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APPLICATIONS OF INTRAOPERATIVE BETATHERAPY IN VETERINARY ONCOLOGY

(*Aplicações da betaterapia intraoperatória na oncologia veterinária*)

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ABSTRACT - Betatherapy is a radiotherapy modality that uses beta radiation applicators used in the treatment of superficial injuries. With the advancement of therapeutic techniques, new clinical protocols of veterinary medicine will be established and betatherapy emerges as an important option for performing radiotherapy procedures, and further studies for the definition of oncological clinical protocols become necessary. This study reports some procedures in animals involving intraoperative betatherapy with a strontium-90 applicator (^{90}Sr). Five procedures were performed, including 1 lioness (*Panthera leo*), 2 rats (*Rattus norvegicus*), 1 equine female (*Equidae*) and 1 rabbit (*Oryctolagus cuniculus*), all with a confirmed diagnosis of neoplasm. The TDF (Time-Dose-Fraction) radiographic model was used to determine the radiological equivalent of the clinical cases. It was observed that the neoplasms in each case (1 to 5) partially differed from those found in the literature on intraoperative betatherapy in veterinary medicine. We observed that the radiologic effectiveness of the treatment was directly related to the value of TDF. Cases 1, 3 and 4 presented TDF values greater than 175, which implies a greater probability of injury control. As observed in the follow-up of the patients, case 5 (lower TDF) presented tumor recurrence only one month after the betatherapy procedure. Betatherapy with Sr^{90} applicators has proven to be feasible and easy to handle for the clinical cases analyzed in this study, especially during intraoperative procedures.

Key words - brachytherapy; strontium-90; veterinary medicine.

RESUMO - A betaterapia é uma modalidade de radioterapia que utiliza aplicadores de radiação beta, os quais são usados no tratamento de lesões superficiais. Com o avanço das técnicas terapêuticas, novos protocolos clínicos da medicina veterinária serão estabelecidos e a betaterapia surge como uma opção importante para a realização de

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procedimentos radioterápicos e consequente estudos para definições de protocolos clínicos oncológicos. O presente estudo relata alguns procedimentos em animais envolvendo betaterapia intraoperatória com aplicador de estrôncio-90 (Sr^{90}). Cinco procedimentos foram realizados, incluindo 1 leoa (*Panthera leo*), 2 ratas (*Rattus norvegicus*), 1 fêmea equina (*Equidae*) e 1 coelho (*Oryctolagus cuniculus*), sendo todos com neoplasia confirmada. O modelo radiobiológico do TDF (Tempo-Dose-Fração) foi usado para determinar o equivalente radiobiológico dos casos clínicos. As neoplasias acompanhadas em cada caso (1 a 5) diferiram parcialmente das que foram identificadas na literatura consultada sobre a betaterapia intraoperatória em medicina veterinária. Foi observado que a efetividade radiobiológica do tratamento está diretamente relacionada com o valor do TDF. Os casos 1, 3 e 4 apresentaram valores de TDF maiores do que 175, o que implica em maior probabilidade de controle da lesão. Conforme observado no seguimento dos pacientes, o caso 5 (menor TDF) apresentou recidiva tumoral com apenas um mês após o procedimento betaterápico. A betaterapia com aplicadores de Sr^{90} mostrou-se exequível e de fácil manuseio para os casos clínicos analisados neste estudo, principalmente nos procedimentos intraoperatórios.
Palavras-chave - braquiterapia; estrôncio-90; medicina veterinária.

INTRODUCTION

Radiotherapy is the medical modality that uses sources of ionizing radiation to treat diseases, especially cancer (Mcniel, 2009). In veterinary medicine, the use of radiotherapy is already established in several countries. In Brazil it is still a procedure under study, but the applications of radiotherapy in veterinary have shown excellent results (Fernandes et al., 2010). The feasibility of the technique depends mainly on the consolidation of the procedures and the success of the therapeutic proposal (Fernandes et al., 2003).

