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Efficacy of Radiation Therapy for the Treatment of Sialocele in Dogs

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Background: Sialocele is a collection of saliva that has leaked from a damaged salivary gland or duct and is surrounded by granulation tissue. Surgery is the recognized first-line treatment. Recurrence rate after surgery is 5–14%. Salivary gland tissue is very sensitive to radiation therapy (RT).

Hypothesis/Objectives: Radiation therapy will be useful for the treatment of sialocele. The aims were to characterize response rate and clinical course of dogs with sialocele treated with RT and to determine a starting dose for clinical use.

Animals: Eleven dogs with sialocele.

Methods: Retrospective study of response and outcome after RT.

Results: All dogs had cervical sialocele. Seven dogs (63.6%) were treated with 3 weekly fractions of 4 Gray (Gy); (total dose, 12 Gy). Three dogs (27.3%) received 4 fractions of 4 Gy (16 Gy) and 1 dog received 5 fractions of 4 Gy (20 Gy) on a Monday-Wednesday-Friday schedule. Six dogs (54%) achieved a complete response (CR), and 5 dogs (45%) achieved a partial response (PR). Three dogs had progression of their sialocele 2, 3, and 9 months after RT; all three had received 12 Gy initially and 2 received 2 additional fractions of 4 Gy (cumulative total dose, 20 Gy) and subsequently achieved remission for >2 years.

Conclusions and Clinical Importance: Radiation therapy is useful for the treatment of recurrent sialocele refractory to surgical management and a minimum total dose of 16 or 20 Gy in 4 Gy fractions appears effective.

Key words: Electron therapy; Mucocele; Salivary gland.

A sialocele (salivary mucocele) is a collection of saliva that has leaked from a damaged salivary gland or duct and is surrounded by granulation tissue.[1] Sialoceles can be cervical, sublingual, pharyngeal, or zygomatic depending on the salivary gland affected. In a large cohort of salivary gland samples submitted for histopathology, sialoceles represented 11% of all submissions from dogs (18/160).[2] Most dogs are asymptomatic and present with a history of a gradually developing, fluctuant, painless mass. Diagnosis usually is made by aseptically aspirating the fluid that is mucoid or viscous in appearance and has low cellularity. The cytology sample can be stained with a mucus-specific stain such as periodic acid-Schiff (PAS) for confirmation of the diagnosis.[3]

Surgery is the treatment of choice for sialoceles and requires complete excision of the involved gland-duct complex to be curative.[4–6] Recurrence of sialocele after surgery occurs in between 5 and 14% of cases. In a recent study of 14 dogs with a pharyngeal sialocele treated with surgery, at least 2 dogs had recurrence of the sialocele during the short postsurgical follow-up period.[7] Only 1 of these dogs could be successfully managed with a second surgery. Another recent report described the successful surgical management of 4 dogs with recurrent sialoceles, supporting that recurrence is a possibility if salivary tissue remains after surgery.[8]

Clinical experience in human patients with head and neck tumors treated with radiation therapy (RT) documents that salivary glands are very sensitive to RT and even a modest total dose can result in severe xerostomia.[9,10] In humans, functional impairment correlates with the volume of salivary gland parenchyma exposed and the total radiation dose.[11] Clinically, xerostomia has been reported after as little as 2–3 fractions of 2 Gray (Gy) each whereas doses >30 Gy generally lead to permanent or semipermanent xerostomia.[12] Furthermore, 1 patient with a persistent salivary fistula and 1 patient with a postsurgical ranula were successfully treated with a total RT course of <30 Gy total dose given in 1.8 or 2 Gy fractions.[13]

Abbreviations:

3DCRT	three-dimensional conformal radiotherapy
BED	biological effective dose
CR	complete response
CT	computer tomography
Gy	gray
MRI	magnetic resonance imaging
PAS	periodic acid-Schiff
PD	progressive disease
PR	partial response
RECIST	Response Evaluation Criteria in Solid Tumors
RT	radiation therapy
SD	stable disease
TTP	time to progression
VRTOG	Veterinary Radiation Therapy Oncology Group

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Our hypothesis was that a relatively low dose of radiation would be useful for the treatment of recurrent sialocele. The aims of our study were to first, identify the response rate and clinical course of dogs with sialoceles treated with a course of RT and second, if radiation was successful, to determine a starting dose for clinical use.

