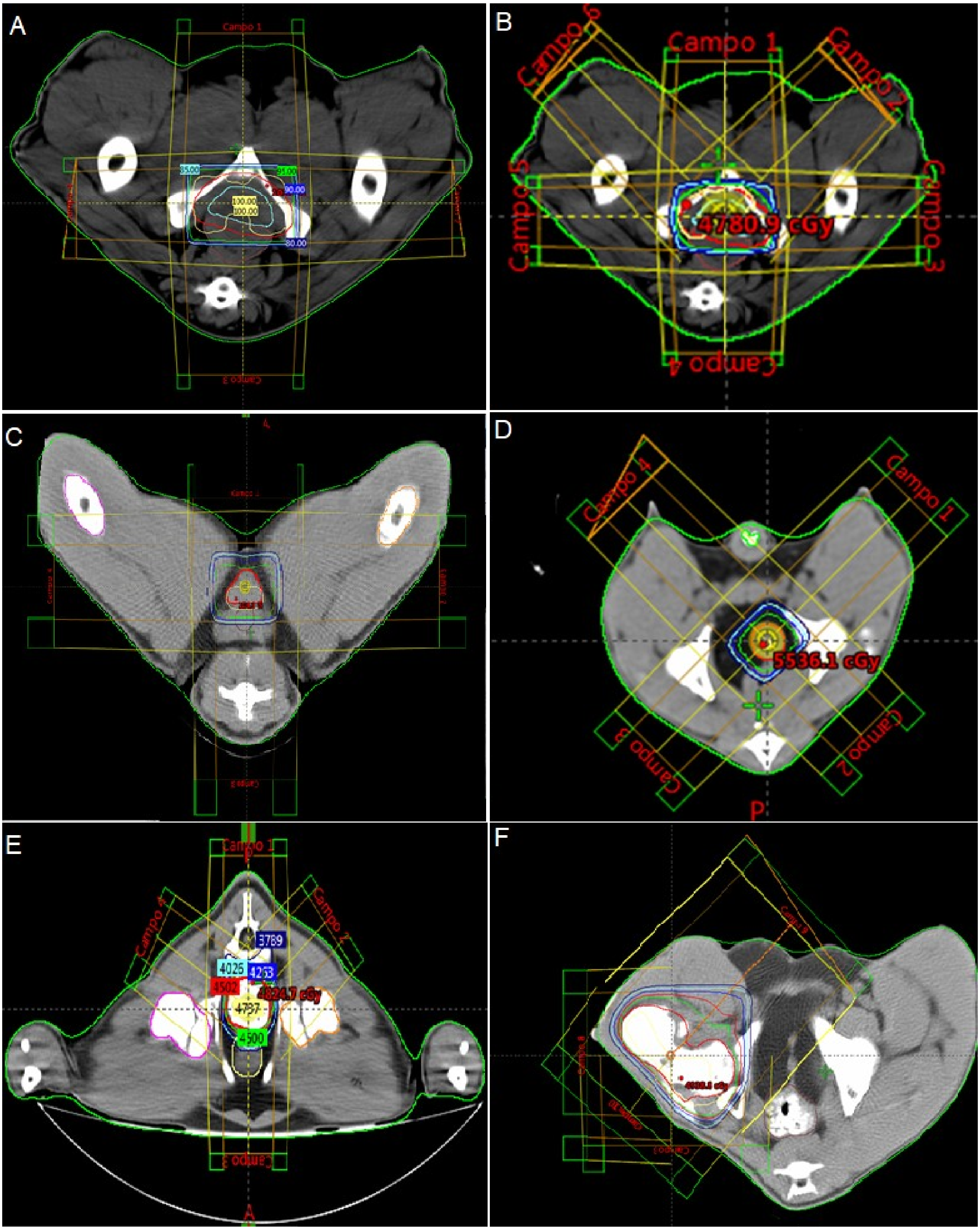

Figure 1 - Tomographic images of radiotherapy plans with their respective irradiation fields and isodose curves in the PTV region. Figure 1.A corresponds to the first planning done on the lioness, where the boxed technique was used, which consists of four parallel-opposite radiation fields. Figure 1.B corresponds to the second plan also with the image of the lioness, where six irradiation fields were used. Figure 1.C illustrates the planning of the coati, where the boxed technique was also chosen. Figure 1.D shows the planning of the bush dog where four irradiation "X" fields were used. Figure 1.E corresponds to the radiotherapy planning of the giant anteater, where four irradiation fields were chosen, two of them parallel-opposite and others at 50° and 300°. Figure 1.F shows the planning of the maned wolf, where seven irradiation fields were used.

In the second case (coati) and in the subsequent cases, only one planning was made, all of which were treated with isocenter techniques at a fixed distance of 100cm for a 6MeV linear energy accelerator.

For the planning of the coati the four-field technique (in box) was also chosen.

