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Stereotactic body radiation therapy for treatment of injection-site sarcomas in cats: 11 cases (2008–2012)

Michael W. Nolan, DVM, PhD, DACVR; Lynn R. Griffin, DVM;
James T. Custis, DVM, MS, DACVR; Susan M. LaRue, DVM, PhD, DACVS, DACVR

Objective—To evaluate outcomes of stereotactic body radiation therapy (SBRT) in cats with injection-site sarcomas (ISS) via assessment of local responses and recurrences, survival times, and complications.

Design—Retrospective case series.

Animals—11 cats with ISS.

Procedures—Medical records of cats that were treated with SBRT for ISS between June 2008 and July 2012 were reviewed; information on patient demographics (age, sex, and breed), oncological histories (including prior treatment and histologic grade), details of SBRT plans (tumor volume, treatment field sizes, and prescription), response to treatment (including toxicoses), progression-free intervals, and survival times were extracted.

Results—Acute radiation-associated toxicoses were infrequent and limited to mild, self-limiting dermatitis and colitis in 2 and 1 of the 11 cats, respectively. No late radiation-associated toxicoses were observed. The objective response rate was 8 of 11 cats; these patients either had a partial or complete response as determined on the basis of CT or physical examination findings. The median progression-free interval was 242 days, and the median overall survival time was 301 days; median follow-up time of censored subjects was 173 days.

Conclusions and Clinical Relevance—SBRT was completed in 3 to 5 days and was well tolerated when used to treat cats with ISS. Measurable tumor responses were achieved in most cats in this study. Stereotactic body radiation therapy provided a means for palliation of ISS; further investigation is required to determine whether SBRT is a valid treatment option for downstaging disease prior to definitive surgery. (*J Am Vet Med Assoc* 2013;243:526–531)

Achieving long-term local control of ISS (also referred to as vaccine-associated sarcomas) in cats is difficult. The most effective local treatment is often considered to be a combination of tumor excision with radiation therapy. However, even when surgical excision of the tumor resulting in complete histologic excision of the margins is combined with full-course, fractionated radiation therapy, local tumor control is disappointing. Local tumor recurrence is reported in 28% to 45% of cases following a combination of surgery and definitive (pre- or postoperative) radiation therapy.[1–4] Investigation of novel treatments aimed at improved local tumor control is therefore warranted.

Stereotactic radiation therapy is an umbrella term, encompassing stereotactic radiosurgery, craniospinal SRT, and SBRT. Stereotactic radiation therapy involves the delivery of high doses of ionizing radiation to tumors in a limited number of treatment sessions (1 to 5). Stereotactic radiation therapy is reserved for treatment of well-delineated bulky or macroscopic tumors. It also relies on accuracy of treatment, which ensures the prescribed dose is delivered to the intended target (tumor) rather than adjacent normal tissues.[5] The term stereotactic radiosurgery is typically reserved for single fraction treatment protocols. Craniospinal SRT describes radiation therapy aimed at tumor targets in the head and neck; tumor localization can be performed with rigid (frame-based) immobilization to ensure reproducible target positioning or can be achieved through image guidance. Stereotactic body radiation therapy describes treatment of tumors in any other part of the body, especially within body cavities. Because rigid immobilization of targets outside the head and neck is difficult, SBRT uses image guidance (via on-board kilovoltage radiography or CT) or real-time tracking systems (involving implantation of transponders that transmit radiofrequency signals to electromagnetic ar-

Abbreviations

ISS	Injection-site sarcoma
PTV	Planning target volume
SBRT	Stereotactic body radiation therapy
SRT	Stereotactic radiation therapy

From the Department of Environmental and Radiologic Health Sciences, Flint Animal Cancer Center, College of Veterinary Medicine and Biomedical Sciences, University of Colorado, Fort Collins, CO 80523.

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Address correspondence to Dr. Nolan (Michael.Nolan@colostate.edu).

rays) to ensure proper localization of the target prior to and during administration of radiation. Additionally, if the target volume's physical location varies with respiratory motion, either respiratory gating or breath-holding techniques can be used to minimize the volume of normal tissue irradiated.

