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Re-irradiation of canine non-lymphomatous nasal tumours using stereotactic radiation therapy (10 Gy x 3) for both courses: Assessment of outcome and toxicity in 11 dogs

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Abstract

No uniformly beneficial treatments exist for dogs with non-lymphomatous nasal tumours (NLNT) that relapse after radiotherapy (RT). Reirradiation may prolong survival and improve quality of life. In this retrospective study, we describe outcomes for 11 dogs that had CT-confirmed locoregional progression of NLNT after an initial course of stereotactic RT (SRT#1; 10 Gy × 3) and were then re-treated with the same type of protocol (SRT#2, also 10 Gy × 3). The median time between SRT #1 and SRT #2 was 243 days (95% CI: 78–385 days). Ten dogs (91%) had a clinical benefit after SRT#1; five dogs (45%) had clinical benefit after SRT#2. Adverse events after SRT#2 included nasocutaneous or oronasal fistula formation ($N = 3$ at 180, 270, and 468 days), seizures ($N = 2$ at 78 and 330 days), bacterial or fungal rhinitis ($N = 2$ at 240 and 385 days), and facial swelling ($N = 1$ at 90 days). All 11 dogs have died, due to disease progression, presumed radiotoxicity, or declining quality of life; in most cases, it was difficult to discern between these conditions. The median overall survival time (OST) from SRT#1 was 745 days (95% CI: 360–1132). The median overall survival time (OST) from SRT #2 was 448 days (95% CI: 112–626). For these dogs, survival was prolonged, but adverse events after SRT#2 were common (8/11; 73%). Therefore, before consenting to re-irradiation with this protocol, pet owners should be counselled about survivorship challenges, including risk for severe toxicities, and persistence of clinical signs.

KEYWORDS
carcinoma, intranasal tumours, radiotherapy, reirradiation, sarcoma

1 | INTRODUCTION

No uniformly beneficial treatments exist for dogs with non-lymphomatous nasal tumours (NLNT) that relapse after radiotherapy (RT), and there is no standard of care. Options that could be considered include: (a) palliative care with medications (e.g., analgesics, anti-inflammatories, antibiotics) only[1]; (b) systemic chemotherapy (including cytotoxic agents, and tyrosine kinase inhibitors),[2,3] and (c) reirradiation using either conventional daily or weekly non-stereotactic forms of RT, or stereotactic radiation therapy (SRT).[4–16] Use of carboplatin and doxorubicin in conjunction with the NSAID piroxicam has been recently described as the sole

treatment of NLNT in dogs, with an overall median survival time of 234 days; however, it is unknown if patients with relapsed tumours after RT would have a similar outcome.[2] Although a prior publication of reirradiation using fractionated RT described only mild acute and late side effects in most dogs,[4] pet owners who chose SRT as the initial treatment option for their pet may decline a longer course of RT due to cost or logistical reasons. Therefore, further study and development of an SRT protocol that minimizes toxicity and prolongs meaningful survival with a good quality of life for most patients is essential.

Although reirradiation (a second course of radiotherapy, RT) has been utilized to treat both recurrent and locally progressive tumours in both people and animals for years, concerns about toxicity, lack of efficacy, and a paucity of standardized protocols may prevent its widespread use, even for radioresponsive tumours.[4–16] In dogs with nasal cancer, most have an initial positive response to radiation treatment but ultimately succumb to locoregional disease progression. Prolongation of survival and sustained improvements in quality of life may be possible with reirradiation.