Material and Methods

Study Design

Retrospective cohort study.

Patient Selection

The medical records of dogs with sialocele presented to the radiation oncology section of the Vetsuisse Faculty of the University of Zürich between January 1997 and June 2006 or to the AOI Animal Oncology and Imaging Center, Hunenberg, Switzerland between August 2008 and January 2017 were retrospectively evaluated. Dogs were included in the study if they had cytologically confirmed sialocele, were treated with a RT protocol, and had adequate follow-up information available including response, date of progression, date, and reason for death. Sialocele volume was calculated using the formula ([π/6] length × width × height), where length, width, and height represented sialocele diameters in 3 mutually orthogonal planes. The longest diameter also was recorded. Data recorded for all dogs included: signalment, location of sialocele, clinical signs and duration, previous treatment, imaging conducted, radiation therapy details, adverse effects, response to therapy, date of progression, and date of death. Cause of death or reason for euthanasia was obtained from the medical record when available or by conversations with the client or referring veterinarian. Some of these dogs have been previously described in the German veterinary literature.[14]

Radiation Therapy Protocol

All dogs were treated with megavoltage radiation after the owner consented to treatment. Radiation therapy was delivered with a linear accelerator[a] or a Betatron[b] using 9–30 million electron volt (MeV) beams. The RT protocol consisted of 3–5 fractions of 4 Gy each for a total dose of 12–20 Gy given in 1–3 fractions per week. Total protocol administration time was 7–22 days. All dogs were treated using a single electron beam field (1 with 9 MeV, 1 with 12 MeV, 2 with 16 MeV, 7 with 30 MeV) with an electron applicator (7 with a 16 × 16 cm field, 4 with a 10 × 10 cm field). Some fields were shaped with a lead shield. Manual planning was used in all dogs. The radiation dose was normalized to the most appropriate isodose line between 90 and 100%. A 0.5 cm water-equivalent bolus sheet positioned on the skin was used in 1 dog. Treatment field margins were set at a minimum of 1–2 cm from the border of the sialocele.

Efficacy Assessment

Physical examination was recommended at 2 weeks after RT then every 3 months thereafter. Follow-up information was obtained by review of the patient record or by telephone communication with the referring veterinarian or client. Sialocele response was determined by physical examination and caliper measurement. Response was measured at the end of RT and on subsequent visits. Response was defined using the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.[15] Therefore, for the sake of response, sialocele size was determined as the longest diameter of the lesion. Using the RECIST criteria, complete response (CR) = disappearance of the entire lesion, partial response (PR) = 30% decrease in the longest diameter of target lesion, progressive disease (PD) = 20% increase in the longest diameter of target lesion, and stable disease (SD) = small changes that do not meet the above criteria. Time to progression (TTP) was defined as the time (days) from the first RT treatment to the time when sialocele progression was noted.

Toxicity Assessment

Radiation therapy toxicity was assessed by review of the patient record maintained during RT and the patient history as reported by the client at subsequent visits. Acute and late radiation effects were assessed and scored according to the toxicity criteria of the Veterinary RT Oncology Group (VRTOG).[16]

Statistical Analysis

Statistical analyses were conducted by 1 of the authors (DMV). Data were censored for TTP if dogs were alive without progression at the end of the study or at the point at which they were lost to follow-up. Curves for TTP were generated by the Kaplan-Meier product-limit method. Variables analyzed for prognostic significance were sialocele response (yes/no), total dose of initial and final radiation (12 Gy, 16 Gy or 20 Gy), number of surgeries, and volume of sialocele. Generated Kaplan-Meier curves were compared by the log-rank test for 2 data sets and the log-rank test for trend (when >2 data sets were entered) with 2-tailed P values reported. A P value of ≤ 0.05 was considered significant.