Radiotherapy in veterinary medicine has found a strong focus in the therapeutic results offered (Andrade and Fernandes, 2015). According to reports in the literature, radiotherapy started in 1927 and, since then, this oncological modality has been growing all around the world (Burk and King, 1997). Research involving this therapeutic modality in animals is growing slowly in Brazil, and the studies point to the need for a deeper understanding of the techniques performed and better knowledge of the applied radiation sources (Vettorato et al., 2017; Vettorato et al., 2019).

Betatherapy is a modality of radiotherapy (brachytherapy) that uses beta radiation applicators and is widely used in the treatment of superficial injuries since beta particles have great ionization power and small reach in the tissue, which means that beta applicators accumulate large doses over small volumes (Scaff, 2010). This practice has become increasingly more available and has been applied in the treatment of neoplasm in several animal species using strontium-90 (^{90}Sr) (Andrade et al., 2004; Kent 2017).

^{90}Sr refers to a radioactive element that can be placed on the surface of a tumor to provide radiation. In this case, the maximum dose is administered on the surface and decreases rapidly, with only about 10% of the administered dose reaching a depth of 3 mm (Fernandes et al., 2007). This property has advantages and disadvantages. Delivering the dose superficially means that it is not effective for deep tumors, but it has the advantage of preventing the dose from reaching deeper and normal tissues, which means that a high dose can be administered without damage to the underlying normal tissue (Kent, 2017). The probe is usually held in a device during treatment to minimize personal exposure, although the dose rate is determined by the age of the individual probe, most treatments can be done in 3 to 5 minutes per application (Fernandes et al., 2007; Kent, 2017).

With the advancement of therapeutic techniques, new clinical protocols in veterinary medicine will be established. In this sense, betatherapy appears as an important option for performing radiotherapy procedures and further studies are needed for the definition of oncological clinical protocols. This study reports some procedures in animals involving intraoperative betatherapy with a ^{90}Sr applicator at the School of Veterinary Medicine and Animal Science (FMVZ), São Paulo State University (UNESP) and the feasibility of this practice in veterinary oncology.

MATERIALS AND METHODS

This research was approved by the FMVZ/UNESP Ethics Committee on the Use of Animals (CEUA) (Protocol No. 0050/2017).

The procedures were performed on five animals belonging to the FMVZ (1 lioness (*Panthera leo*), 2 rats (*Rattus norvegicus*), 1 female horse (*Equidae*) and 1 rabbit (*Oryctolagus cuniculus*), all of which had a confirmed diagnosis of neoplasm.

All betatherapy procedures were performed with the same ^{90}Sr applicator (model Amershan - SIA 20-1102 ML), calibrated at the Brazilian Institute for Energy and Nuclear Research (IPEN/CNEN-SP) calibration laboratory on 13/01/2009.

The Time-Dose-Fraction (TDF) radiobiological model (ORTON and ELLIS, 1973) was used to determine the radiobiological equivalent of the clinical cases treated in this work.

RESULTS

In the first case (1) is of a lioness *(Panthera leo)*, approximately 14 years old, unneutered, obtained from a private breeding ground. The animal was sent to the Center for Medicine and Research on Wild Animals (CEMPAS) with a history of weight loss and possible recurrent vaginal prolapse 2 months ago.

After applying chemical restraint, the physical condition of the animal was examined, revealing a pedunculated mass approximately 20 cm in length, reddish in color and fibroelastic consistency, located on the floor of the vagina. The mass was submitted to cytopathological and histopathological exams, the results being compatible with leiomyosarcoma.

