Stereotactic body radiation therapy for treatment of soft tissue sarcomas in 35 dogs

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OBJECTIVE
To describe response rate, tumor progression, patient survival times, prognostic factors associated with tumor progression and patient survival times, and radiation toxicoses (acute and latent) in dogs treated with curative-intent stereotactic body radiation therapy (SBRT) for soft tissue sarcomas (STS).

ANIMALS
35 client-owned dogs with STS treated with curative-intent SBRT between October 2011 and May 2017.

PROCEDURES
Medical records were reviewed to identify dogs that underwent SBRT. Dogs with oral tumors, hemangiosarcoma, or histiocytic sarcoma were excluded. Data collected included patient-, STS-, and SBRT-related information, including follow-up information pertaining to tumor progression and patient survival time for ≥ 6 months, unless tumor progression or patient death occurred sooner.

RESULTS
Objective measurements allowing for evaluation of tumor response were available for 28 dogs, of which 13 (46%) had either a partial (10/28 [36%]) or complete (3/28 [11%]) response. Twenty-four dogs died, and the medians for progression-free survival time, time to progression of disease, overall survival time, and disease-specific survival time were 521, 705, 713, and 1,149 days, respectively. Low histologic grade and extremity locations of STSs were positive prognostic factors for patient survival times. Acute adverse effects were limited to skin, and 1 dog underwent limb amputation because of a nonhealing wound.

CONCLUSIONS AND CLINICAL RELEVANCE
Results indicated that SBRT for STS was well tolerated in most dogs and provided local tumor control. Additional studies are needed to determine the best SBRT protocol for treatment of STSs in dogs. (*J Am Vet Med Assoc* 2020;256:102–110)

Soft tissue sarcomas are a heterogenous group of malignant mesenchymal tumors (eg, fibrosarcoma, peripheral nerve sheath tumor, schwannoma, hemangiopericytoma, myxosarcoma, and undifferentiated sarcoma) that comprise approximately 15% of the tumors of skin and subcutaneous tissues in dogs.[1] These tumors tend to have similar biologic behaviors, characterized by local invasiveness and low to moderate metastatic potential, that correspond with their histologic grade.[2]

ABBREVIATIONS

CI	Confidence interval
DSS	Disease-specific survival time
GTV	Gross tumor volume
HR	Hazard ratio
OS	Overall survival time
PFS	Progression-free survival time
PTV	Planned target volume
SBRT	Stereotactic body radiation therapy
STS	Soft tissue sarcoma
TTP	Time to progression

For most dogs with STS, local control of the tumor is the primary goal of treatment. Surgical resection with wide margins has been associated with an approximately 15% risk of local tumor regrowth.[2] Conventional radiation therapy as a single treatment modality does not appear to result in durable local tumor control.[3] For instance, a study[3] of 33 dogs with a macroscopic STS that underwent radiation therapy (between 35 and 55 Gy total dose divided into 10 fractions and administered on Mondays, Wednesdays, and Fridays) shows that the probability of tumor regrowth within 12 months ranged from 33% to 75%, depending on the total radiation dose received. However, a curative-intent treatment with combined marginal excision of bulky sarcomas (eg, excised to < 3 cm^3 tumor remaining) followed by conventionally fractionated radiation therapy has provided long-term local tumor control (eg, median disease-free interval of 1,082 days [n = 48][4] and median OS of 1,851 days [35][5]) in dogs. Further, a study[6] shows that 48 dogs

with microscopic STSs treated with hypofractionated radiation therapy of 24 to 32 Gy divided into fractions of 6 to 8 Gy/wk had a median PFS of 698 days and an unreached median DSS.[6] Palliative hypofractionated radiation therapy protocols, such as involving 24 to 32 Gy divided into 3 to 5 fractions and resulting in a median PFS of 155 (n = 16) to 419 (50) days, have also been reported for dogs with STSs.[7–9]

Stereotactic body radiation therapy is the term applied for the delivery of image-guided, high-dose radiation therapy to tissues outside of the CNS with tumor-ablative intent within a course of treatment that does not exceed 5 fractions.[10] With the use of advanced image guidance and radiation delivery techniques that allow sparing of normal tissue through conformal dose delivery and accurate patient setup, SBRT delivers high-dose radiation fractions to tumors and minimal radiation doses to surrounding organs at risk.[10] In addition to the use of this avoidance rather than fractionation to spare normal tissues, SBRT uses high-dose fractions (> 8 to 10 Gy) that have been suggested to kill tumor cells by endothelial cell apoptosis, a different mechanism than the DNA-damaging mechanism of low-dose fractions used in conventionally fractionated radiation therapy.[11] High-dose fractions may cause apoptosis of tumor endothelial cells, thereby increasing tumor cell death and causing local vascular damage that in turn results in indirect killing of tumor cells and increased antitumor immunity.[11] However, others have argued that the clinical success of SBRT is simply a result of the equivalent or higher biologically effective dose of radiation that can be delivered to the tumor when normal tissue is avoided, but not a result of a different mechanism of tumor cell death.[12] Although attractive potential advantages of SBRT, compared with conventionally fractionated radiation therapy, include fewer treatments and acute adverse effects and no need for marginal resection, the decision to use curative-intent SBRT for STS in dogs should be based on the expectation that high doses of radiation per fraction provide comparable antitumor efficacy to conventionally fractionated radiation therapy.