Few studies have been published documenting the efficacy and toxicity associated with reirradiation for nasal tumours in dogs. In one study of nine dogs, reirradiation utilizing finely fractionated radiation protocols was utilized to treat recurrent nasal tumours. The median fractional doses for the first and second courses were 2.8 and 2 Gy, respectively. The median total doses for the first and second courses were 50 and 36 Gy, respectively.[4] Acute and late radiotoxicity were mild in most cases, with ocular complications being the primary reported side effect. In another multi-institutional retrospective study, various hypofractionated RT protocols were used initially and for reirradiation (at the time of clinical relapse); 37 dogs were described. The median fractional doses for the first and second courses were 7 and 8 Gy, respectively; the median total doses for the first and second courses were 24 and 20 Gy, respectively. Ocular toxicity was also reported, necessitating enucleation in one dog.[9] In both studies, most dogs had a clinical benefit from reirradiation. Another commonality between the two studies was the use of traditional "forward" treatment planning. Since publication of these studies, access to technologies that permit planning and delivering of more conformal radiotherapy are now widely available in veterinary medicine, and are increasingly utilized in management of NLNT.[4,7,10–12,17] A single case report describes use of such technologies to reirradiate a dog with NLNT, and that experience provides proof-of-concept for improved ocular sparing versus more conventional (forward planned) RT.[7] The purpose of this retrospective case series is to build upon that shared knowledge, and describe the outcomes and toxicities experienced by a group of dogs whose NLNTs were initially treated with 3-fraction SRT (30 Gy total), and later at the time of local (intranasal) disease progression, reirradiated using the same approach.

2 | MATERIALS AND METHODS

A bi-institutional retrospective study of dogs with NLNT was performed. A radiation therapy-specific database was used to identify cases that were treated both initially ("SRT#1") and at the time of tumour progression ("SRT#2") with a single stereotactic radiation therapy protocol (10 Gy × 3) between October 2014 and July 2018. Patient characteristics and outcome information were gathered from medical records. The study was initiated in July 2019 to ensure adequate follow-up time after SRT#2 (i.e., to try to ensure that radiotoxicities would be captured during the study period for dogs that lived >1 year after treatment, though dogs did not have to live for >1 year after treatment to be included in the study). A previously published, veterinary-specific radiotoxicity grading scheme was used to classify toxicities whenever possible.[18]

Dogs were included if they had biopsy-confirmed NLNT. Recommended staging tests prior to both courses of SRT included bloodwork, radiographs and/or CT scans to evaluate for thoracic metastasis or other co-morbidities, and bilateral mandibular lymph node aspirates to assess for lymph node metastasis. Follow-up examinations were recommended at 21, 42, 90, 180, 270, and 365 days after each course of SRT, and CT scans were recommended at 90-120-day intervals to objectively assess response to therapy. Additional follow-up information was also obtained through phone and email contact with owners and referring specialists and/or primary care veterinarians at 90 to 120-day intervals. The modified Adams' staging system was used to categorize tumours based on CT scans.[8,12]

Radiation treatment planning and delivery methods varied slightly between the two institutions and details of the protocol were previously published for one of the institutions (see supplemental material 1 for a description from both institutions). The primary difference between treatment planning between the institutions was that institution #1 included a 5–10 mm expansion from the gross tumour volume (GTV) within the nasal cavity to create the planning target volume (PTV), and institution #2 utilized a 1–4 mm expansion of the GTV to create a combined CTV (Clinical Target Volume)/PTV. Both institutions utilized IMRT planning and volumetric image-guided radiation delivery, and treatment prescriptions in which at least 95% of the prescribed dose was delivered to the PTV with each fraction were utilized.

Dosimetric information obtained from the treatment planning computer was recorded for each case. This included doses given to 2% ($D_{2\%}$), 50% ($D_{50\%}$), and 98% ($D_{98\%}$) of the GTV. The goal of adding these values was to avoid assessment of a plan by using point doses only (as point doses may represent the dose received by an insignificant volume e.g., 1 voxel); $D_{2\%}$ represents the near-maximum dose, while $D_{98\%}$ represents the near-minimum dose. Further plan assessment using the median dose ($D_{50\%}$) was also incorporated since the mean dose could be affected by point doses.[19,20]

2.1 | Statistical analysis

Kaplan–Meier curves to calculate survival were generated, and Log-Rank tests were performed using Prism 8 for Windows (GraphPad Software, Inc). Estimates of the median values and 95% confidence intervals were generated using JMP Pro version 14.1.0 (SAS

Institute, Inc). The overall survival time after SRT#1 was calculated from the last day of SRT#1, and the survival time after SRT#2 was calculated from the from the last day of SRT#2. Due to the small sample size, additional assessment for prognostic factors was not performed.

2.2 | Cell line validation statement

Not applicable.