The animal was submitted to general inhalation anesthesia so a computed tomography exam could be performed in the diagnostic imaging sector. The tomography was performed on a Shimadzu CT scanner (model SCT 7800 TC Helicoidal 1-channel), before and after the injection of intravenous contrast, in order to characterize the location and extent of the neoplasm and plan the surgery and betatherapy. In the images, the presence of vaginal mass was noted, with soft tissue attenuation values between 20 and 60 Hounsfield Units (HU), measuring approximately 14.0 cm x 4.32 cm x 4.76 cm (craniocaudal x dorsoventral x lateral) and showing slight homogeneous enhancement after injection of the contrast medium.

The surgical procedure was then chosen, and the mass was excised at its base before betatherapy was applied. The urethra was kept probed during the intervention to avoid iatrogenic trauma.

Betatherapy was performed on February 5, 2016, the current radioactive activity of plate 1 was 34.21 mCi / 1265.32 MBq and the dose rate was 27.24 cGy/s. The animal received a single dose fraction, which was distributed in 12 fields due to the extent of the injury and the size of the active volume of plate 1. The exposure time in each radiation field was two minutes, corresponding to a dose of radiation of 3,269 cGy (in each field). The radiotherapy procedure lasted for a total time of 24 minutes. Next, the vaginal mucosa was sutured.

The animal showed good recovery and, two weeks after the procedure underwent a tomographic examination, which revealed a circumscribed area with partially defined edges was visible, with soft tissue attenuation values, approximately between 20 and 60 HU, measuring about 4.50 cm x 3.85 cm x 4.24 cm (craniocaudal x dorsoventral x lateral), located on the vaginal bottom and without evidence of enhancement after injection of the intravenous contrast medium, but causing a slight dorsal displacement of the final portion of the descending colon. The images suggested a healing process in the vaginal fundus, considering the injury in involution. The animal returned to its place of origin and, after six months, died from accidental causes unrelated to the neoplasm.

The second case (2) refers to a female Wistar rat *(Rattus norvegicus)*, belonging to a vivarium, which was referred to CEMPAS due to an increase in volume in the abdominal wall region, whose evolution time has not been determined.

Upon physical examination, there was an extensive and firm increase in volume, located in the region of the thoracic and abdominal mammary glands, suggestive of a tumor. Contrast computed tomography was performed in order to determine the extent of the neoplasm for surgical and betatherapy planning.

The tomographic images showed the presence of the mass in the abdominal wall, with attenuation values of approximately 50 HU to 60 HU, measuring about 6.12 cm x 4.32 cm x 4.82 cm (craniocaudal x dorsoventral x lateral).

Betatherapy was performed on March 29, 2018, the current activity of plaque 1 was 32.47 mCi / 1201.39 MBq and the dose rate was 25.86 cGy/s. With the animal under general injectable anesthesia, a total unilateral mastectomy was performed. After surgical excision of the tumor mass, the animal had a cardiorespiratory arrest during the exposure of the fourth field and died. The time for each field was one minute, 1552 cGy per field. Figure 1 illustrates intraoperative betatherapy, after tumor excision. The tumor mass was forwarded for histopathological examination, the result of which was simple tubular breast carcinoma.

The third case (3) was a female Wistar rat (*Rattus norvegicus*), belonging to a vivarium, which was referred to CEMPAS due to the presence of a nodule in the right inguinal region observed for approximately 15 days. Upon examination, a well-circumscribed nodule of approximately 11 cm in diameter was observed, affecting the region of the right abdominal and inguinal breasts, with a multilobed aspect, firm consistency, not adhered and not ulcerated. The cytological examination of the mass was suggestive of carcinoma.

A computed tomography scan with contrast was performed to characterize the location and extent of the neoplasm and plan the surgical procedure and betatherapy. The images demonstrated the presence of the mass with attenuation values between 50 to 60 HU, measuring about 4.37 cm x 2.43 cm x 3.54 cm (craniocaudal x dorsoventral x lateral).