To our knowledge, the use of SBRT in dogs with STSs has not been reported. The primary objective of this retrospective study was to describe response rate, tumor progression, and survival times in dogs with an STS treated with curative-intent SBRT. A secondary objective was to report prognostic factors associated with tumor progression and patient survival times. A tertiary objective was to describe acute and latent radiation toxicoses in dogs undergoing SBRT.

Materials and Methods

Medical records review

The retrospective study protocol was submitted to the University of Saskatchewan's Animal Research Ethics Board and Behavioral Research Ethics Board and was determined to be exempt from review. The medical records of the Veterinary Centers of America in Canada; Western Veterinary Specialist and Emergency Centre in Calgary, Alberta; and the Western College of Veterinary Medicine in Saskatoon, Saskatchewan were searched for records of dogs with a cytologic or histologic diagnosis of STS that underwent curative-intent SBRT between October 2011 and May 2017. To be eligible for the study, dogs also had to have had complete medical records and adequate follow-up information. Adequate follow-up was defined as information in the medical record pertaining to tumor progression and patient survival time for ≥ 6 months, unless tumor progression or patient death occurred sooner. Dogs with oral tumors, hemangiosarcoma, or histiocytic sarcoma were excluded from the study because, compared with other STSs, oral STSs tend to be more aggressive and hemangiosarcoma and histiocytic sarcoma have higher metastatic rates.[1,5]

Data collection

Data collected from the medical records included patient signalment (age, breed, sex, and body weight), tumor information (location, histologic type and grade, systemic staging, and previous treatments), radiation treatment plan details, adjuvant treatment, and outcome. In addition, follow-up data collected from the medical records and through communications with referring veterinarians and owners included information pertaining to adverse effects of radiation, response to treatment, tumor progression, date of detected tumor progression (local or metastatic), additional treatments, survival time, and cause of death.

Treatment planning and SBRT

Diagnostic procedures performed at the discretion of the primary clinician to stage STSs in dogs included CBC, serum biochemical analyses, urinalysis, thoracic radiography, thoracic CT, abdominal ultrasonography, and cytologic examination of lymph node fine-needle aspirate samples. Inverse radiation treatment planning for intensity-modulated radiotherapy was performed by 1 of 3 board-certified veterinary radiation oncologists (including MNM and GNM) using treatment planning software.[a,b] Gross tumor volume was defined as the entire contrast-enhancing mass evident on CT, with 2 mm of skin excluded from the GTV and no clinical target volume added. The PTV included a 3- to 5-mm isotropic expansion from the GTV, excluding 2 mm of skin. The goal of planning was for 100% of the PTV to receive ≥ 95% of the prescribed radiation dose, and for 100% of the GTV to receive 100% of the prescribed dose. Heterogeneity correction was used during radiation therapy planning. In addition, organs at risk were contoured on the basis of tumor location. For instance, the brain was contoured from the location of the most rostral CT image slice on which the brain was visible to the most caudal CT image slice on which the connection

of the brain to spinal cord was visible. Skin was defined as both the 2-mm and 3-mm thicknesses of tissue immediately adjacent to the outer body contour, and radiation doses for both definitions of skin were recorded in the study because both thicknesses are used for dose calculation by veterinary radiation oncologists. The dose constraints for critical organs[13] were used in planning.

Dogs underwent general anesthesia and were positioned with a vacuum deformable body cushion[c] in sternal, dorsal, or lateral recumbency, depending on tumor location, for the treatment planning CT and SBRT. For dogs with tumors located on the head, treatment also included use of a thermoplastic neck cushion,[d] custom-made bite block stand, thermoplastic bite block[e] and head mask[f] (used at the Western College of Veterinary Medicine) or a custom head immobilization stand, foam immobilization system,[g] and head mask[h] (used at the Western Veterinary Specialist and Emergency Centre). The treatment planning CT slice thickness was 2.0 mm for all dogs, and pre- and postcontrast scans were obtained. For dogs treated at the Western Veterinary Specialist and Emergency Centre, proper patient positioning was verified with megavoltage portal radiographic images compared side by side with digitally reconstructed radiographs in treatments provided before May 2013, megavoltage portal radiographic images and a patient position verification and correction system[i] in treatments provided between May 2013 and May 2015, and cone-beam CT and on-board imaging software[j] in treatments provided after May 2015. For all dogs treated at the Western College of Veterinary Medicine, kilovoltage portal radiographic images and cone-beam CT images, alone or in combination, were used with on-board imaging software[j] to verify and correct patient positioning. Pretreatment quality assurance was performed by γ analysis with a 2-D multidetector array[k] on individual fields. A passing quality-assurance score was defined as a minimum threshold of 95% γ for a 3-mm distance to agreement and a 3% absolute dose difference. Machine quality assurance at both facilities included a daily output evaluation with an ion chamber-based device[l] with a tolerance limit of 2% combined with an accuracy assessment of the digital match of the earlier obtained 2-D orthogonal kilovoltage images with the on-board imager of the treatment unit. Monthly quality assurance included isocenter verification of gantry, collimator, and couch rotations within a tolerance of 1 mm and verification of the coincidence of the imager beam and treatment beam.

