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Radiotherapy in the treatment of sinonasal neoplasms in dogs

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ABSTRACT: Sinonasal neoplasms represent approximately 1% of all neoplasms and represent a major challenge for treatment. The treatment of nasal tumors must be local, and radiotherapy can be a good option in these cases. This study evaluated the therapeutic response of canine sinonasal neoplasms to megavoltage radiotherapy, and consequently, its influence on the survival and quality of life of these animals. We included 26 dogs with sinonasal neoplasms through histopathological and cytological examination. Dogs were treated with radiotherapy at total doses of 42–54 Gy (for carcinomas) and 45 Gy (for sarcomas) in 15–18 fractions of 2.8–3.0 Gy. Tumor staging was performed based on skull tomography. The most frequent clinical signs of sinonasal neoplasms were sneezing, nasal noise, and epistaxis. Acute side effects were mild and more frequent. Survival was evaluated based on tumor stage, obtaining a mean overall survival of 329 days (95% confidence interval, 229–428) and a median of 252.5 days. The survival time in animals in stage T3/T4 was significantly shorter than that in those in stage T1/T2 ($P < 0.05$). Moreover, 86.4% of the treated animals showed clinical improvement. Radiotherapy was well tolerated by dogs and effective in controlling sinonasal neoplasms.
Key words: dogs, nasal cavity, neoplasms, oncology, radiation.

Radioterapia no tratamento de neoplasias sinonasais em cães

RESUMO: As neoplasias sinonasais representam cerca de 1% de todas as neoplasias e constituem um grande desafio para o tratamento. O tratamento de tumores nasais deve ser local e a radioterapia pode ser uma boa opção nesses casos. O objetivo do trabalho foi avaliar a resposta terapêutica das neoplasias sinonasais caninas à radioterapia de megavoltagem e, consequentemente, sua influência na sobrevida e qualidade de vida desses animais. Foram incluídos 26 cães diagnosticados com neoplasias sinonasais por meio de exame histopatológico e/ou citológico. Os cães foram tratados com radioterapia nas doses totais de 42 a 54 Gy (para carcinomas) e 45Gy (para sarcomas) em 15 a 18 frações de 2.8Gy a 3.0Gy, respectivamente. O estadiamento tumoral foi realizado com base na tomografia de crânio. Os sinais clínicos mais frequentes foram espirros, ruído nasal e epistaxe. Os efeitos colaterais agudos foram mais frequentes e todos de leve intensidade. A sobrevida foi avaliada de acordo com o estágio do tumor obtendo-se uma média de sobrevida global de 329 dias e mediana de 252.5 dias (intervalo de confiança de 95%; IC = 229-428). Animais em estágio T3/T4 apresentaram tempos de sobrevida significativamente menores quando comparados aos pacientes em estágio T1/T2 ($P < 0.05$). Dos animais tratados 86.4% apresentaram melhora clínica. A radioterapia foi bem tolerada pelos cães e se mostrou eficaz no controle das neoplasias sinonasais.
Palavras-chave: cães, cavidade nasal, neoplasias, oncologia, radiação.

INTRODUCTION

Sinonasal neoplasms affect animals with an average age of 10 years (SONES et al., 2013). In dogs, they comprise < 1% of all neoplasms, with a slight overrepresentation of male dogs and medium to large breeds, and tumors of epithelial origin are the most diagnosed, such as adenocarcinomas and squamous cell carcinomas (MALINOWSKI, 2006; COHN, 2020). Both tumors of epithelial and mesenchymal origins tend to be locally invasive, with a reported metastasis rate of approximately 31%, with the lymph nodes and lungs being the most frequent metastasis sites (SNYDER et al., 2008; BOWLES et al., 2016).

The most common clinical signs in dogs with nasal disorders include uni- or bilateral mucopurulent secretion, sneezing, halitosis, respiratory rales, epistaxis, and exophthalmos (FINCK et al., 2015; COHN, 2020). Furthermore, nasal secretions lasting >14 days and are predominantly bloody are highly suggestive of neoplasia (PLICKERT et al., 2014).