3 | RESULTS

A total of 11 dogs of various breeds met the criteria for inclusion; 8 were neutered males and 3 were spayed females and they ranged in age from 4 to 14 years (median, 9 years). Body weight ranged from 11 to 42 kg (median, 29 kg). Eight had carcinomas and three had chondrosarcomas. Modified Adams' tumour stage at the time of initial treatment (SRT#1) included T1 ($N = 2$), T2 ($N = 4$) and T4 ($N = 5$; two of these dogs had stage T4b disease). No dogs had MRIs to aid in target delineation. None had evidence of locoregional or systemic metastasis at diagnosis. Although none were treated with systemic chemotherapy after SRT#1, some received concurrent medications including non-steroidal anti-inflammatory drugs. Patient outcomes for four dogs in this study were also included in a prior publication.[10]

Four dogs were rechecked by the attending radiation oncologist as recommended at 3- and 6-week intervals after SRT#1, and the remainder were rechecked by their primary care veterinarians or did not have rechecks performed to assess radiotoxicities during this timeframe. The subjective assessment of clinical benefit (as assessed by pet owners and attending clinicians) to SRT#1 was complete ($N = 5$) or partial ($N = 5$) resolution of nasal signs (10/11 dogs: 91%) or stable clinical signs ($N = 1$). Acute radiotoxicities (those occurring within 90 days following treatment) after SRT#1 were limited to grade 1 skin or oral cavity toxicity,[18] and none had late radiotoxicities reported prior to SRT#2 except for diffuse leukotrichia in the radiation field.

All dogs had an initial recheck CT scan at a median of 4 months (range, 3–10 months) after SRT#1; results included complete ($N = 2$) and partial ($N = 8$) responses and progressive disease ($N = 1$; this was the dog whose clinical response to treatment was stable rather than improved), as defined by RECIST criteria for solid tumours.[21] The total number of recheck CT scans performed after SRT#1 in each dog was 1 ($N = 1$), 2 ($N = 6$), 3 ($N = 2$), 4 ($N = 1$), and 5 ($N = 1$). CT-confirmed disease progression occurred in all dogs prior to SRT#2. These CT scans were utilized to create new treatment plans for SRT#2. Adams' modified stage had progressed in 2 dogs (stage T2 to stage T4 and stage T2 to stage T3). In one dog that had multiple CT scans spanning a period of 3.5 years between SRT#1 and SRT#2, complete response of the tumour was seen on CT scans after SRT#1, and then at the CT scan prior to SRT#2, progressive disease was noted that was confirmed as tumour recurrence via histopathology (Figure 1). In this dog,

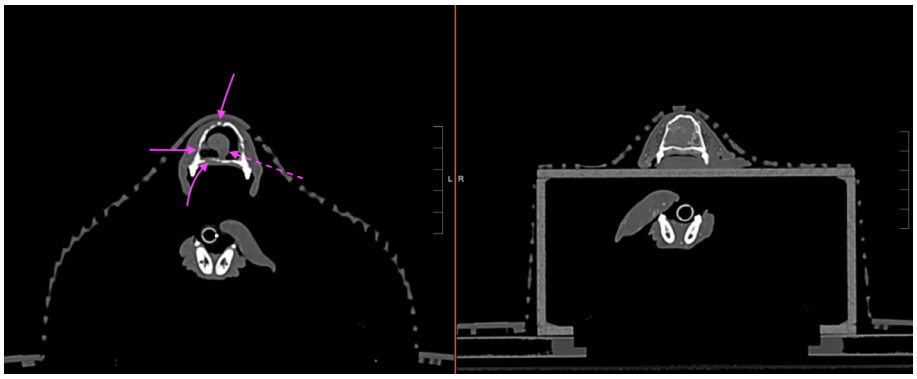

FIGURE 1 Transverse, bone window CT scan images at the same level of the nasal cavity of a dog at the time of tumour recurrence (left; prior to SRT#2) and prior to any treatment (right; 3.5 years earlier prior to SRT#1). In the left image, solid arrows show multiple areas of bone thinning during the time following SRT#1. The dotted arrow shows tumour recurrence (confirmed to be carcinoma on histopathology)