Dogs underwent SBRT delivered by a megavolt x-ray produced by a linear accelerator.[m] To limit the radiation dose to the skin, SBRTs were performed without bolus materials (radiotherapy tissue-equivalent material placed on the skin to alter the radiation dose delivered to underlying tissues), and dogs underwent SBRT daily on 2 or 3 consecutive days. All SBRTs had a single isocenter and were coplanar.

Treatment data collected included the prescribed dose of radiation delivered to the tumor, number of treatment fractions, total treatment delivery period, volumes of GTV and PTV, and target coverage (the volume of PTV receiving < 95% of the prescribed dose and the volume of GTV receiving < 100% of the prescribed dose). The overall biologically effective dose was calculated with the following formula[14]:

$$n \times d \left(1 + \frac{d}{\alpha/\beta} \right)$$

where n = number of fractions; d = dose per fraction; and α/β = fractional sensitivity of the tissue (10 Gy in the present study). The minimum biologically effective dose within the GTV was calculated in the same manner, with d = lowest point dose within the GTV per fraction.

Outcome

Adverse effect to SBRT were scored,[15] and tumor responses were assessed.[16] Complete response was defined as the disappearance of all measurable lesions. Partial response was defined as ≥ 30% reduction of the longest diameter of the tumor. Progressive tumor disease was defined as ≥ 20% increase in the longest diameter of the tumor or the appearance of new lesions, alone or in combination. Stable disease was defined as between < 30% reduction and < 20% increase of the longest diameter of the tumor. Objective response was defined as either a complete or partial response. Tumor measurements to assess response were obtained by physical examination. The best recorded response for each dog was used for statistical analysis.

Statistical analysis

All analyses were completed by an analytic epidemiologist (CLW) who used a commercial software program.[n] The OS was defined as the number of days from the start of SBRT to the day of death, and dogs alive at the end of the study period or lost to follow-up were censored. The DSS was defined as the number of days from the start of SBRT to the day of death as a result of tumor progression or treatment-related complications, and dogs alive at the end of the study period, lost to follow-up, or that died of unrelated causes were censored. The TTP was defined as the number of days from the start of SBRT to the day of documented tumor progression (local or metastatic) in dogs that later died of tumor-related causes, and dogs alive at the end of the study period, lost to follow-up, or that died without evidence of tumor progression were censored. The PFS was defined as the number of days from the start of SBRT to the day of documented tumor progression (local or metastatic) in dogs that later died of any cause, and dogs alive at the end of the study period or lost to follow-up without evidence of tumor progression were censored. Overall survival time, DSS, TTP, and PFS were evaluated with Kaplan-Meier survival analysis and the Cox

test of equality, also known as the Cox proportional hazards regression. Patient-related potential risk factors examined in the analysis included dog age, body weight, and sex; tumor histologic grade[2] and location (extremities, head, or all other locations); treatment of a recurrent tumor (yes vs no); and surgical intervention after radiation (yes vs no). Tumor dose-related potential risk factors examined included radiation protocol, total radiation dose, GTV, and biologic effective dose within the GTV (overall and minimum). Values of $P < 0.05$ were considered significant.

Results

Animals

Thirty-five dogs with STS diagnosed on the basis of histologic (n = 31) or cytologic (4) examination findings were included in the study. The median age and body weight at the time of SBRT was 9.9 years (range, 2.1 to 16.5 years) and 23.1 kg (50.8 lb; range, 3.1 to 41.8 kg [6.8 to 92.0 lb]). Of the 35 dogs, 20 (57%) were castrated males, 13 (37%) were spayed females, 1 (3%) was a sexually intact male, and 1 (3%) was a sexually intact female. The grade of STS was noted in the medical records of 27 dogs **(Table 1)**.

Table 1—Anatomic locations and grades* of STSs in 35 client-owned dogs treated with SBRT between October 2011 and May 2017.

STS characteristics	No. (%) of dogs
Anatomic location	
Extremity	20 (57)
Body	12 (12)
Head	3 (9)
Tumor grade*	
1	16 (60)
2	9 (33)
3	2 (7)

*Reported in 27 dogs.

Table 2—Summary data for SBRT administered to the 35 dogs described in Table 1.

	SBRT protocol		
Fractions	Radiation dose/ fraction (Gy)	Total radiation dose/ protocol (Gy)	No. (%) of dogs
3	9	27	16 (46)
3	10	30	11 (31)
3	12	36	3 (9)
3	14	42	1 (3)
3	16	48	3 (9)
2	16	32	1 (3)

Table 3—Maximum radiation dose (Gy) delivered to skin (2- and 3-mm thicknesses) and bone as organs of risk during SBRT of the dogs described in the previous tables stratified by total number of fractions of SBRT performed.

