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Beta therapy with ⁹⁰strontium as single modality therapy for canine squamous cell carcinoma in third eyelid

Betaterapia com estrôncio-90 como modalidade única de terapia para o carcinoma de células escamosas na terceira pálpebra em cães

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ABSTRACT

The purpose was to evaluate the effectiveness of beta-radiation with strontium-90 as single modality treatment of canine third eyelid squamous cell carcinoma (SCC). Nine dogs diagnosed with third eyelid SCC were treated with strontium-90. Radiation therapy was administered in four fractions of 100cGy per site every four days and at a depth of 0.2cm (Strontium-90 build' up) in each fraction. Radiation with beta therapy was well tolerated in all animals with no occurrence of radiation induced cataracts. In all cases, there were increased signs of conjunctival inflammation around the mass, which subsided with topical anti-inflammatory. Two dogs required surgical treatment for local tumor recurrence at 150 days and 352 days. In the remaining seven cases, disease free interval ranged from 1239 days to 2555 days. Beta therapy using ⁹⁰Sr may be a valid alternative for the treatment of third eyelid SCC in dogs.

Key words: beta-radiation, radiotherapy, ocular tumor, adnexa ocular, dogs.

RESUMO

O objetivo foi avaliar a eficácia da betaterapia com estrôncio-90 como modalidade única de tratamento em carcinomas de células escamosas (CEC) da terceira pálpebra de cães. Nove cães foram diagnosticados com CEC da terceira pálpebra, que foram tratados com estrôncio-90. A radioterapia foi administrada em quatro frações de 100cGy por local, a cada quatro dias e a uma profundidade de 0,2cm em cada fração. A betaterapia foi bem tolerada por todos os animais, sem ocorrência de catarata induzida pela radiação. Em todos os casos, houve um aumento dos sinais de inflamação da conjuntiva ao redor da neoformação, as quais cederam com o uso de anti-inflamatório tópico. Em dois cães houve a necessidade de tratamento cirúrgico, pois houve recorrência local do tumor aos 150 dias e aos 352 dias. Nos outros

sete casos, o intervalo livre de doença variou entre 1.239 dias e 2.555 dias. Betaterapia usando ⁹⁰Sr pode ser uma alternativa válida para o tratamento do CEC da terceira pálpebra em cães.

Palavras-chave: radiação beta, radioterapia, tumor ocular, anexa ocular, cães.

INTRODUCTION

The canine third eyelid (TE) is affected by a number of inflammatory and neoplastic conditions as well as anatomical malformations that may require surgical correction (MARTIN et al., 1988). Canine TE neoplasms is uncommon, but mastocytomas (HALLSTRO, 1970), hemangiomas (PEIFFER et al., 1978), hemangiosarcomas (LIAPIS & GENOVESE, 2004), angiokeratomas (GEORGE & SUMMERS, 1990), lymphomas {Hong, 2011, Mucosa-associated lymphoid tissue lymphoma of the third eyelid conjunctiva in a dog} (HONG et al., 2011) and squamous cell carcinoma (SCC) (LAVACH & SNYDER, 1984) have been reported.

The most frequently neoplasm of the third eyelid in all species is SCC (SLATTER, 2001; HENDRIX, 2007). In dogs and cats, ultraviolet radiation exposure, hypopigmented areas and chronic irritative diseases are conditions that predispose to the development of this tumor (BARRIE et al., 1982; BERNAYS et al., 1999; MILLER & DUBIELZIG,

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2007). SCC has been reported to arise from both the palpebral side and the bulbar side of the third eyelid, and it may appear with a dark color and when extensive, SCC may invade the orbit (LAVACH & SNYDER, 1984). Excision of the third eyelid has been reported as curative (PEIFFER et al., 1978; LAVACH & SNYDER, 1984). However, the excision of the entire nictitans should not be taken lightly because significant undesirable sequelae such as ocular drying and chronic keratitis frequently result (LAVACH & SNYDER, 1984; LIAPIS & GENOVESE, 2004). Others therapies, as cryosurgery, have been reported (REBHUN, 1998). Alternatively, the cryosurgery can be used as a single modality or as an adjuvant to excision in advanced canine conjunctival melanomas and SCC (WALKER et al., 1986). Some tumors may be responsive to chemotherapy (e.g., lymphoma, mast cell tumors) and/or local radiation therapy (SCC) (LAVACH & SNYDER, 1984).