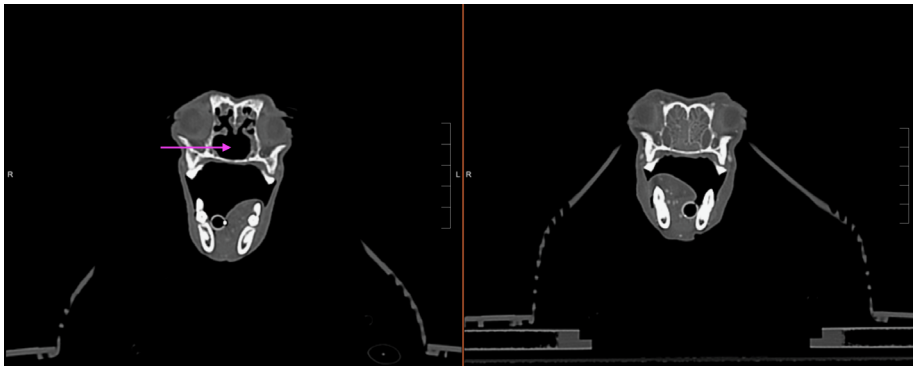

FIGURE 2 Transverse, bone window CT scan images at the same level of the nasal cavity of a dog, 2 years after SRT#1. The solid arrow shows diffuse turbinate loss and an "empty" nasal cavity. This dog had biopsy-confirmed bacterial rhinitis that was treated with oral and intranasally-instilled antibiotics

Adams' stage went from stage T4 (prior to SRT#1) to stage 1 (prior to SRT#2). That patient also had severe chronic bacterial rhinitis and diffuse bone thinning over time within the treatment field after SRT#1 (Figures 1 and 2). In another dog that had multiple CT scans between SRT#1 and SRT#2, partial response of the tumour was seen on CT scans after SRT#1, and then at the CT scan prior to SRT#2, progressive disease was noted; in this dog, Adams's stage went from stage T4 to stage T3. Recheck systemic staging tests prior to SRT#2 revealed presumed thoracic metastasis in one dog with a nasal carcinoma.

The median time between SRT#1 and SRT#2 was 243 days (95% CI: 78–385 days). The median time to first event after SRT #2 was 277 days (95% CI: 224–710 days); the difference is not statistically significant (log-rank test; $p = .1323$) (Figure 3). All dogs completed the intended protocols for both courses. Four dogs were treated every other day rather than daily for SRT#2; this decision was made by clinicians due to concerns about proximity of the tumour to the skin or palatal mucosa, with the goal of decreasing dose intensity to those tissues by delivering the dose with a day off in-between fractions. Dosimetric information can be found in supplemental materials 2.

Three dogs were rechecked by the attending radiation oncologist as recommended at 3- and 6-week intervals after SRT #2, and the remainder were rechecked by their primary care veterinarians or did not have rechecks performed to assess radiotoxicities during this timeframe. One dog had focal caudal oral cavity mucositis (VRTOG grade 1), one dog had ocular discharge of unknown aetiology that became chronic for the remainder of the dog's life, and the others did not have noted side effects during the 3–6-week timeframe after SRT #2. The subjective assessment of clinical benefit (as assessed by pet owners and attending clinicians) to SRT#2 was partial resolution of nasal signs ($N = 5/11$: 45%; CT scan confirmed objective tumour response in 2 of these dogs), stable clinical signs ($N = 3$), or no improvement ($N = 2$; CT scan documented stable disease in one of these dogs, though clinical improvement was not noted). One dog was lost to follow-up after SRT#2 until the time of death, so a response was unable to be determined. No dogs had a complete resolution of nasal signs after SRT #2. For the dogs that had a partial clinical response to SRT #2, the duration of response was unable to be definitively determined since the nasal signs did not resolve completely.

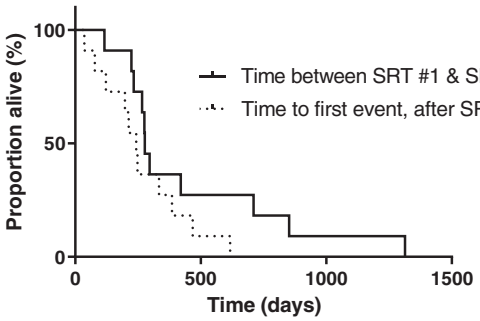

FIGURE 3 The event-free survival time for 11 patients treated with re-irradiation for recurrent non-lymphomatous nasal tumours. The median time between SRT #1 and SRT #2 was 243 days (solid line; 95% CI: 78–385 days); the median time to first event after SRT #2 was 277 days (dashed line; 95% CI: 224–710 days); the difference is not statistically significant (log-rank test; $p = .1323$)