Organs of risk	2 fractions (n = 1)	3 fractions (n = 34)*
Skin		
2-mm thickness	27.7	26.9 (22.8–46.2)
3-mm thickness	30.2	28.6 (24.1–49.4)
Bone	34.8	30.7 (27.0–53.4)

*Data are reported as median and range.

Treatment planning

Within 4 weeks before starting SBRT, a CBC and serum biochemical analyses were performed on all 35 dogs, thoracic radiography was performed on 17, and thoracic CT was performed on 13. Thoracic imaging was not available for the remaining 5 dogs. No evidence of thoracic metastatic disease was found in any of the 30 dogs that underwent diagnostic imaging. One dog had a tumor on its muzzle and an enlarged mandibular lymph node noted on physical examination and CT. Results of cytologic examination of a fine-needle aspirate sample of the enlarged lymph node were suggestive of a reactive process, and the lymph node was not treated with SBRT. Concurrent diseases noted in the medical records included valvular heart disease (n = 3), hepatopathy (2), mild azotemia (1), and immune-mediated polyarthritis (1). Five dogs underwent SBRT for local tumor recurrence following an earlier surgical excision, and the median duration between surgery and SBRT was 222 days (range, 43 to 693 days). Two other dogs also had surgery before SBRT but underwent SBRT for residual macroscopic STSs, not tumor recurrence. The remaining 28 dogs had not undergone previous surgical treatment for their STSs.

Treatment with SBRT

Protocols for SBRT consisted of 3 fractions of 9 to 16 Gy (n = 34) or 2 fractions of 16 Gy (1; **Table 2**). The number of irradiation beams ranged from 5 to 9. Organs at risk that were contoured on the basis of tumor location included the eye (globe and lens), brain, ear, lower gastrointestinal tract, urinary bladder, lungs, heart, bone, and skin. Regarding target coverage, the median volume of PTV that received < 95% of the prescribed dose was 2.06 cm^3 (range, 0 to 21.3 cm^3) and the median volume of GTV that received < 100% of the prescribed dose was 17.35 cm^3 (0 to 504.9 cm^3). For the 34 dogs that received 3 fractions, the median maximum radiation dose to bone was 30.7 Gy and to 2- and 3-mm skin was 26.9 and 28.6 Gy, respectively **(Table 3)**.

Additional treatment

After SBRT, 8 dogs had surgery to remove residual macroscopic STSs (n = 3), treat progressive tumor disease (4), or treat adverse effects to SBRT (1). Three different dogs had tumor progression and underwent additional radiation therapy (a single dose of 20 Gy [n = 2] or 2 fractions of 9 Gy for a total dose of 18 Gy [1]). Metronomic chemotherapy with chlorambucil and piroxicam was initiated in 1 dog with a high-grade STS at the time that tumor progression was detected.

Outcome

Information about acute adverse effects from radiation was available for 20 of the 35 (57%) dogs. Five of the 20 dogs had no acute adverse effects; however, 15 dogs had acute adverse effects, all affecting the skin. When the acute adverse effects of radiation were scored on a scale from 0 (unchanged from baseline) to 3 (confluent moist desquamation and edema with or without ulceration, necrosis, or hemorrhage),[15] 9 dogs had a score of 1, 3 dogs had a score of 2, and 3 dogs had a score of 3. Two of the 3 dogs with a score of 3 recovered with medical management; however, the third dog underwent amputation of a limb because of a nonhealing wound and was still alive at the end of the study period with no evidence of tumor progression at 476 days. This dog had received 48 Gy divided into 3 fractions of 16 Gy, with a maximum dose to 2- and 3-mm skin thicknesses of 39.0 and 41.5 Gy, respectively.

Objective measurements allowing for evaluation of tumor response were available for 28 dogs. An objective response was observed in 13 of the 28 (46%) dogs (10 [36%] had a partial response and 3 [11%] had a complete response). The remaining 15 of 28 (54%) dogs had stable disease.

None of the 3 dogs with a complete response had evidence of local recurrence at the end of the study period, with 173, 486, and 1,073 days of follow-up after SBRT; however, tumor progression was documented in 13 other dogs. Twelve of these 13 dogs had local tumor progression, with a median TTP of 282 days (range, 71 to 713 days). Metastatic tumor progression was documented in 4 dogs, with a median TTP of 433 days (range, 85 to 713 days). Metastases occurred in the lungs (radiographic diagnosis; n = 3) or a regional lymph node (histologic diagnosis; 1). The dog with metastasis to a lymph node did not have evidence of local tumor progression. Overall, the median TTP was 705 days (range, 71 to 1,583 days; **Figure 1**), and the median PFS was 521 days (range, 19 to 1,583 days; **Figure 2**).