Beta radiation is a particulate radiation consisting of high-speed electrons, which are rapidly attenuated by biological tissues (2 MeV beta particles have a range of only 1cm in water) (LOMMATZSCH, 1977; REBHUN, 1990; KIRWAN et al., 2003; DONALDSON et al., 2006). These characteristics make it very useful for superficial radiation treatments where deep tissue penetration is undesirable. Strontium-90 (^{90}Sr) an unstable fission product of uranium-235 (^{235}U) has been found to be a clinically useful source of beta radiation as it has a long half-life (28.7 years) and emits only high-energy beta particles as it decays (McLAUGHLIN et al., 1993; KIRWAN et al., 2003). The effects of beta-ray (^{90}Sr) as a single modality of treatment for SCC of the third eyelid have not been reported in dogs. This treatment may have advantages when compared to the other modalities described in the literature (PEIFFER et al., 1978; LAVACH & SNYDER, 1984; LIAPIS & GENOVESE, 2004), and offers a non-invasive alternative to surgical excisions.

The objective of this study was to evaluate the effectiveness of beta-radiation with ^{90}Sr as a single modality treatment of third eyelid SCC in the dogs.

MATERIALS AND METHODS

Medical records of patients treated for third eyelid tumors with single modality ^{90}Sr radiation therapy between 2007 and 2012 at the São Paulo State University, Veterinary Medicine Faculty (UNESP, Araçatuba, Brazil) – Veterinary Teaching Hospital – were reviewed. These included nine mixed-breed dogs with SCC that involved the palpebral side of the third eyelid.

Complete ophthalmic examination of both eyes was performed in all dogs using slit-lamp biomicroscopy (Slit Lamp SL-15-Kowa, Tokyo, Japan). Fluorescein staining and Schirmer Tear Test 1 (STT-1, Ophthalmo®, São Paulo, SP, Brazil) were performed before and after treatment in all dogs. Diagnosis of SCC was based on the presence of neoplastic or dysplastic/hyperplastic epithelial cells on the exfoliative cytology, characterized by a large quantify of epithelial cells clustered showing marked pleomorphism, anisocytosis, anisokaryose and prominent nucleoli performed by a veterinary pathologist.

All nine dogs were treated with beta therapy using ^{90}Sr radiation in four or six sessions at four days intervals. For each session of beta therapy, the animals were sedated with chlorpromazine (1.0 mg/kg, IV) and optical topical anesthesia with proximetacaine hydrochloride (Anestalcon®, Alcon) was administered.

Using a ^{90}Sr ophthalmic probe of 15mm diameter, a dose based on the tumor size (Table 1) was administered to the surface of the tumor. Radiation dose ranged between 100 and 105 cGy/min, according to the radioactive source test reported by calibration of photon and beta ray sources used in brachytherapy (IAEA-TECDOC-1274, Viena, March, 2002). The fraction dose per second was 27.5cGy^{-1} for the 15-mm applicator. The radiation dose per site was 200cGy at 0.2cm depth in each fraction. The deep dose percentage (relative dose) is characterized as the decrease of the dose relative to the depth of tissue (Table 2). Total doses ranged between 800 and 1200 cGy. The dose on surface of the tumor in each session was 200cGy, and the dose at 2mm of depth was 68cGy, or 30.4% of the dose delivered on the surface.

Treatments extended 3-11 mm beyond the visible tumor margins depending on tumor size. Treatments were performed in four sessions for six cases (dogs #1, #2, #3, #6, #7 and #8), and six sessions for three cases (dogs #4, #5 and #9). The time of each session was variable until the total dose for each case. The interval between each radiation session was four days. After each treatment, the applicators were disinfected according to the protocol mandated by the veterinary hospital's service for hygiene. A radiation physicist examined the applicators annually according to hospital protocol. Table 1 lists all cases, and total radiation doses utilized on each one.