In 8/11 (73%) patients, events that negatively impacted the patient's quality of life occurred after SRT#2. The first events to occur after SRT#2 included nasocutaneous or oronasal fistula formation ($N = 3$ at 180, 270, and 468 days), seizures ($N = 2$ at 78 and 330 days; these dogs had stage T4b disease at the time of diagnosis), biopsy-confirmed bacterial rhinitis ($N = 1$ at 385 days), biopsy-confirmed fungal rhinitis ($N = 1$ at 240 days), facial swelling that responded to antibiotic therapy ($N = 1$ at 90 days). The first event after SRT#2 was death in the remaining dogs that did not have a known event prior to their deaths at 122, 198, and 617 days after SRT#2.

CT scans were performed in 3 patients and an MRI was performed in 1 patient after treatment. The dog with fungal rhinitis was treated with clotrimazole intranasal infusions as well as oral antifungals; although the clinical signs of fungal rhinitis improved, the fungal plaques never visibly resolved. Numerous CT scans were performed (120, 180, 240, 330, and 365 days after SRT#2) to assess the response to treatment and as part of the diagnosis and monitoring for fungal rhinitis (that was diagnosed at 240 days after SRT#2 via rhinoscopy and biopsy). The dog with bacterial rhinitis was treated with oral and intranasal antibiotic infusions and debridement of the nasal cavity

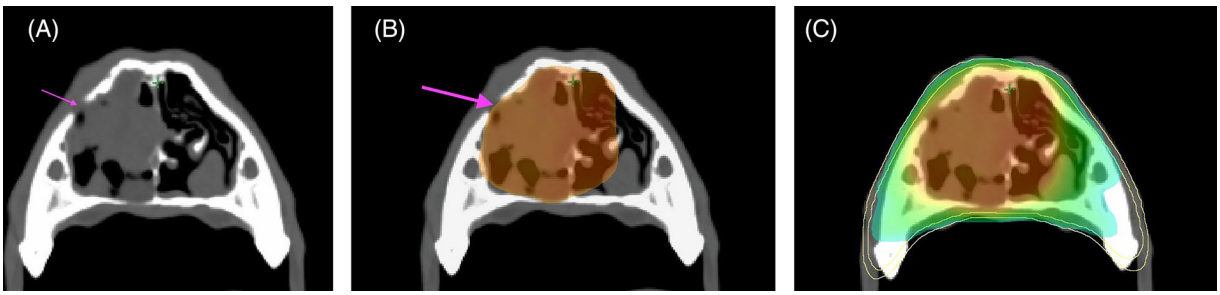

FIGURE 4 (A–C) Transverse, bone window CT scan images of the nasal cavity in a dog with a nasal carcinoma that developed a nasocutaneous fistula after SRT#2. In figure a, the solid arrow shows the area of bone thinning and adjacent tumour. (B) The dose in colour wash shows the dose to the tumour adjacent to the bone at 30 Gy. (C) The skin contour is shown (2 mm internal margin from the body contour); the full-thickness skin dose (in green) is 12 Gy overlying the tumour

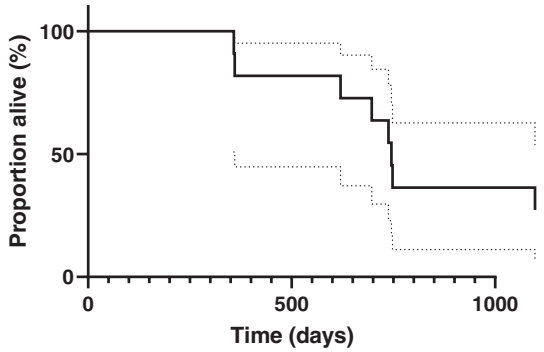

FIGURE 5 The overall median survival time from SRT#1 to death for 11 patients treated with re-irradiation for recurrent non-lymphomatous nasal tumours. Median overall survival time: 745 days (solid line) (95% CI: 360–1132, dashed lines)