Eleven dogs were alive at the end of the study period; however, 24 had died. Although necropsies were not performed on any of the dogs, the underlying cause of death noted in the medical record was related to the STS or SBRT in 9 of the 24 dogs. One of these 9 dogs was euthanized because of a suspected radiation-induced tumor, evidenced on radiography with an osteoproliferative and lytic lesion and a pathological fracture in the humerus that was in the SBRT field. Previously, this dog had undergone SBRT twice, originally receiving 3 fractions of 9 Gy (38 months earlier) for an STS and then a single dose of 20 Gy (22 months earlier) for a local recurrence of the STS. After the second SBRT, this dog also underwent surgery (20 months earlier) to remove residual gross tumor. The maximum radiation dose to the bone in this dog was 27.9 Gy for the first SBRT treatment and 16.94 Gy for the second SBRT treatment.

Fourteen dogs died of causes unrelated to their SBRTs or irradiated STSs, including euthanasia because of mobility issues in 5 dogs, nonmetastatic pulmonary disease in 3 dogs, a femoral fracture in 1 dog with a primary tumor located on the muzzle, ascites of unknown cause in 1 dog with a primary tumor located at the base of the tail, lymphoma in 1 dog, gastric carcinoma in 1 dog with a primary tumor located on the thoracic wall and for which the owners elected euthanasia 60 days after SBRT, wobbler syndrome in 1 dog, and lymphocytic hepatitis that progressed to liver failure in 1 dog with a primary tumor located at the base of the tail and for which the owner elected euthanasia 24 days after SBRT. The remaining dog

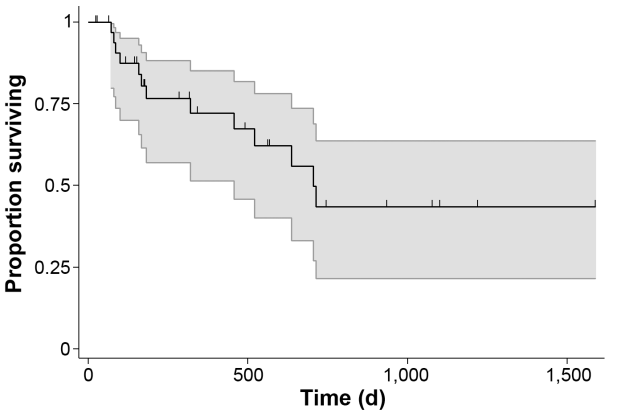

Figure 1—Kaplan-Meier survival curve for TTP for 35 client-owned dogs with STS treated with SBRT between October 2011 and May 2017. The TTP was calculated from the first day of SBRT to the day of documented tumor progression (local or metastatic) in dogs that later died of tumor-related causes. Dogs alive at the end of the study period, lost to follow-up, or dead without evidence of tumor progression were censored. Median TTP was 708 days (range, 71 to 1,583 days). Steps on the curve represent the death of ≥ 1 dog, tick marks represent dogs that were censored, and the shaded area represents the 95% CI at each time point.

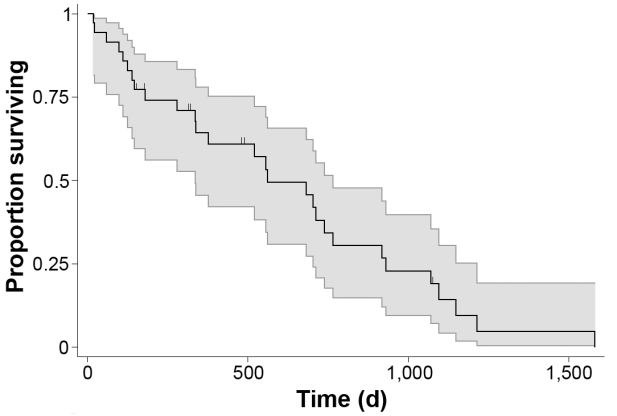

Figure 2—Kaplan-Meier survival curve for PFS for the dogs described in Figure 1. The PFS was calculated from the first day of SBRT to the day of tumor progression (local or metastatic) diagnosis in dogs that later died of any cause. Dogs alive at the end of the study period or lost to follow-up without evidence of tumor progression were censored. Median PFS was 521 days (range, 19 to 1,583 days). ***See*** Figure 1 for the key.

that died was brought by the owner to the hospital dead, and the owners did not report any clinical signs before the sudden death, which made us suspect an unrelated underlying cause, such as cardiac disease. This dog did not have clinical signs of tumor progression and did not undergo necropsy.

The median OS was 713 days (range, 19 to 1,583 days; **Figure 3**), and the median DSS was 1,149 days (range, 99 to 1,583 days; **Figure 4**). Because of the small sample size, only simple unadjusted models were examined. Factors determined to be prognostic in relation to survival times were STS grade and anatomic location. The median OS, DSS, and PFS were significantly (P = 0.01, P = 0.03, and P = 0.02, respectively) longer in dogs with grade 1 or 2 STSs (558, 1,149, and 456 days, respectively; n = 25) than in those with grade 3 STSs (99, 99, and 80 days, respectively; n = 2). Dogs with grade 3 STSs had significantly increased risk of death (OS HR, 2.8; 95% CI, 0.6 to 14; P = 0.012), including death as a result of tumor progression or SBRT-related causes (DSS HR, 10.0; 95% CI, 1.3 to 83; P = 0.029) and death for any reason after documented progressive tumor disease (PFS HR, 8.1; 95% CI, 1.5 to 45.0; P = 0.017), than did dogs with lower-grade STSs (grades 1 or 2; n = 25). Similarly, the median OS and PFS were significantly (P = 0.049 and P = 0.036, respectively) longer in dogs with STSs located on their extremities (931 and 705 days, respectively; n = 20) than in dogs with STSs located elsewhere on their bodies (337 and 166 days, respectively; 15). Dogs with STSs in locations other than on extremities had significantly higher risk of death (OS HR, 2.4; 95% CI, 1.0 to 5.9; P = 0.049), including death for any reason after documentation of progressive tumor disease (PFS HR, 1.4; 95% CI, 0.1 to 2.7; P = 0.036), than did dogs with STSs on their extremities. Other factors evaluated, including tumor volume, were not meaningfully prognostic for survival times, and no factors evaluated were prognostic of tumor progression.