After each session of beta therapy, the animals received dexamethasone ointment (Maxitrol®, Allergan, Brazil) twice a day for 4 days. A telephone interview with the owners was conducted as follow-up to determine progress beyond the last

Table 1 - Cases and outcome of dogs with SCC, treated with Strontium-90 irradiation. Araçatuba, 2014.

Case	Eye	Diameter* (mm)	Total of fractions (total dose-CyG)	Last clinical examination (days)	Last owner contact (days)	Tumor recurrence
1	OS	5 X 5	4 / (800)	98	1543	None
2	OS	5 X 3	4 / (800)	287	2009	None
3	OD	4 X 3	4 / (800)	394	1239	None
4	OD	11 X 6	4 / (1200)	298	2555	None
5	OD	7 X 5	4 / (1200)	189	2033	None
6	OS	4 X 4	4 / (800)	198	2005	None
7	OS	3 X 2	4 / (800)	150	290	Yes (150 days)
8	OS	5 X 4	4 / (800)	352	665	Yes (352 days)
9	OD	6 X 4	4 / (1200)	149	1789	None

*The tumors had on average a height of 2 mm. (Legend: OD=oculus dexter; OS=oculus sinister).

hospital visit. Whenever recurrence occurred, follow-up treatment was pursued.

RESULTS AND DISCUSSION

To the authors' knowledge, this is the first report of the use of beta-radiation (^{90}Sr) as single modality treatment of canine SCC in third eyelid. Radical excision of the third eyelid is the current standard of care (SAITO et al., 2004; HENDRIX, 2007), but it can result in undesirable sequelae, such as ocular drying and chronic keratitis (SAITO et al., 2001; SAITO et al., 2004). To avoid these complications, the authors were motivated to study the effects of beta radiation as an alternative treatment for SCC of the third eyelid.

Nine dogs were diagnosed with SCC during the period of time included in this study. Males and females were affected in the same proportions (5F:4M), and mean age at the time of diagnosis was 5.2 years (range 3-7 years old). The mass was reported to have been noted by the owners, on average one month prior to presentation, as a small purple nodule attached to the third eyelid (palpebral side). Seven of the 9 cases had previously been treated elsewhere with presumptive diagnosis of conjunctivitis, using topical anti-inflammatory medications. In addition to the mass lesion, other observed ocular signs included epiphora, mucopurulent ocular discharge and protrusion of the

third eyelid (cases #4 and #5). SCC comprises up to two-thirds of feline eyelid and third eyelid tumors (LAVACH & SNYDER, 1984) and has a predilection for the lower eyelid and medial canthus of the white cats. Ocular SCC is less frequent in dogs, but in both species increased exposure to solar radiation, lack of adnexal pigmentation, and possibly chronic ocular surface irritation are believed to be the predisposing factors (SAITO et al., 2001). All animals included in this study lived in a region of high solar incidence and this condition may have contributed to the relative young age of incidence (mean of 5.2 years) in our population. The age prevalence for TE SCC in the dog has not been reported, but all animals in this study had a history of chronic inflammation of third eyelid conjunctiva, and it is possible that solar exposure and chronic inflammation might have both contribute to tumor development at a relatively young age.

The palpebral and bulbar sides of third eyelid were examined. In all 9 cases the tumors involved solely the palpebral side of third eyelid. The lesions ranged in diameter from 3.0 to 11.0mm and had an average height of 2.0mm. The SCC was unilateral in all cases and these neoplastic lesions were primary tumors. Fluorescein staining was negative bilaterally in all animals and at all time periods. Schirmer Tear Test (STT-1) before and after treatment was of 13.7 ± 2.1 mm/min and 12.8 ± 1.97 mm min⁻¹, respectively.