The definitive diagnosis of nasal neoplasia is obtained through histopathological analysis from the biopsy. In cases of neoplastic disease, tomography can determine the disease extent. Destruction of the nasal septum, cribriform plate, nasopharynx, and periorbital region and brain invasion (25% of cases) are important factors in therapeutic planning (MAYER et al., 2019; WOODRUFF et al., 2019). In addition to its diagnostic

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value, tomography can also be a good indicator of prognosis (ADAMS et al., 2009).

Treatment of nasal tumors in dogs should focus on local control of the disease because of the low metastatic rate. Surgery, as a single therapy, has been discouraged because data indicate increased morbidity after rhinotomy without an increase in survival (RASSNICK et al., 2006). In most cases, adequate surgical margins cannot be obtained due to compromise of adjacent structures. Megavoltage radiotherapy is the most recommended treatment, contributing to increasing survival and improving the quality of life of animals (YOON et al., 2008).

Sinonasal tumors represent a challenge in oncological treatment. Due to the scarcity of information on the treatment of sinonasal neoplasms in Brazil, this study evaluated the response of sinonasal neoplasms to radiotherapy and their possible side effects and to compile the main epidemiological and clinical data related to the disease.

MATERIALS AND METHODS

The study was conducted in a private clinic in Rio de Janeiro, which specialized in oncological care and treatments. The animals undergoing radiotherapy were of the canine species of both sexes, representing different breeds and ages, and were diagnosed with sinonasal neoplasia obtained through computed tomography and cytological and histopathological examination.

We excluded those not having the clinical conditions to undergo multiple anesthetic procedures and those suspected of distant metastases on previous imaging tests. We included those who underwent previous therapies, such as surgery and chemotherapy, but they were only evaluated in terms of survival time and not the remission rate. We compiled data on age, race, sex, and clinical signs, time of evolution, and diagnosis/histological type of neoplasia.

Staging was based on computed tomography of the skull following the study by ADAMS et al. (2009). Based on this scheme, animals classified as stage T1 had a tumor confined to the nasal cavity in addition to the turbinates without bone involvement. Dogs in T2 had bone involvement other than the turbinates but without evidence of orbital involvement or subcutaneous/submucosal mass. Dogs in T3 already had orbital involvement or subcutaneous/submucosal mass (nasopharynx involvement). Finally, in dogs in T4, the tumor already causes lysis in the cribriform plate. We also used computed tomography in the radiotherapy planning stage.

We used cobalt therapy (Co60) from the Theratron 780C model, with a beam stopper. The radiotherapy protocol used was standard fractionation based on 15–18 fractions performed five times weekly (Monday to Friday). Thus, a total dose of 42–54 and 45 Gy divided into fractions of 2.8–3.0 and 3.0 Gy was used for carcinomas and sarcomas, respectively. The animals undergoing radiotherapy were anesthetized, and the main clinical parameters were monitored in an attached room to protect the team from the radiation.

The tumor volumes before and after treatment was compared to assess response to treatment, and the percentages of reduction and increase in volume were calculated. Thus, the total disappearance of the tumor was considered complete remission, and the reduction of at least 50% of the original tumor volume was considered partial remission. By contrast, an increase in tumor volume or tumor remains unchanged after the radiotherapy protocol indicates progressive disease or lack of response, respectively.

The time of clinical improvement was considered from the time of diagnosis to total absence of clinical signs (decrease/absence of epistaxis and sneezing, reduction in tumor volume when macroscopically visualized). To identify and treat side effects, when necessary, the patients were followed up weekly during the first month after the end of the sessions. Side effects were noted based on severity and time of onset based on the toxicity scale established by the Veterinary Radiation Therapy Oncology Group (LADUE & KLEIN, 2001). Overall survival time was considered from the time of diagnosis to death.

For descriptive statistical analysis, nominal or ordinal variables were presented as frequency, and continuous variables were presented as mean, standard deviation, and median. The Shapiro–Wilk test was used to assess data normality. Subsequently, the nonparametric Kruskal–Wallis H and Mann–Whitney U tests were used to determine the associations between the study variables. The overall survival time in days was evaluated based on the event of interest (death) when compared with the clinicopathological factors and therapeutic approach. The analysis was performed using the Kaplan–Meier nonparametric statistical test. Thus, general survival curves were obtained for each variable. The log-rank test was used to compare the accumulated survival curves between different categories of the same variable. The significance level was 5%, and the confidence interval (CI) was 95%, with statistical significance at $P < 0.05$. All analyses

were performed in IBM SPSS statistical software for science for Windows (version 23.0, IBM Corp., Armonk, NY, USA).