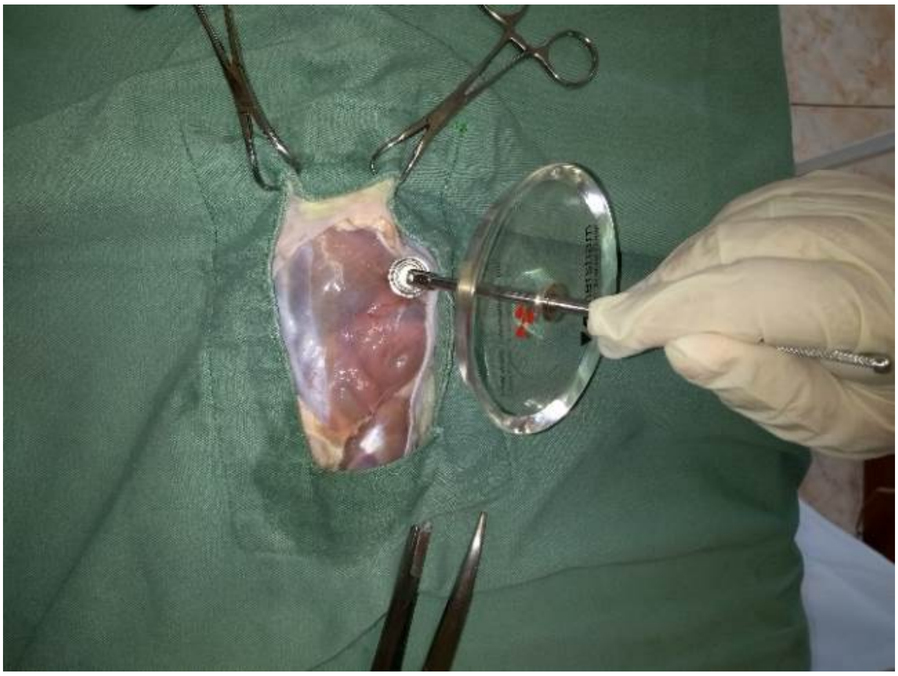
Figure 1 - Betatherapy applied to the surgical bed, after excision of a mammary tumor, in a female Wistar rat - *Rattus norvegicus* (Case 2).

Betatherapy was performed on June 28, 2018, the activity of the betatherapy plate was 32.27 mCi / 1194.13 MBq and the dose rate was 25.70 cGy / s. With the animal under general inhalation anesthesia with isoflurane, a regional mastectomy was performed including right abdominal and inguinal breasts. After surgical excision of the tumor mass, the animal received a single fraction of a dose of 3084 cGy, released in each of the nine treatment fields. The irradiation time per field was two minutes. The total time of the betatherapy procedure was 18 minutes. The animal did not evolve properly in the postoperative period, with reduced food intake, before dying three days later. The mass was forwarded for histopathological examination, the result of which was fibroadenoma.

The fourth case (4) analyzed refers to a female horse (*Equidae*), belonging to a private property in the Rubião Júnior District in Botucatu - SP, Brazil, which was referred to FMVZ, due to the presence of volume increases in the orbital region for approximately three months. Upon physical examination, multinodular dermal tumor masses located in the infra and left supra-orbital regions were found, with the presence of ulceration. A histopathological biopsy confirmed the diagnosis of cutaneous schwannoma.

Betatherapy was performed on April 8, 2016, the radioactive activity of the Sr90 applicator was 34.07 mCi / 1260.42 MBq with a dose rate of 27.13 cGy/s. The surgical procedure was performed at the private property. Therefore, the animal was sedated with detomidine and anesthetic block with lidocaine was applied to the infratrochlear, supraorbital, lacrimal and zygomatic nerves. After tumor excision, the animal received a single dose fraction, which was distributed in 16 radiation fields, 10 fields in the infra-orbital region and six supra-orbital fields. Each field was exposed to a radiation time of two minutes corresponding to a dose of 3,256 cGy. The total procedure time was 32 minutes. Figure 2 illustrates the intraoperative betatherapy of the horse (*Equidae*).