Cytological preparations from impression smears and tissue scrapings can be of limited diagnostic value in many conditions (PETSUKSIRI et al., 2008), but exfoliative cytology allowed the diagnosis of SCC of the third eyelid in all dogs in the present report. Biopsies and exfoliative cytology have been also used in the diagnosis of corneolimbic SCC in horses (REBHUN, 1998). Fine-needle aspirates

Table 2 - Deep dose percentage (relative dose) of the strontium-90 (beta therapy) in SCC with 2.0mm of the thickness (by IAEA - TECDOC 1274; Viena, March, 2002). Araçatuba, 2014.

Deep (mm)	0.0	0.5	1.0	1.5	2.0
% dose	100.0	76.6	57.0	41.9	30.4

may be difficult to perform safely at this site unless the patient is anesthetized, and many find it preferable to collect a total excisional biopsy of the lesion once the patient is under general anesthesia (PETSUKSIRI et al., 2008). Excisional biopsy, however, would have compromised the main objective of this study, which was to observe the effects of beta therapy (⁹⁰Sr) as a single modality of treatment, avoiding surgery. Incisional biopsy would have been ideal, but the tumors in these cases were too small to provide incisional samples without compromising the evaluation of the experimental treatment.

Beta-radiation therapy is reported to provide local control of tumors that may invade the orbit (LAVACH & SNYDER, 1984). In horses, combined keratectomy, strontium-90 radiation and permanent bulbar conjunctival grafts was reported to be effective in at least 83% of the cases of corneolimbic squamous cell carcinoma (MOSUNIC et al., 2004). The use of beta-radiation on limbal lesions has been also described as highly effective in horses (LOMMATZSCH, 1977; REBHUN, 1990; REGUEIRO et al., 2002; DONALDSON et al., 2006), as was local surgical resection and adjunctive strontium-90 beta for canine limbal melanoma (CEREZO et al., 1990). The authors conclude that ⁹⁰Strontium therapy produced excellent cosmetic results from the owners' perspective.

SCC of the third eyelid may result in corneal damage and corneal vascularization or pigmentation (LAVACH & SNYDER, 1984). Fluorescein staining was performed before and after ⁹⁰Sr radiation with negative results in all dogs at all times. Tumor location restricted to the palpebral side of the third eyelid may be associated with the absence of signs of corneal ulceration in this population of dogs. Values of STT-1 before and after treatment remained unchanged. Radiation (⁹⁰Sr) is reported to penetrate only 0.2cm deep when doses similar to those in this study are utilized (MORRIS & DOBSON, 2001). Consequently, it is unlikely that significant radiation would have reached the third eyelid gland that has a deeper anatomical location.

One of the advantages of this procedure was the lack of general anesthesia necessary. Sedation and topical anesthesia allowed completion of the procedure without complications. SCCs are of epithelial origin, and therefore responsive to radiation therapy, making these tumors ideal targets for local radiation (CEREZO et al., 1990).

Conjunctival inflammation was observed after treatment, but was likely entirely due to local effects of radiation, and not to infection or primary inflammation

of the tumor itself. Anti-inflammatory therapy may reduce the size of tumors that are infected or inflamed (LAVACH & SNYDER, 1984). Topical administration of corticosteroids, efficiently reduced this ocular signal, similarly to what was reported in 85% human patients with conjunctival lymphoma treated with Strontium-90-Yttrium-90 (REGUEIRO et al., 2002).

Tumor recurrence occurred in two of our patients, at 150 days (case #7) and 352 days (case #8) post-radiation. Recurrence was also reported in 5 of 38 horses, at an average of 449 days post-radiation (ranging from 29 days to 900 days) (MOSUNIC et al., 2004). The recurrence rate among patients of this study was low, suggesting that topical beta-radiation can be an effective treatment modality for SCC of the third eyelid in dogs, similarly to conjunctival carcinoma in human patients (CEREZO et al., 1990). Petsuksiri et al. (2008) related the primary radiotherapy for SCC of the eyelid in human patients, and the report concluded that the radiotherapy provides excellent locoregional control with reasonable complications rates and should be considered an alternative to surgery in selected patients. The non-invasive nature of the procedure described here when compared to surgical excision may prove to be a great advantage of radiation.