Results

Patient Demographics

Eleven (11) dogs met study inclusion criteria. Three were spayed females, 1 was an intact female and 7 were intact males. Median age was 5 years (range, 2–11 years). Median weight was 25 kg (range, 9.4–40 kg). Two were Huskies and 2 were Belgian shepherds and there was 1 each for the following breeds: German shepherd, Bruno jura hound, Dachshund, Hovawart, Wolfspitz, Labrador retriever, and Cocker spaniel. Clinical signs at the time of presentation were swelling in the neck area (n = 4), neck and intermandibular swelling (n = 5), or swelling at the level of the parotid salivary gland (n = 2). The duration of clinical signs ranged from 1 to 96 months, with a median of 9 months. All but 2 dogs had their sialoceles treated with surgery before RT with a median 2 surgeries (range, 1–4). Detailed surgical reports were unavailable for review. Cytology of the swelling confirmed the presence of saliva in all cases. Periodic acid-Schiff staining was performed and was positive in 4 dogs. Seven dogs also had cytologic evidence of neutrophilic or mixed inflammation. Culture was performed and was negative in 3 dogs. Only 2 dogs had advanced local imaging; 1 had a magnetic resonance imaging (MRI) and 1 had computed tomography (CT). Median sialocele volume at the beginning of RT was 162 cm^3 (range, 5.6–490 cm^3), and the median longest diameter was 10 cm (range, 4–18 cm).

RT

All dogs were treated with 4 Gy per fraction. The first 7 dogs were treated with a protocol of 3 weekly doses of 4 Gy to a total dose of 12 Gy. Of these 7 dogs, 2 had sialocele recurrence and they received 2 additional weekly doses of 4 Gy to a total dose of 20 Gy. The second group of 3 dogs received 4 doses of 4 Gy for a total dose of 16 Gy on a Monday-Wednesday-Friday schedule. The final dog received 5 doses of 4 Gy for a total dose of 20 Gy on a Monday-Wednesday-Friday schedule. Positioning of dogs for RT was dorsal recumbency (n = 4) or lateral recumbency (n = 7). A minimum of 1 cm (n = 5) or 2 cm (n = 6) margins were used around the sialocele, and bolus material was described as being used as needed. The median treated volume was 528 cm^3 (range, 126–1,259 cm^3).

Toxicity and Response

Acute toxicity effects were evaluated in 5 dogs, and no acute toxicity was reported. Late toxicity effects were evaluated in 6 dogs, and 2 had grade 1 late effect on skin characterized by some alopecia. Sialocele response was evaluable in all dogs. Using the RECIST criteria, 2 dogs were classified as CR, 7 as PR and 2 as SD at the end of RT. The overall best response recorded at any point during follow-up was CR in 6 dogs and PR in 5 dogs. In all dogs achieving PR, the clinical impression was that remaining disease mass represented thickening from scar or granulation tissue, although histologic or cytologic assessment was not performed to confirm the absence of saliva.

Outcome

Overall, 3 dogs had recurrence of their sialocele at 2, 3, and 9 months post-RT. All had originally received a total dose of 12 Gy and all were treated with a 30 MeV electron field. Two of the 3 were retreated with 2 additional weekly doses of 4 Gy with 1 subsequently achieving PR and the other CR. One retreated dog (original recurrence at 9 months post-RT) did not exhibit progression and was lost to follow-up at 19 months after retreatment. The other (original recurrence at 2 months) had recurrence 27 months after retreatment and ultimately was euthanized because of the sialocele after 32 months. The remaining recurrence (3 months post-RT) was not retreated and the recurrence had not progressed when the dog was lost to follow-up at 11 months. The median TTP for all dogs was not reached, and a 70% 1-, 2-, and 3-year progression-free survival was observed (Fig 1). No statistically significant differences ($P > 0.15$) were observed based on total dose, number of previous surgeries, CR vs PR (final response), or size. At the time of data analysis on March 15, 2017, 1 dog had died as a consequence of sialocele at 32 months, 1 dog died of unrelated cause after 87 months, and the others were lost to follow-up (median, 17 months; range, 6–43 months).

Discussion

Our small retrospective case series highlights the successful role of RT in the treatment of sialocele. All 11 dogs had control of their sialocele after a course of RT. Three (27%) of 11 dogs had recurrence of their sialocele within 12 months of RT, all had received a total dose of 12 Gy. Two of 3 dogs that had recurrence were successfully retreated with an additional course of RT.