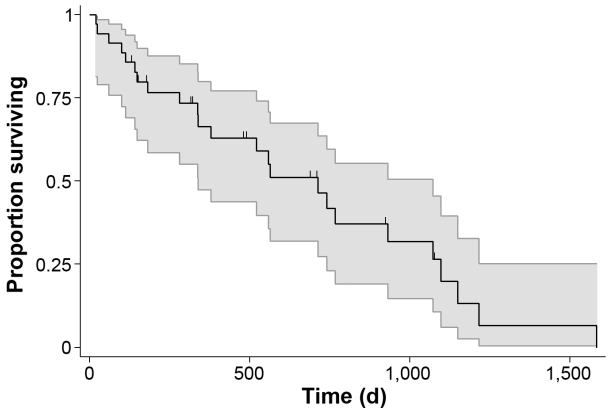

Figure 3—Kaplan-Meier curve for OS for the dogs described in the previous figures. The OS was calculated from the first day of SBRT to the day of death. Dogs alive at the end of the study period or lost to follow-up were censored. Median OS was 713 days (range, 19 to 1,583 days). ***See*** Figure 1 for the key.

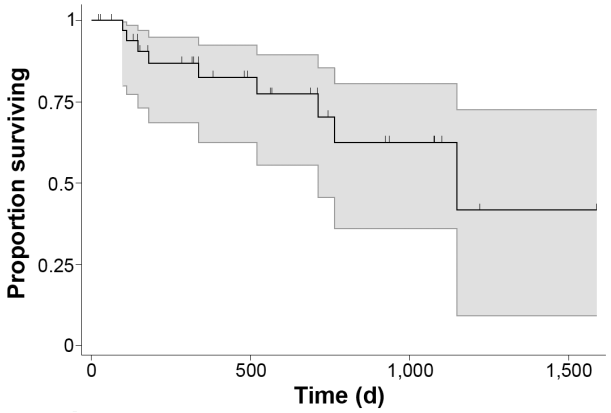

Figure 4—Kaplan-Meier curve for DSS for the dogs described in the previous figures. The DSS was calculated from the first day of SBRT to the day of death as a result of tumor progression or treatment-related complications. Dogs that were alive at the end of the study period, lost to follow-up, or died of cause unrelated to their STS or SBRT were censored. Median DSS was 1,149 days (range, 99 to 1,583 days). ***See*** Figure 1 for the key.

Discussion

Findings indicated that SBRT for STS in dogs of the present study resulted in a median TTP of 705 days and a median PFS of 521 days, similar to the median time to recurrence of 700 days in an earlier study[4] of 48 dogs. In contrast, a study[5] of 35 dogs shows that the median time to recurrence was not reached but was > 798 days. Because the median time to tumor recurrence was not reached in that study,[5] comparing those findings with our findings for TTP was difficult. However, a different study[6] shows that the PFS was 698 days for 48 dogs treated with surgery followed by a hypofractionated radiation therapy protocol, which was a PFS longer than the 521-day PFS in the present study. A few reasons could explain our shorter PFS. For instance, some dogs in the present study underwent SBRT because their tumors were too large to be removed surgically, whereas all dogs in the previous study[6] had surgical treatment; thus, a selection bias could have contributed to the difference in results. In addition, because patients that die of any cause are included in PFS calculations, differences between the groups of dogs studied could have contributed to differences in PFS results. For example, some dogs in the present study had concurrent disease that led to an early death following treatment, such as a dog with concurrent lymphocytic hepatitis that progressed to liver failure and was euthanized 24 days after SBRT, a dog that developed pleural effusion without evidence of metastatic tumor progression was euthanized 19 days after SBRT, a dog with gastric carcinoma died 60 days after SBRT, and a dog with an enlarged lymph node but with cytologic results indicative of a reactive lymph node before SBRT was documented to have had metastatic tumor progression to the regional lymph node 85 days after SBRT.

Because of the rapid progression of disease in this last dog, we suspected that the cytologic sample obtained during staging may not have been representative and that metastasis to the lymph node may have already occurred by the time of STS diagnosis. However, the particular lymph node in this dog was not treated with SBRT on the basis of cytologic examination results. The outcomes in these dogs not only served as examples of potential differences in dogs of the present study, compared with those of a previous study,[6] but also illustrated the need for proper patient selection for SBRT. Although STSs have a low risk of metastatic disease, we recommend thorough staging that may include thoracic and abdominal diagnostic imaging to help detect concurrent diseases.