The total dose was 4500cGy, with 25 fractions of 180cGy. No filters were used, and the weight was the same for all fields.

For the third planning done, which represents the tomography of the bush dog in which four fields were arranged at an angle of 45°, 135°, 225° and 315°, forming an "X", a technique used to decrease dose in OAR. The weights were higher in fields one and three, worth two.

The total dose was 5400cGy, with 27 fractions of 200cGy. Filter was used only in field one.

In the fourth planning done, which represents the tomography of the giant anteater, four fields were used, two of them ventral (0°) and dorsal (180°) and the others at 50º and 300º, with only the 180º field with greater weight, of 1.6.

The total dose was 4800cGy, with 24 fractions of 200cGy. No filters were used.

In the fifth and last planning done, which represents the maned wolf tomography, seven fields were used, four of them normal with angles of 45°, 180°, 220° and 270°, with weights of 1.2, 1.3, 1.3 and one respectively. And three other fields used with the field-in-field technique with the same angles at 45°, 220°, 270° with a weight of 0.1. Using multiple fields allows less dose to be delivered directly to the OAR.

According to Martins et al. (2012) the field-in-field technique shows great improvements regarding the homogeneity of dose delivery, adding smaller fields within a main field. These subfields are collimated in overdose regions, following the contour of the isodose curve, and part of the main field weight is distributed to the subfields, improving uniformity and gradient.

The total dose was 4800 cGy, with 16 fractions of 300cGy, recommended for the treatment of osteosarcoma in dogs (Coomer et al., 2009). The margins chosen to adjust the MLC were 0.5 cm in all directions of the PTV. Isodoses were normalized (at the maximum point). A 45° field filter was used.

The DVH x volume (Figure 2) was analyzed for the target volume (PTV) and for the OAR. In all simulated radiotherapy plans, the constrained dose values of the OAR remained within the acceptable limit (Table 1), according to their respective DVH.