RESULTS

We followed 26 animals (14 males and 12 females) with sinonasal neoplasms throughout the study. Their age varied between 6 and 15 years, with a mean of 10.96 years. The most frequent clinical signs were epistaxis (69.2%; n = 18) and sneezing (53.8%; n = 14), followed by nasal deformity (38.5%; n = 10), respiratory noise and dyspnea (34.6%; n = 9), bulging palate (23.1%; n = 6), and enophthalmos/exophthalmos (19.2%; n = 5). The relationship between clinical signs and survival time was not significantly different.

Of the 26 animals, 18 (69.2%) had carcinoma, ranging from adenocarcinoma to squamous cell carcinoma. Moreover, 5 (19.2%) animals had sarcomas, varying between undifferentiated sarcomas and chondrosarcomas. The diagnosis was inconclusive in three animals even after biopsies and cytology.

In terms of survival time, we only evaluated those that died. Survival time ranged from 43 to 1309 days (mean, 329 days, and median, 252.5 days) (95% confidence interval).

The percentage of animals with stage T4 was 42.3% (n = 11), revealing cribriform plate lysis and brain invasion. Subsequently, 23% (n = 6), 19.2% (n = 5), and 15.3% (n = 4) had stages T2, T3, and T1, respectively. Staging was a variable with statistical difference (P = 0.018), with survival times in patients in stages T3 and T4 after treatment being shorter than those in patients in stages T1 and T2 (Figure 1).

We excluded eight animals from the direct evaluation of the response rate, but we evaluated them in relation to the time of clinical improvement and survival. Of the excluded animals, tomography was not repeated in six animals after the end of treatment, and the two who underwent surgery were excluded from the radiotherapy response calculation.

We evaluated the response to therapy in 18 animals, with 13 (72.2%) presenting partial remission (PR) with a reduction between 20% and 88% of the initial tumor volume. Complete remission (CR), progressive disease (PD), and lack of response were observed in three animals (16.7%), two animals (11.1%), and one animal, respectively (Figure 2). Moreover, two of the excluded patients were considered to have PD due to worsening signs, although CT scan was not repeated after treatment.

Dogs that experienced partial remission had a mean survival time of 320 days (95% confidence interval CI = 220–420) and a median of 193 days, while patients with progressive disease had a mean survival time of 184 days. (CI = 99–268) and median of 157 days. Compared to these, dogs that achieved a state of complete remission lived significantly longer (P = 0.006), with a mean and median survival time of 835 days (CI = 795–875) and 815 days, respectively.

After treatment, 84.6% (22/26) of the animals showed improvement; that is, the animals being asymptomatic. The time to clinical improvement varied between 0 and 1088 days, with a mean and a median of 324 and 181 days, respectively. Only one animal presented chest tomography findings compatible with pulmonary metastasis after the end of treatment. The absence of facial deformity demonstrated a statistically significant association with the clinical improvement of these animals (P = 0.01). Therefore, all animals not presenting facial deformity showed clinical improvement. However, four of seven animals (57.1%) that presented facial deformity obtained the same result.

Acute side effects were more frequent (dry and wet radiodermatitis, alopecia, hyperemia in the oral mucosa, mild mucositis, conjunctivitis, and keratoconjunctivitis sicca) and ranged from mild to moderate, with only one animal showing a serious side effect. All 26 animals presented reversible acute side effects, mainly on the skin, oral cavity, and eyes, and they were adequately treated with antibiotic and/or corticosteroid therapy, when necessary. No patient presented acute effects associated with the central nervous system.

DISCUSSION

Of the 26 animals with sinonasal neoplasms, the number of males was greater than that of females, which was consistent with the literature (MALINOWSKI, 2006; MASON et al., 2013). However, the number of our participants was insufficient to conclude about sexual predisposition in nasal neoplasms. Other studies showed an equal proportion of incidence between males and females, which may corroborate an absence of sexual predisposition (KUBICEK et al., 2016). Their mean age was 11y ears, according to , the age range observed in other studies (MASON et al., 2013; SONES et al., 2013), highlighting the greater tendency for nasal neoplasms to occur in elderly dogs.