Stereotactic radiation therapy is similar to conventional palliative-intent radiation therapy in that it is hypofractionated and therefore uses large doses per fraction. However, the total prescribed doses of radiation are substantially lower than those associated with conventional curative-intent protocols (which often exceed 50 Gy) and it differs from palliative-intent radiation therapy in how it is delivered. Stereotactic radiation therapy is a precision technique, which has a geometric advantage over conventional radiation therapy in that it is able to deliver high doses to the target volumes, while sculpting the beam such that normal tissues receive less dose in comparison to conventional protocols. Whereas conventional hypofractionated palliative-intent radiation therapy is typically delivered once weekly to allow normal tissues time to heal from radiation injury, the physical sparing of normal tissues achieved with SRT techniques allows for more frequent administration, with radiation fractions typically administered either daily or every 48 hours. Clinically, this difference translates into a potential improvement in tumor control probability when SRT is used. For example, it is expected that 30 Gy delivered as 3 daily 10-Gy fractions will be more biologically effective than 30 Gy delivered in 3 weekly 10-Gy fractions. Several factors contribute this this improvement in effectiveness relative to total administered dose. First, the shorter protocols associated with SRT not only avoid accelerated repopulation of tumors, but also limit the effect of normal tumor repopulation or growth (compared with finely or coarsely fractionated radiation therapy). Second, some scientists and clinicians speculate that in addition to inducing lethal effects via extensive DNA damage leading to chromosomal damage that causes mitotic catastrophe, high dose per fraction radiation therapy also causes cell death via generation of ceramide through the acid sphingomyelinase pathway, which activates caspases and leads to apoptosis. It has been shown in mice that SRT induces vascular endothelial apoptosis at a high rate and therefore leads to tumor death by indirect microenvironment changes (eg, hypoxia or pH change), which alter the tumor cell's ability to repair DNA damage.[6,7] Furthermore, recent studies[8–11] of soft tissue sarcomas as well as several other disease processes suggest that targeted high dose per fraction radiation therapy may have effects outside the defined treatment field (ie, the PTV). The reason for this effectiveness is unknown, although it has been proposed that despite steep dose gradients outside the PTV, microscopic tumor cells outside the gross tumor volume may receive a sufficient dose to inhibit tumor growth; inactivation of cells within the gross tumor volume via ablative radiation effects may result in loss of autocrine and paracrine growth stimulants, which are needed to support growth of residual tumor cells; bystander effect may mediate cell death within 5 to 7.5 mm of a cell that has been directly hit; and there may be post-irradiation immune responses that either inhibit tumor growth or lead to phagocytosis of residual neoplastic cells.[12–16] In summary, there are more radiobiological considerations to determining effectiveness of a given radiation therapy prescription than total dose alone, and these differences make it difficult to directly compare doses (and clinical outcomes) associated with different forms of radiotherapy (eg, SRT vs fractionated radiation therapy vs conventional hypofractionated palliative radiation therapy).

Several authors have recently reported on the use of SBRT in management of soft tissue sarcomas in human patients. Dhakal et al[8] reported outstanding local control with minimal toxic effects when treating pulmonary metastases of soft tissue sarcomas; their study[8] lacks long-term follow-up, but suggests that SBRT may be used in a curative fashion when treating limited metastases. Roh et al[9] documented an 88% overall response rate, with 42.9% of cases completely regressing, 37.1% partially regressing, and 8.6% with stable disease within 2.5 months after the start of SBRT when treating head and neck tumors that recurred after prior treatment with surgery and radiation therapy. In that study,[9] median survival time was 16 months, with 17 of 44 patients eventually developing local progression. Levine et al[10] reported on results in 14 patients with spinal sarcomas (primary or metastatic) treated with stereotactic spinal radiation therapy. Of the 7 primary lesions treated with curative intent, 2 had complete remission, 3 had partial regression, and 2 had recurrence (at 12 and 45 months); 33% of patients treated in the preoperative setting achieved complete remission, and 4 of 4 patients treated in the postoperative setting maintained local control. Patients in this cohort that had stage IV disease at the time of treatment had mixed results, with all having local or systemic progression at the time of death.[10]

Still, outcomes of SBRT for treatment of soft tissue sarcomas in humans have been mixed. Because this treatment modality can result in durable tumor regression, it is suggested that there may be a role for treating unresectable or recurrent sarcomas with SBRT as either monotherapy or as part of a multimodal treatment plan. Currently, the usefulness of SBRT in the management of ISS in cats is unknown. It is expected that an optimized dose and fractionation scheme delivered via SBRT will be more efficacious than previously reported palliative radiotherapy protocols and that outcomes may in fact rival those attained through use of multimodal treatment. The safety and efficacy of SBRT should ultimately be rigorously investigated through a controlled clinical trial. To examine prephase variables before proceeding with a prospective trial, the objective of the study reported here was to retrospectively assess local tumor control, overall survival time, and development of toxicity following SBRT in cats with ISS.

Materials and Methods

Case selection—A descriptive retrospective analysis of data from cats for which there was intent to complete SBRT for ISS at the Animal Cancer Center at Colorado State University between June 2008 and July 2012 was performed. Histologic or cytologic evidence of a sarcoma at a previous site of injection as well as complete local and systemic staging (including CBC, serum

biochemical profile, urinalysis, 3-view thoracic radiographs, and regional CT of the tumor) were requisite for inclusion. For each cat, clients were offered SBRT for treatment of their pet's ISS if the tumor was deemed unlikely to be effectively surgically cytoreduced by a veterinary surgical oncologist, if disease had recurred after prior surgery (with or without adjuvant radio- or chemotherapy), or, for palliative purposes, if the client declined standard definitive treatment options.