Beta-radiation was well tolerated by all dogs in this study. There were no signs of discomfort during the procedure and the dogs did not develop blepharospasm or ocular discharge post-treatment. Two dogs presented with ocular discomfort before the diagnosis (cases #4 and #5) had subjectively decreased intensity of blepharospasm and ocular discharge after the second session of beta therapy. No evidence of intraocular inflammation was observed. Keratitis, periocular dermatitis and cataract have been described in human patients with conjunctival lymphoma treated with beta-radiation (REGUEIRO et al., 2002). The characteristics of the beta-ray emissions then, limited penetration that makes Strontium-90β so suitable for superficial ophthalmic applications (CEREZO et al., 1990) might have contributed to absence of cataracts among the patients of this study. Also, the treatment was carried out on the third eyelid surface and not on the sclera or conjunctiva where the proximity to the lens would be greater increasing the risk of lens damage. An increase in conjunctival inflammation around the mass was observed in all cases during treatment, but the signs subsided with the use of topical anti-inflammatory after two weeks. No evidence of cataracts was seen in any of the dogs during the follow-up period.

Two dogs were surgically treated for tumor recurrence, when the owners declined additional

radiation therapy. Tumor recurrence was diagnosed at 150 days (dog#7) and 352 days (dog#8) post-radiation. The radiation dosages and optimal radiation delivery protocols for conjunctival tumors in dogs have not been established (CEREZO et al., 1990). Our results suggest that the dose and fractionation protocols empirically used in these 9 patients can be curative in cases of canine third eyelid SCC, with minimal side effects. It remains to be seen whether or not ^{90}Sr topical radiation is effective as a rescue treatment after recurrence, and whether or not it improves the outcome of local tumor excision when used in

combination. Median dose of radiation delivered at each application was 200cGy at 0.2cm, resulting in a total median surface tumor dose of 933.3cGy. The average time to achieve the desired dose per session was 7.5 seconds, and the total maximum dose utilized was 1200.0cGy (cases #4, #5 and #9).

Seven/nine dogs remained disease-free with long term follow-up. The mean follow-up time was 1722 ± 427 days (range 1239 to 2555 days). Figure 1 illustrates the typical gross appearance of SCC of the third eyelid during early and late period of treatment, and beta therapy procedure (#case 5).