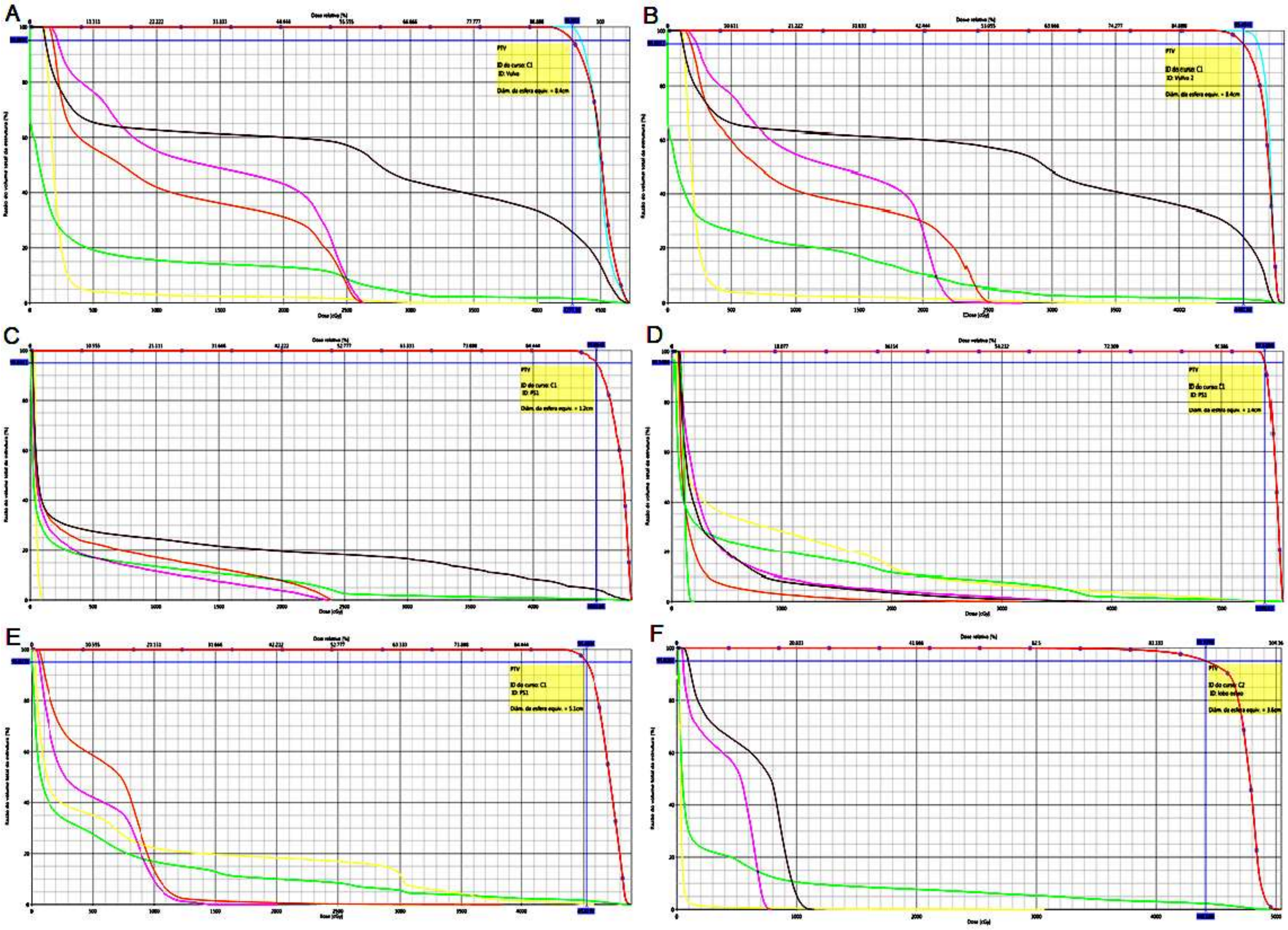

Figure 2 - Histograms of dose x volume of radiotherapy plans performed. The X axis represents the dose in cGy and the Y axis the ratio of the total volume of the structure in %. Figures 2.A, 2.B, 2.C, 2.D, 2.E and 2.F represent the first planning of the lioness, the second also of the same lioness, coati, bush dog, giant anteater and maned wolf, respectively.

Comparing the two lioness plans made with four fields and six fields, we observed that the second plan obtained lower dose values in the OAR, indicating that an increase in the number of fields may result in a dose reduction in the OAR.

For the planning of the bush dog, only the penile bone was not analyzed because it did not present reference to dose values described in the literature, however, it received a very low dose compared to the other OAR.

The protocol established for the Radiotherapy service of HC-FMB at UNESP, says that the main physical parameter evaluated is that at least 95% of the PTV receives 95% of the prescribed dose, after which it is analyzed if the upper limit of 7%, which is the one established by the International Commission for Radiation Units and Measures (ICRU) has been exceeded. If the two parameters are within the limits, the plan can be approved, otherwise, if the maximum dose value exceeds the dose value stipulated by the ICRU, the planning hot spot (maximum dose point) is evaluated. With the hot spot within the PTV the planning can be approved. As the tumors do not have a uniform shape, it is impossible to follow strict criteria for approval of the plan, the most important from the clinical point of view is to treat the tumor with less dose in the organs at risk.

Only the maned wolf did not stay within the established limit that 95% of the PTV received at least 95% dose, and this received a lower dose than this established, probably because the size of the simulated mass is exacerbated and very close to the surface, which does not allow homogeneous dose distribution. This, perhaps, could be solved by using boluses on the spot.

The total prescribed dose varied between 4,500cGy and 5,400 cGy. The radiation dose choice is made by the radiotherapist and in these cases it was chosen in the literature, mainly from humans.

The dose described for the maned wolf simulation was obtained based on reports of osteosarcomas in dogs due to the frequent involvement of this neoplasm in the species (Comer et al., 2009).

The determination of the dose protocol is mainly influenced by the patient's clinical conditions and disease stage, which also interferes with the number of radiotherapy fractions, which varied between 28 to 39 fractions in humans. Fewer fractions should be performed on animals, due to their more difficult execution, due to multiple factors, as well as availability of owners, sedation of animals and cost of treatment. For wild animals, reducing the number of fractions can minimize management stress.

Another limitation is due to the conditions of animal management, such as the animal's tolerance during anesthetic procedures in each dose fraction, as each case has to be considered during radiotherapy planning. Due to the animal's limitation in tolerating anesthesia conditions, many international veterinary radiotherapy services adopt radiotherapy protocols with dose lowering (higher doses and less treatment fractions) (Burk e King, 1997; Larue e Gordon, 2013; Farrelly e McEntee, 2014). However, protocols based on human medicine, such as 25 fractions, were chosen in this study precisely to evaluate the behavior of the isodose curve in the tissues of the animals in each case.

The tolerance of normal tissues to radiation is not only a function of the dose, but also of the fractionation and volume of the irradiated organ. For dose fractions, we try not to stray too far from the daily dose of 180 to 200cGy, which is the traditional fractionation used in external radiotherapy. For this work, only the dose of the last planning (maned wolf) exceeded the dose traditionally used, being 300cGy divided into 16 fractions, which is frequently seen in the dose protocols for animals.

The number of radiation fields, as well as their respective weights and the filters used for each clinical case are defined by the medical physicist who assesses the need to achieve a better distribution of radiation dose in the PTV and less dose in the organs at risk. For the five animals analyzed, the minimum of fields used was four and the maximum of seven.

CONCLUSIONS

The methodology applied for the use of TPS Eclipse in veterinary radiotherapy planning proved to be feasible and can present itself as an important tool to improve veterinary oncological therapeutic approaches.

In order for radiotherapy planning to take place with excellence, the work of many professionals is necessary, from doctors, veterinarians, medical physicists and radiology technicians, showing the great multidisciplinarity of the area.

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