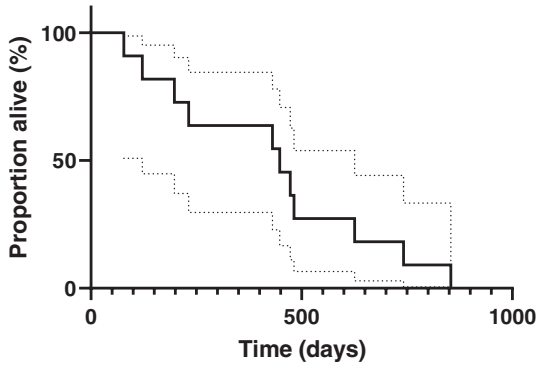

FIGURE 6 The overall median survival time from SRT#2 to death for 11 patients treated with re-irradiation for recurrent non-lymphomatous nasal tumours. Median overall survival time: 448 days (solid line) (95% CI: 112–626, dashed lines)

via rhinoscopy-guided flushing. The dog that had the MRI performed developed seizures 330 days after SRT #2, and the MRI confirmed further intracranial invasion of the nasal tumour into the brain as compared to prior to SRT#2 (Adams' stage T4b tumour).

Fistulas were treated with oral antibiotics as needed to treat secondary presumed osteomyelitis/osteoradionecrosis and gentle debridement of the area at home by the owner and/or by a veterinarian. Wound closure was not attempted in any dog. One dog with a nasocutaneous fistula that developed 240 days after SRT#2 in an area of bony lysis adjacent to the tumour (Figure 4A–C) also had persistent epistaxis after SRT#2, and a unilateral (ipsilateral to the tumour) carotid artery ligation was performed. The dog lived for several months and remained an active hunting dog, and the owners reported that the fistula minimally impacted his quality of life. Radiation treatment plans for dogs that developed fistulas were reviewed to attempt to identify risk factors for development (such as thin bone or mucosa over the site where the fistula developed, high point dose of radiation near the skin or bone adjacent to the fistula), and none were consistently identified in this small group of dogs.

For the 3 dogs with death as their first event, deaths were attributed to overall decline and poor quality of life in 2, and the remaining dog was lost to follow-up after SRT#2 and was euthanized as the next documented event (primary care veterinarian stated that the euthanasia was due to "disease progression" but no further information was available).

All dogs are deceased from disease progression, presumed SRT-associated toxicity, or declining quality of life; in most cases, it was difficult to definitively discern between these conditions and no clients allowed necropsy on their pets. The overall median survival time from SRT#1 to death was 745 days (95% CI: 360–1132) (Figure 5). The overall median survival time from SRT#2 to death was 448 days (95% CI: 112–626) (Figure 6).

4 | DISCUSSION

For the group of dogs described herein, survival was prolonged. However, after SRT#2, quality of life was frequently compromised by problems that included fistulas, infections, and tumour progression. These types of problems can develop as a complication of RT, but they can also develop as a complication of the cancer itself.[10,17,22,23]

In the present study, 73% of dogs (8/11) experienced adverse effects that negatively impacted their quality of life. One of the challenges of documenting adverse effects, especially "late" radiotoxicity (i.e., toxicity occurring after the acute toxicity period any time during the remainder of the patient's life) in dogs with nasal tumours is that the clinical signs of radiotoxicity overlap with those caused by tumour recurrence or persistence, and testing including cross-sectional imaging does not always differentiate between them.[10,22,23] Differentiating between bacterial/fungal osteomyelitis (dogs with abnormal nasal anatomy such as those with nasal tumours that destroy the normal nasal epithelium are predisposed to these infections) versus osteoradionecrosis (i.e., radiotoxicity) is also challenging. In a publication describing side effects to bone in dogs after orthovoltage RT, osteoradionecrosis was the diagnosis when the following conditions were met: (a) fractured bone within the RT field without known external trauma, (b) onset >4 months after RT, (c) lesion histologically confirmed as non-neoplastic or did not progress on subsequent imaging.[22] In dogs with nasal tumours that have some degree of bony lysis (nearly every case), it would be difficult to determine osteoradionecrosis versus osteomyelitis. Thus, we suggest that in many cases, a continuum of chronic changes in the nasal cavity because of both tumour and radiotoxicity are present in patients where clinical signs such as nasal discharge persist. Even in dogs with oronasal or nasocutaneous fistulas, where RT seems to be most likely implicated due to dose to the skin overlying the tumour, it is possible that both tumour recurrence/progression and/or osteomyelitis could be comorbid factors.[10,23] In each case where late radiotoxicity is suspected, a CT scan followed by rhinoscopic biopsy would ideally be performed to document tumour recurrence versus infection and to perform a deep tissue culture to direct antimicrobial or antifungal therapy. A recent publication described differences in the nasal microbiome of healthy dogs and compared to those with chronic rhinitis and/or nasal tumours; this difference may predispose dogs with nasal tumours to chronic or antibiotic-resistant bacterial infections.[24]