Another factor that could have explained the shorter TTP and PFS in the present study, compared with previous studies,[4–6] was tumor grade. A 2008 study[17] shows a 10% local recurrence for grade 1 STSs of the extremities in dogs following marginal excision. Dogs with grade 1 STSs treated solely with SBRT were included in the present study, and because SBRT was the only treatment modality for some dogs, their responses to treatment could all be attributed to SBRT. In contrast, the proportion of grade 1 STSs among dogs with an STS histologic grade in previous studies was 21 of 38 (55%) dogs,[4] 14 of 25 (56%) dogs,[5] and 14 of 46 (30%) dogs,[6] and the surgical treatment with or without radiation treatment in those studies may have resulted in longer TTP and PFS in some dogs. In addition, the present study included 2 dogs with grade 3 STSs, whereas a previous study[4] did not include any dogs with grade 3 STSs.

In the present study, the median OS and DSS were 713 and 1,149 days, respectively, which contrasted with previously reported medians of OS (1,108 days[5] to median not reached[4]) and DSS (1,851 days[4] to median not reached[5,6]). Our inclusion of dogs with concurrent diseases that died in short periods of time after SBRT may have contributed to our shorter OS, and although we censored these patients for the calculation of DSS, our findings for DSS were shorter than the median DSS of 1,851 days reported previously.[4] Another possible explanation for the shorter survival times in dogs of the present study, compared with previous studies[4–6] in which dogs underwent surgery followed by conventionally fractionated radiation therapy, was the presence of residual macroscopic tumors because not all dogs in the present study underwent surgical treatment. Compared with microscopic tumors, macroscopic tumors contain higher numbers of cells that could lead to a higher rate of recurrence and an increased risk of somatic mutations. Additional mutations within STSs of dogs in the present study may have led to a more aggressive tumor phenotype at the time of tumor progression. Future investigations with surgical removal of STSs following SBRT in dogs may address this issue.

Outcomes in the present study appeared superior to outcomes reported for dogs undergoing hypofractionated palliative protocols.[7–9] For instance, the median PFS was 521 days in our study, compared with median PFSs between 155 and 419 days in previous studies[7–9] involving palliative radiation therapy. The median OS of 713 days in our study also compared favorably with the median OSs of 309 to 513 days in those same studies.[7–9] The consecutive daily administration SBRT in our study may have resulted in the improved outcomes by allowing less time for cellular repair between fractions, compared with treatments with longer durations between treatment fractions.

To our knowledge, this is the first report of SBRT for nonintranasal STSs in dogs. In 11 cats, however, SBRT was used to treat injection-site sarcomas and yielded outcomes including a median TTP of 242 days and a median OS of 301 days.[18] It was possible that longer tumor control was achieved in dogs of the present study (median TTP, 705 days) because spontaneously occurring STSs, as were treated with SBRT in the present study, are typically less biologically aggressive than feline injection site sarcomas.

Results indicated that dogs with grade 3 STSs had greater hazards of death, death as a result of tumor progression or SBRT-related causes, and death for any reason after documentation of progressive tumor disease than did dogs with grade 1 or grade 2 STSs. These findings were consistent with previous reports[4–6,17] and highlighted the need for a histologic diagnosis when treating STSs. Although 31 dogs in our study had histologic diagnosis of STS and 27 had graded tumors, 4 dogs had cytologic diagnosis of STS, and tumor grading would have been beneficial in providing a prognosis. However, biopsy sites can dehisce and become nonhealing ulcers. In some cases, it may be appropriate to treat patients on the basis of cytologic diagnosis.

Our findings also indicated that dogs with STSs located on their extremities had lower hazards of death, including death for any reason after documentation of progressive tumor disease. It was possible that dogs with tumors in these locations lived longer than the remaining dogs in the present study because no vital organs were affected by local recurrence and tumor progression. In addition, longer time could have been required for such tumors to progress and negatively affect quality of life.

Tumor volume was not meaningfully prognostic for tumor progression or survival times in dogs of the present study. It was possible, however, that tumor volume was prognostic but was not detected as such because of low power in the present study. Nonetheless, given this finding and the fact that a subset of dogs in the present study underwent SBRT because their tumors were too large to surgically achieve microscopic STS, we recommend that SBRT be considered in dogs with STSs too large for surgical removal.

Most dogs in the present study tolerated SBRT well, with acute adverse effects limited to the skin and only 1 dog requiring surgical intervention. A probable radiation-induced tumor was diagnosed in 1

dog that underwent SBRT twice. Stereotactic body radiation therapy may be associated with a higher risk of late adverse effects, including secondary neoplasia, because of higher cumulative late damage to normal tissue around the tumor, compared with conventionally fractionated radiation therapy. We may have underestimated the true incidence of late effects as necropsies were not performed on any dogs and some dogs died of unrelated causes ≤ 6 months after SBRT.