Figure 2 - Betatherapy procedure performed in the orbital region in an equine - *Equidae* (Case 4).

The animal presented good recovery during the first months (Figure 3). In the sixth month after the procedure, the owner reported that the female horse (*Equidae*) was pregnant and without signs of local tumor recurrence.

Figure 3 - Animal recovery after four months of the betatherapy procedure (Case 4).

The fifth case (5) was a six-year-old male rabbit (*Oryctolagus cuniculus*) from a private property, who was referred to CEMPAS due to hypoxia and swelling at the base of the ear for about 25 days. Physical examination identified a tumor mass of approximately 3.5 X 3.0 X 2.5, bilobed, non-ulcerated, fibroelastic, adhered, located on the face near the base of the right ear.

A cytopathological examination was performed, which was suggestive of malignant epithelial neoplasia of cutaneous attachment. Additionally, radiographic examinations of the head and thorax were performed, revealing no bone involvement or signs suggestive of lung metastasis.

Betatherapy was performed on April 26, 2019, at the time, the ^{90}Sr plaque activity was 31.63 mCi / 1170.34 MBq and the dose rate was 25.19 cGy/s. For the procedure, the rabbit (*Oryctolagus cuniculus*) was sedated with midazolam and morphine, followed by general inhalation anesthesia with isoflurane. After excision of the tumor mass with a margin of around 1-1.5 cm, the animal received a single fraction of a radiation dose of 1,511 cGy in each of the 11 treatment fields with an exposure time of one minute in each field. The total procedure time was 11 minutes.

Subsequently, the tissues were approached with sutures. As it was an old animal and due to the risks related to anesthetic maintenance, the previously described exposure time was chosen. Figure 4 illustrates the intraoperative betatherapy of the rabbit

(*Oryctolagus cuniculus*) after excision of the tumor mass. The mass was forwarded for histopathological examination, the result of which was a poorly differentiated malignancy.

Figure 4 - Intraoperative betatherapy procedure, after excision of a tumor mass located on the face, near the base of the right ear, in a rabbit (*Oryctolagus cuniculus*). (Case 5).

The animal returned to the owner the following week and during the first month after the operation presented good recovery. In the second month after the procedure, other tumor masses appeared, one in the region of the right pinna and the other in the region of the face close to the zygomatic bone. Due to the animal's advanced age, palliative therapies (nutraceutical, ozonized oil and acupuncture) were chosen. The animal died four months after the betatherapy procedure, due to a cause unrelated to the tumor.

Table 1 explains the main information about the five clinical cases followed at FMVZ. The TDF values calculated from the clinical cases treated in this work are shown in Table 2.

Table 1 - Betatherapy procedures performed at FMVZ/UNESP.

Case	1	2	3	4	5
Animal / species	Lion *(Panthera leo)*	Wistar Rat *(Rattus norvegicus)*	Wistar Rat *(Rattus norvegicus)*	Equine *(Equidae*)	Rabbit (*Oryctolagus cuniculus)*
Neoplasm	Leiomyosarcoma	Breast carcinoma	Breast fibroadenoma	Schwannoma cutaneous	Malignant epithelial neoplasm of cutaneous attachment
Date	02/05/2016	03/29/2018	06/28/2018	04/08/2016	04/26/2019
Current activity (mCi/MBq)	34.21/ 1265.32	32.47/ 1201.39	32.27/1194.13	34.07/1260.42	31.63/ 1170.34
Dose rate (cGy/s)	27.24	25.86	25.70	27.13	25.19
Number of fractions	1	1	1	1	1
Number of Fields	12	4	9	16	11
Exposure time per field (s)	120	60	120	120	60
Total exposure time (s)	1440	240	1080	1920	660
Total dose (cGy)	3,269	1,552	3,084	3,256	1,511

Legend: mCi/MBq = milicurie/Megabecquerel; cGy/s = centigray per second.