The most frequent clinical signs were sneezing, epistaxis, respiratory noise (sign of nasal obstruction), and signs of more advanced disease, such as nasal deformity, bulging palate, and exophthalmos, which are widely described in the literature (MASON et al., 2013; FINCK et al., 2015).

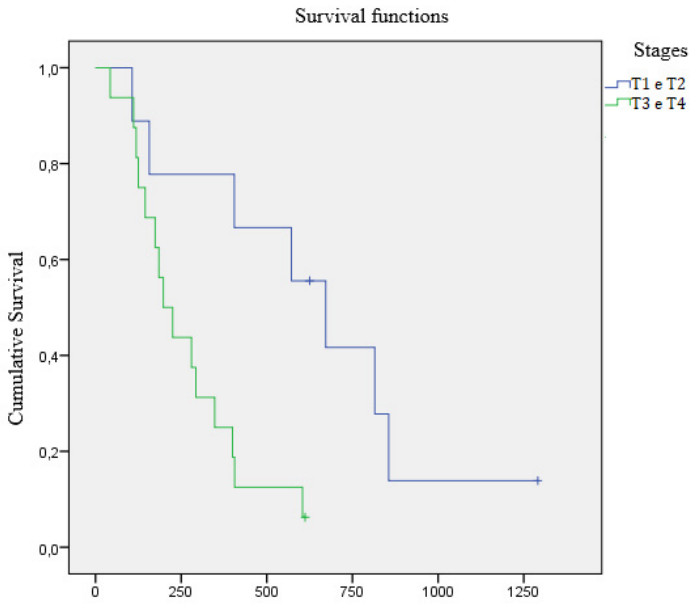

Figure 1 - Comparative survival time in days between stages T1/T2 and T3/T4 of patients undergoing radiotherapy.

The use of tomography staging proposed by ADAMS et al. (2009) was more appropriate in relation to survival and clinical improvement. Most patients (42.3%) were classified as stage T4, indicating a tendency toward a late diagnosis of nasal neoplasms, with data similar to that by another author who also reported regional metastases in 6.1% of the animals, which was not observed in the present study (MEIER et al., 2022). However, we obtained data superior to those evidenced by WOODRUFF et al. (2019), who reported cribriform plate invasion in 14% of animals. Another study reported the late diagnosis of nasal neoplasia, evidenced by cribriform plate destruction in 59% of the animals (MASON et al., 2013). Different stages of the disease can affect the response to therapy. Other studies also reported the association among tumor volume, presence in the nasal cavity, survival, and response of animals to therapy (CZICHON et al., 2022).

The late diagnosis may be due to the similarity of the clinical signs of nasal neoplasia to other upper respiratory tract diseases (fungal/ bacterial rhinitis, severe periodontal disease, foreign body) (COHN, 2020). Using skull radiography as a screening test is a common veterinary routine, or even using antibiotics based on the presumptive diagnosis of bacterial rhinitis; although, uncommon, which causes delays in the diagnosis of nasal neoplasia and treatment initiation (COHN, 2020).

Considering the tumor volume before and after treatment, 72.2% (13/18) and 16.7% (3/18) of the animals showed PR and CR, respectively, which were similar to those obtained by FOX-ALVAREZ et al. (2020) who observed PR and CR in 60% and 10% of animals at the end of treatment, respectively. They also showed a clinical improvement rate of approximately 85%, which was similar to that obtained in the present study. The mean time for clinical improvement was 329 days, slightly longer than that observed in another study (FUJIWARA et al., 2013).

Tolerance to treatment was considered good because most patients had mild to moderate side effects, with acute effects being more frequent and reversible. The most common adverse effects affected the eyes, skin, ocular, and oral mucosa, areas included in the irradiated field. Acute effects on the central nervous system were not observed and are generally related to radiotherapy planning, which were consistent with the existing veterinary literature, wherein radiotherapy toxicity tends to be mild in the treatment of this neoplasia (FUJIWARA et al., 2013; POIRIER et al., 2020). No late effects on the bone or central nervous system were observed.