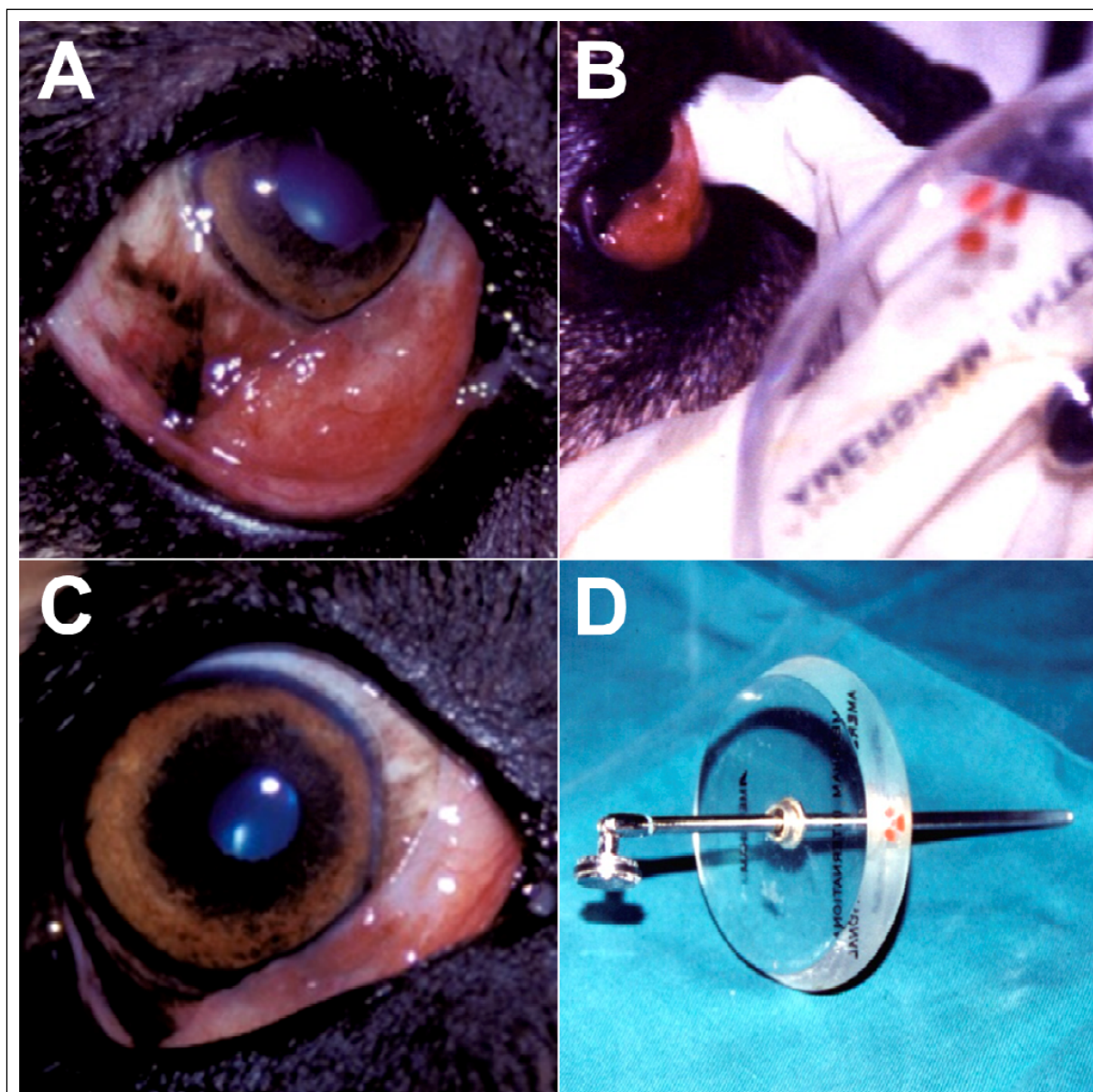


Figure 1 - Canine squamous cell carcinoma in third eyelid (#case 5). (A) Proliferative pink mass at the first clinical examination. (B) Procedure of the Beta therapy with ^{90}Sr radiation. (C) Appearance of the third eyelid after 2033 days of follow-up. (D) ^{90}Sr probe.

The results of this study indicate that strontium-90 radiation can be an effective approach in the treatment of canine SCC of the third eyelid. The association of this therapy with local surgical excision of the lesions may also be a promising alternative to surgery alone and may approximate the excellent control rates reported after simple surgical excision followed by 30Gy beta radiation from a ⁹⁰strontium in human superficial conjunctival SCC (KEARSLEY et al., 1988).

Nonetheless, because recurrence following this modality of treatment is reported to occur in 2 of 9 cases within 8 months, it is important to re-examine patients at least every 6 months, in an effort to identify recurrence early cases. This research emphasizes the importance of performing periodic ophthalmic examination and impression cytology and/or exfoliative cytology to screen patients for early tumor recurrence.

In conclusion, topical beta therapy using ⁹⁰Sr seems to be an efficacious alternative for the treatment of SCC of the third eyelid in dogs. Further investigations into the combination therapy using beta therapy and limited surgical excision with preservation of the third eyelid in similar or slightly more advanced cases are warranted.

ETHICS COMITTEE AND BIOSECURITY

The authors of the article entitled "Beta therapy with ⁹⁰strontium as single modality therapy for canine squamous cell carcinoma in third eyelid" declared, for all due purposes, that the project that gave rise to the present data has not been submitted for evaluation of the Ethics Committee of the Universidade Estadual Paulista "Julho de Mesquita Filho" (UNESP) but they are aware of the content of the Brazilian resolutions of the National Council for Control of Animal Experimentation - CONCEA <<http://www.mct.gov.br/index.php/content/view/310553.html>> which involves animals.

Thus, the authors assume full responsibility for the presented data and are available for possible questions, should they be required by the competent authorities.

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