Table 2 - TDF values for the treated clinical cases.

Case	cGy/s Mean	Exposure time (s)	Dose (cGy)	Number of fractions	$d^{1,538}$	TDF
1	27.464	120	3.296	1	257,397.100	193.46
2	26.070	60	1.564	1	81,813.020	61.49
3	25.914	120	3.110	1	235,397.464	176.93
4	27.351	120	3.282	1	255,767.171	192.24
5	25.396	60	1.524	1	78,584.137	59.06

Legend: cGy/s = centigray per second; TDF = Time-Dose-Fraction.

DISCUSSION

Regarding the tumor types referring to the animal species of each case (1 to 5), these apparently differed from those already described about betatherapy in veterinary medicine (Rebhun, 1998; Théon and Feldman, 1998; Knottenbelt and Kelly, 2000; Reed and Bayly, 2000; Andrade et al., 2004; Mcentee, 2004; Mosunic et al., 2004; Goodfellow et al., 2006; Turrel et al., 2006; Donaldson et al., 2006ab; Hammond et al., 2007; Plummer et al., 2007; Montgomery et al., 2010; Nagata et al., 2011; Pignon et al., 2011; Ware and Gieger, 2011; Gardhouse et al., 2014; Nickilin et al., 2014; Knottenbelt et al., 2015; Nevile et al., 2015; Brandão et al., 2015; Berlato et al., 2016; Kent, 2017).

Although reports of betatherapy in lion (*Panthera leo*) have not been identified, there are several studies with ^{90}Sr in domestic cats, used for the treatment of oral and nasal squamous cell carcinoma, mastocytomas, melanomas, limb hemangiosarcomas and superficial eye conditions and conditions benign (Godden, 1988; Goodfellow et al., 2006; Turrel et al., 2006; Donaldson et al., 2006ab; Hammond et al., 2007; Montgomery et al., 2010; Nagata et al., 2011). The radiation dose used in the lion (*Panthera leo*) was 3,269 cGy, distributed in 12 fields, which allowed the tumor to be controlled during observation. In cats (*Felis catus*) with mastocytomas, the radiation dose has varied from 120 to 150 cGy, in varying numbers of fields (1 to 9), with an average survival time of 1075 days (Turrel et al., 2006). For squamous cell carcinoma in cats (*Felis catus),* the radiation dose was 5000 cGy administered in five fractions, which prevented the disease from recurring during a follow-up period of 134 to 2043 days (Goodfellow et al., 2006). In addition, in a study with 11 domestic dogs (*Canis lupus familiaris*) in which partial cystectomy was performed due to transitional cell carcinoma, betatherapy with ^{90}Sr was performed in four applications of five minutes of exposure, totaling a dose of 3000 cGy, and no tumor recurrence was observed during a six-month follow up period (Andrade et al., 2004).

In the two cases of spontaneous neoplasia in rats (*Rattus norvegicus*), a simple tubular mammary carcinoma and another of fibroadenoma, the single radiation doses were 1552 and 3084 cGy, respectively, which were considered safe for the size of the animals. However, it was not possible to evaluate the evolution of the treatment, since both animals died. In a study on the effects of beta radiation on the healing of skin wounds in rats (*Rattus norvegicus albinus, Rodentia mammalia*), a 1.5 cm ^{90}Sr plate with an activity of 50 mCi and an energy of 0.54 megaelectronsvolts (MeV) was also used), using 10 fractions at a dose of 250 cGy, with an exposure time of 13.8 seconds each, totaling a maximum dose of 2500 cGy (Pereira-Filho et al. 1998), which is a total dose similar to that used in the aforementioned cases.