These results likely are a result of the high sensitivity of the salivary gland to even modest doses of RT.[9–11] The exact mechanism of action of RT on the salivary gland is undetermined, but at least 3 mechanisms to explain the phenomenon have been hypothesized. One is direct damage to the DNA of the salivary gland cells by radiation-induced oxidative species. The second is cytotoxic damage to the cells initiated by the release of toxic materials from the cells themselves. The third is the induction of apoptosis by an intracellular mechanism.[17] Studies of humans receiving definitive RT have shown a rapid diminution of salivary flow during the first 2 weeks of RT. After 2 weeks of RT at doses of 20 Gy, the parotid and submandibular or sublingual salivary glands retained only 20% of their original salivary flow and function did not recover by 6 weeks after RT.[18] A study by 3-dimensional conformal radiotherapy (3D-CRT) techniques to treat the primary tumor while maintaining the dose threshold to the contralateral parotid gland to 26 Gy reported that with salivary gland scintigraphy, the mean loss of secretion function was 67% in the spared parotid gland and 100% in the treated parotid when using conventional 2 Gy per fraction definitive protocols.[19] The number of dogs in our study was too small to draw conclusions on the total dose required but because all dogs that received a minimum of 16–20 Gy in 4–5 fractions did not have sialocele recurrence, it appears that protocols delivering this minimum would be a useful starting point. To support this conclusion, we can use the biologically effective dose (BED) which is an approximate quantity by which different radiotherapy fractionation regimens may be compared with less bias.

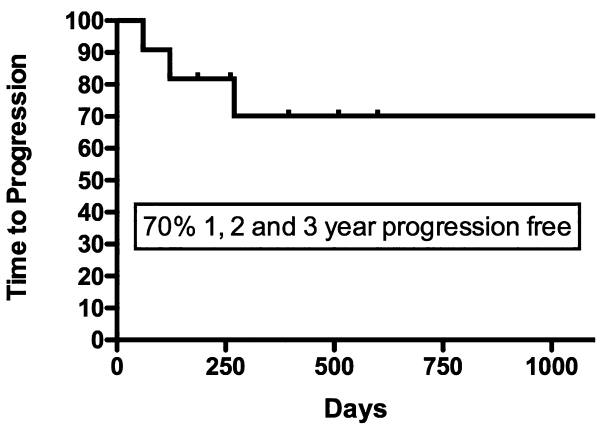

Fig 1. Kaplan-Meier limit product graph for time to progression of the eleven dogs with sialocele treated with radiation. Tick marks indicate censored cases.

The formula used is as follows:

$$\mathrm{BED} = nD(1 + [D/(\alpha/\beta)])$$

where n = number of fractions, D = dose/fraction, and nD = total dose.

An α/β of 3 Gy generally is applied for late responding tissues (late effects) and 10 Gy for acute responding tissue and tumors (acute effects). By convention, BED is expressed in units of $Gy_{\alpha/\beta}$ to indicate the effects to which the results apply. The salivary glands α/β ratio for permanent xerostomia has been reported to be 3 Gy.[20] The BED Gy_3 values for the human salivary gland limit of 20 Gy in 10 fractions or 26 Gy in 13 fractions versus our canine protocol of 12 Gy in 3 fractions, 16 Gy in 4 fractions, or 20 Gy in 5 fractions would be 33.3 Gy_3 and 43.33 Gy_3 versus 28 Gy_3, 37.33 Gy_3, and 46.67 Gy_3, respectively. These findings indicate that the 16 or 20 Gy in 4 Gy per fraction protocol used in our study would be similar to the tolerated dose of human salivary gland tissue.

Furthermore, all of our patients were treated with electron beam therapy and none of them had computed treatment planning, so it is possible that the dose achieved at the level of the salivary gland was under or overestimated, and it is possible that with use of more modernized treatment planning systems, the exact dose necessary to cause the clinical endpoint could be determined.

Limitations of our study include the small number of cases and its retrospective nature that made specific details (e.g., previous surgeries, dosimetry data) unavailable for critical review. Only 2 of the 11 dogs were followed until death, which limits our interpretation of the total dose of RT required to provide lifetime control, but median follow-up was 17 months. Additional prospective studies will be required to elucidate the dose required for lifetime control of sialocele.

Conclusions

A course of RT at a relatively modest total dose can be used to control sialocele in dogs and could be recommended for recurrent sialocele refractory to surgical management.

Footnotes

[a] Dynaray LA20, Clinic 2100 DMX, Varian, Zug, Switzerland
[b] BBC, Baden, Switzerland

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Conflict of Interest Declaration: Authors declare no conflict of interest.

Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

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