To the author's knowledge, there is no body of literature describing histopathologic changes in tissues of the canine nasal cavity after any form of RT (that could be gathered via rhinoscopy or necropsy), which could be an additional area of future study.

Few other studies have documented outcomes in dogs with nasal tumours following reirradiation with SRT. As part of a larger study that included 28 dogs with various nasal tumour types treated with SRT, Mayer, et al. reported reirradiation of 6 cases with SRT protocols that differed from their original protocol.[11] Protocols for SRT#1 included 9 Gy per fraction for a total dose of 27 Gy in 3 fractions ($N = 4$), 10 Gy per fraction for a total dose of 30 Gy in 3 fractions ($N = 1$), and 20 Gy in a single fraction ($N = 1$); for SRT#2, protocols were 10 Gy per fraction for a total dose of 20 Gy in 2 fractions ($N = 5$) and 20 Gy in a single fraction. There was no description why certain protocols were chosen for each patient. The start of SRT#2 ranged from 163 to 916 days after the first course (median 323 days), and the survival times after SRT#2 ranged from 28 to 651 days (median 220 days; the overall median survival time for all dogs in the study was 388 days). The reported late side effects in these six dogs included one each of vision loss in the eye contralateral to the tumour and seizures (neither cross-sectional imaging nor necropsies were performed to document the definitive cause of these signs). It is difficult to directly compare results of this study to the present report since the extent and duration of follow-up after SRT#2 was not described; therefore, the incidence and severity of late radiotoxicities could be underestimated.

The overall median survival time in this study was 745 days from the start date for SRT #1, which is longer than the 586 days in a previous report from one of our institutions.[10] Selection bias may play a role in this study, since the majority of dogs (10/11, 91%) in this study all had clinical benefit from the first course of treatment and had pet owners who were willing to pursue recheck CT scan(s), staging tests, and additional therapies at the time of tumour progression. In addition to SRT #2, these pet owners also consented to treatment for bacterial and fungal osteomyelitis and salvage procedures such as carotid artery ligation to attempt to further help prolong and improve their pet's quality of life.

Historical veterinary literature describing reirradiation suggests that the duration of improvement of clinical signs and/or tumour control is only about half as long as with the second course of irradiation.[4,6] In those reports, the reirradiation protocol was generally less intensive (lower total dose and dose/fraction) than the initial treatment, and treatment was well tolerated. This suggests that more dose intensity for subsequent RT might be more efficacious without causing undue harm to the patient. In the patients described here, reirradiation was delivered without any sort of dose de-escalation. Although five dogs (45%) had a clinical benefit after SRT#2, ongoing clinical signs of nasal disease and/or toxicities occurred in the majority. The chronic morbidity after SRT#2 could be at least partially attributable to the high cumulative lifetime doses to the tumour and OAR; this is certainly an area ripe for future study (e.g., development of strategies for improving locoregional control achieved with the initial course of RT to avoid the need for reirradiation, attempting systemic chemotherapy to delay or prevent the need for additional RT, use of radiosensitizers that would allow radiation dose-de-escalation, and/or use of radioprotectors).[25,26]

5 | CONCLUSIONS

Although most dogs (8/11; 73%) developed complications after SRT#2 that negatively impacted their quality of life, some (5/11; 45%) of the dogs clinically improved for some period after SRT#2, and survival times were long. This indicates a potential clinical benefit. Therefore, with the proviso that pet owners be carefully educated about potential toxicities, and the possibility of persistent or worsening clinical signs, reirradiation with SRT could be considered as a salvage procedure for dogs with locoregionally recurrent NLNT.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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