Limitations of the present retrospective study included the wide range of prescribed radiation doses and protocols. There was also a lack of standardized follow-up in regard to tumor response and adverse effects. We also included dogs with cytologic diagnosis of STS, for which tumor grading was not possible. Nonetheless, the clinical signs in these dogs were consistent with STS; thus, we had a high level of confidence in the diagnosis. However, it was possible that dogs with a cytologic diagnosis were affected by another neoplasm. Another limitation was the lack of histologic evaluation to confirm tumor progression. Other processes, such as necrosis and hemorrhage, could account for tumor enlargement.[19] None of the dogs underwent necropsy, and the 3 dogs with presumed metastatic lung disease could have had another tumor that caused the metastatic nodules in the lungs evident with radiography.

Another limitation was the use of megavoltage portal radiographic images in the treatment planning for some dogs in the early phase of the present study. Accurate patient positioning is critically important for SBRT, and plan delivery may not have been optimal for patients positioned on the basis of portal radiographic images; therefore, the use of such images for positioning may have resulted in areas of some tumors not receiving the intended dose. A cone-beam CT should be used for patient setups when image registration is on the basis of soft tissue structures.

Results indicated that SBRT for STS was well tolerated in most dogs and provided local tumor control in dogs of the present study; however, tumor control appeared shorter in dogs of our study, compared with dogs of previous studies[4–6] that underwent excisional surgery followed by conventionally fractionated radiation therapy. Stereotactic body radiation therapy may be recommended for dogs with STSs too large to be removed surgically or when owners of dogs with STSs decline surgical intervention. We believe that increasing the total radiation dose (ie, by increasing either the number of fractions [eg, to 4 or 5 fractions] or the radiation dose per fraction) and performing surgical intervention after SBRT may provide longer TTP and survival times in dogs with STS.

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The authors declare that there were no conflicts of interest.

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Footnotes

a. Clinac 2100C, Varian Medical Systems Inc, Palo Alto, Calif.
b. Clinac 2100EX, Varian Medical Systems Inc, Palo Alto, Calif.
c. SecureVac, Bionix Radiation Therapy, Toldeo, Ohio.
d. Thermoplastic U-Frame Mask, Klarity Medical Products, Newark, Ohio.
e. EZ Bolus Thermoplastic Pellets, Klarity Medical Products, Newark, Ohio.
f. Green ProfileFrame extended head mask, Klarity Medical Products, Newark, Ohio.
g. InstaForm, CDR Systems, Calgary, AB, Canada.
h. LT-Thermoplastic, CDR Systems, Calgary, AB, Canada.
i. TheraView, Cablon Medical, Leusden, Netherlands.
j. On-Board Imager Advanced Imaging, Varian Medical Systems Inc, Palo Alto, Calif.
k. MapCHECK 2, Sun Nuclear Corp, Melbourne, Fla.
l. CHECKMATE 2, Sun Nuclear Corp, Melbourne, Fla.
m. Eclipse, Varian Medical Systems Inc, Palo Alto, Calif.
n. Stata SE, version 14, StataCorp LLC, College Station, Tex.

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From this month's *AJVR*

Effect of 3% chloroprocaine hydrochloride when used for median and ulnar regional nerve blocks in lame horses

Lindsey H. Boone et al

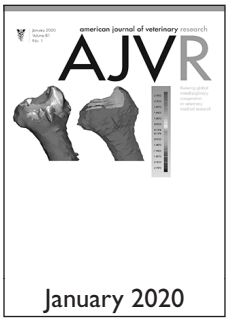
OBJECTIVE
To assess onset of analgesia for 3% chloroprocaine hydrochloride and 2% mepivacaine hydrochloride when used for median and ulnar nerve blocks in lame horses.

ANIMALS
6 naturally lame horses.

PROCEDURES
A crossover experiment was conducted. Horses were assigned to 1 of 2 treatment groups (3% chloroprocaine or 2% mepivacaine). Median and ulnar nerve blocks were performed in the lame limb with the assigned treatment. Lameness was objectively evaluated before treatment administration and at various points for 120 minutes after treatment with a wireless inertial sensor-based motion analysis system. Following a 7-day washout period, horses then received the other treatment and lameness evaluations were repeated.

RESULTS
Median and ulnar nerve blocks performed with 3% chloroprocaine resulted in more consistent, rapid, and profound amelioration of lameness than did blocks performed with 2% mepivacaine. Lameness decreased more between 20 and 40 minutes after injection when 3% chloroprocaine was used than when 2% mepivacaine was used. Complete resolution of lameness was detected a mean of 9 minutes after injection when median and ulnar blocks were performed with 3% chloroprocaine and a mean of 28 minutes after injection when performed with 2% mepivacaine.

CONCLUSIONS AND CLINICAL RELEVANCE
3% chloroprocaine had a more rapid onset and provided better analgesia for median and ulnar nerve blocks in horses with naturally occurring lameness, compared with 2% mepivacaine. These favorable properties suggest that 3% chloroprocaine would be useful for performance of median and ulnar regional nerve blocks during complicated lameness evaluations. (*Am J Vet Res* 2020;81:13–16)



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