The mean survival obtained was 329 days, this is a superior result to that described by other authors in studies in which other therapeutic approaches were used, such as surgery and

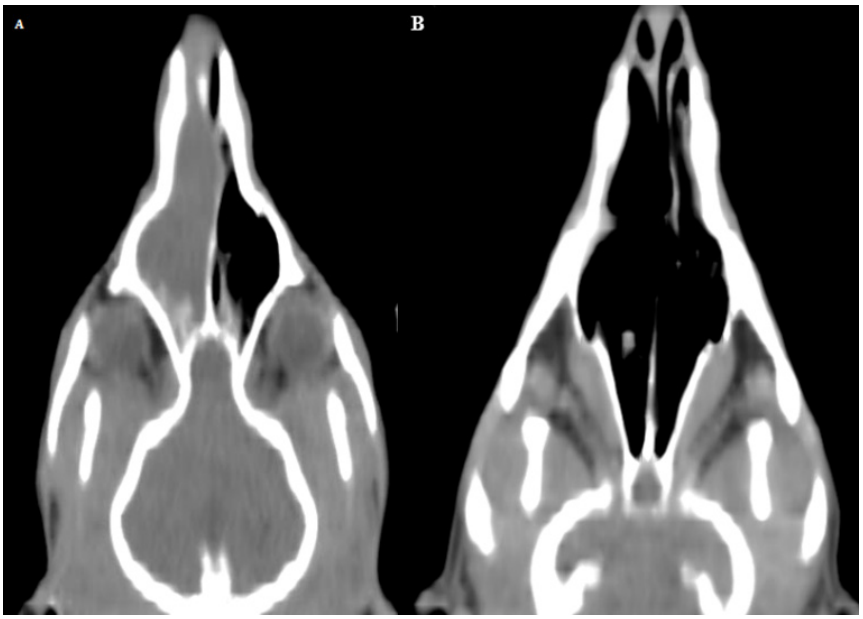

Figure 2 - Computed tomography of the skull of a patient with nasal neoplasia (carcinoma) undergoing radiotherapy, before (A) and after (B) treatment, classified as complete remission. In (A), a soft tissue obliterates the left nasal cavity, and nasal and ethmoturbinate bones are lysed. In (B), maintenance of associated lytic foci is observed, but without soft tissue involvement.

intensity-modulated radiotherapy. (BOWLES et al., 2016). The median of 252.5 days (95% CI: 92.2 – 493.7) is lower than that obtained by MEIER et al. (2022). Other studies used standard fractionation protocols with doses ranging between 42 and 54 Gy and also observed mean survival times of >400 days (ADAMS et al., 1998; YOON et al., 2008). These data are significant, demonstrating that radiotherapy can be a good option as a sole therapy for nasal neoplasms, considering that most patients treated had an advanced disease stage. The treatment will directly influence the time and quality of life patients diagnosed with nasal neoplasia.

Although controversial, most studies report an association between the disease stage and prognosis, which tends to be worse with the occurrence of cribriform plate destruction and brain invasion (MAYER et al., 2019; WOODRUFF et al., 2019). The data obtained corroborates with the literature because a significant statistical difference was reported in relation to survival when the clinical stage was evaluated. Patients with more advanced disease stages had a worse prognosis (shorter overall survival time). The staging system proposed by ADAMS et al. (2009) was adequate to establish the prognosis of patients undergoing treatment.

CONCLUSION

Radiotherapy can increase the survival and quality of life of patients with nasal neoplasia, causing minimal side effects, and is well tolerated by the canine species.

Clinical signs, such as facial deformity, may be associated with a shorter time to clinical improvement in patients with nasal tumors treated with radiotherapy. These signs demonstrated a tendency toward late diagnosis. Patients with more advanced disease stages tend to have shorter survival times.

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHORS' CONTRIBUTIONS

Supervision and project administration: SCSC, JIF. Investigation and formal analysis: DCCA. Formal analysis: FBFS. Writing – original draft: DCCA, NLL. All authors critically revised the manuscript and approved the final version.

BIOETHICS AND BIOSECURITY COMMITTEE APPROVAL

The study was approved by the Comissão de Ética no Uso de Animais (CEUA) of the Universidade Federal Rural do Rio de Janeiro (UFRRJ) under protocol 8505171018.

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