Although there are reports of cutaneous Schwannomas in horses (*Equidae*), these tumors are considered infrequent in the species (Schöniger et al., 2011). In this study, the female horse (*Equidae*) with cutaneous Schwannomas in the supra and infra-orbital regions responded positively to intraoperative betatherapy with ^{90}Sr, with single radiation doses of 3256 cGy. Generally, in horses (*Equidae*), intraoperative treatment with ^{90}Sr is performed to treat the residual tumor after incomplete excision (Théon and Feldman, 1998). In cases of periorbital sarcoids, there are reports of radiation doses of 10,000 cGy, divided across 5 days, during 5 minutes of exposure (Knottenbelt and Kelly, 2000). On the other hand, in cases of periocular squamous cell carcinomas, the local radiation doses were 25,000 cGy, which had a success rate of 89% and had no reports of complications. Therefore, there is a difference in doses. Andrade et al. (2015) evaluated the efficacy of betatherapy with ^{90}Sr as a unique treatment modality in squamous cell carcinomas of the third eyelid of nine dogs (*Canis lupus familiaris*), which was administered in four fractions of 100 cGy per site every four days. Betatherapy was well tolerated in all cases, but there was local tumor recurrence in two animals after 150 days and 352 days, and in the other seven, the disease-free interval ranged between 1239 and 2555 days.

The rabbit (*Oryctolagus cuniculus*) with malignant epithelial neoplasia of the cutaneous annex evaluated in this study showed very rapid tumor recurrence after treatment. One hypothesis was that the exposure time (60 seconds) and the radiation dose (1511 cGy) used in the procedure were of insufficient potency, since this type of neoplasm is very aggressive and due to the location of the injury, may not have been removed to a sufficient extent. There is a report of a case of amelanotic melanoma in a rabbit (*Oryctolagus cuniculus*), in which radiotherapy with ^{90}Sr in a single dose of 15,000 cGy radiation for each of the three fields of the lesion and exposure time of six minutes on the resected surgical bed surface (activity of the radioactive source of 27.6 mCi and dose rate of 41.7 cGy/s) presented a survival time of six months without signs of local recurrence (Brandão et al., 2015).

In this study, no adverse reactions were detected due to beta radiation in the assisted animals. However, the side effects of betatherapy have already been evaluated in some rodent species and, in general, the tissues affected by beta radiation have changed similarly to those treated by comparable doses of X-rays (Friedell, 1951; Friedell, 1954; Snider and Raper, 1951; Fukuyama et al., 1959). In the eyelids of dogs (*Canis lupus familiaris*) and cats (*Felis catus*), corneal healing, conjunctivitis, keratopathy and subsequent effects, such as scleral thinning and focal scleromalacia, have been described as adverse effects (Donaldson et al., 2006b; Nagata et al., 2011; Nevile et al., 2015). In dogs (*Canis lupus familiaris*), less than three months after treatment, conjunctivitis, corneal scarring, granulation tissue formation, focal scleromalacia, deep sclerism, globe perforation, sectoral cortical cataract, localized bullous keratopathy and corneal lipidosis were identified; whereas over three months, deep scleral slippage, lipid keratopathy, deep scleromalacia, deep scleral tuning, deep scleral thinning, globe perforation and lipid keratopathy were detected (Donaldson et al., 2006ab).

The use of betatherapy in veterinary oncology has proven to be feasible for the clinical cases analyzed in this research. The therapeutic result achieved is directly related to the animal's clinical conditions, disease staging and, mainly, dependent on the quality of the applied radiation dose distribution. The feasibility of the betatherapy procedure involves a multidisciplinary team composed mainly of veterinarians with knowledge in oncology, medical physicists, and technologists in radiology, all with adequate training in radiotherapy and radiological protection.

CONCLUSIONS

Betatherapy with ^{90}Sr applicators proved to be feasible and easy to handle for the clinical cases analyzed in this work. The radioactive sources emitting beta particles do not require great care with radiological protection in comparison with other radioactive sources, which contributes to the viability of their handling in veterinary radiotherapy, especially in intraoperative procedures.

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