Medical records review—A medical records review was performed. Information relating to cat demographics, oncological histories, details of radiation therapy plans, response to treatment, local tumor control, toxicity development, and overall survival time was extracted. Timing of follow-up examinations and restaging lacked uniformity; when possible, information about extent and duration of tumor responses, normal tissue toxicoses, and overall survival time was obtained through review of medical records and verbal follow-up with primary care veterinarians and pet owners.

Radiation therapy—Computerized 3-D treatment planning was used to treat cats. Pre- and postcontrast simulation CT scans were obtained with patients immobilized in a cushion[a] to minimize interfraction variability of target tissue localization. Patient positioning was variable and determined on a case-by-case basis depending on location of the primary tumor. Grossly evident tumor was delineated with the CT scan and defined as the gross tumor volume. There was no field expansion to account for potential subclinical disease (ie, the clinical target volume was the same as the gross tumor volume). A uniform field expansion of 2 to 5 mm comprised the isotropic PTV and accounted for possible intra- and interfraction variations in target position, shape, and size. This expansion varied depending on the anatomic location of the tumor and the comfort level of the prescribing radiation oncologist and attending medical physicist. Inverse planning was performed at a treatment planning workstation.[b] Prescriptions for SBRT ranged from 24 to 32.5 Gy delivered in 3 to 5 fractions either on consecutive or alternating days (5.4 to 10 Gy/fraction administered over 3 to 7 days). Institutional standards for radiation prescriptions in SBRT plans were applied; dose was prescribed to the PTV, with the prescribed isodose covering at least 95% of the PTV and a global dose maximum no greater than the 150% isodose line. Treatment plans typically involved 6 to 11 isocentrically placed coplanar or noncoplanar 6 MV x-ray beams, which were shaped with dynamic multileaf collimation in a sliding-window fashion to achieve intensity modulation. Plans were constructed with iterative inverse planning with heterogeneity corrections to meet specified goals for both tumor and target volumes and organs at risk (defined as normal tissues within and surrounding the treatment field). Bolus was not used. Organs at risk varied with location of the primary tumor, but usually included skin (delineated as a 2-mm-thick structure with the outer margin defined by the body contour) and variably included the spinal cord, heart, lungs, small intestine, colon, kidneys, and ureters. Dose constraints generally adhered to guidelines set by the American Association of Physicists in Medicine, with modifications based on the size of cats relative to humans (eg, the American Association of Physicists in Medicine dose constraint for colon recommends a maximum point dose of 28.2 Gy in 3 fractions of SBRT, with no more than 20 cm^3 exceeding 24 Gy; given that the total volume of colon in humans far exceeds that in domesticated cats, we adhered to the maximum point dose of 28.2 Gy by limiting the volume receiving 24 Gy in 3 fractions to no more than 1 cm^3).[5] A conformity index was calculated as previously described.[17] Briefly, conformity index = $TV_{PIV}^2/TV \bullet PIV$, where TV_{PIV} is volume of the target (PTV) covered by the prescription isodose, TV is 95% of the target volume, and PIV is the prescription isodose volume. Individual treatment plan review was performed by an American College of Veterinary Radiology board-certified veterinary radiation oncologist and an American Board of Radiology–certified therapeutic medical physicist. Patient-specific plan quality assurance was performed for each field comprising the treatment plan with gamma analysis comparing treatment plan data with that measured with a portal dosimetry system.[c] As accepted by most medical physicists evaluating intensity-modulated radiation plans devised for treatment of tumors in human patients, a minimum of 95% gamma for a 3-mm distance to agreement and a 3% absolute dose difference was defined as a passing quality-assurance score. In vivo dosimetry was not performed.

All patients were anesthetized for treatment; protocols varied and were developed on the basis of each patient's medical history and health status but generally included opioid premedications, followed by either anesthesia induced with IV administration of propofol and benzodiazepine and maintained with inhalation of isoflurane or anesthesia induced and maintained with isoflurane alone (complete gas anesthesia). Daily image-guided patient position verification was performed with on-board kilovoltage cone-beam CT. Following position verification, SBRT was delivered with a linear accelerator.[d]

Statistical analysis—Tumor control was reported according to published guidelines.[18] Response criteria were not evaluated at a standardized time point and are therefore reported as the best recorded response. When available, comparison of pre- and post-SBRT CT images was used to document completeness of response; for cats where post-therapeutic imaging was not performed, physical examination findings were used to quantify response. Survival time was defined as the time from the first fraction of radiation therapy until the time of first event or death. Local tumor control was described with Kaplan-Meier analysis of progression-free survival time. Events were defined as disease progression; patients lost to follow-up were censored at the time of last contact, and those that had not had an event were censored at the time of data analysis. Overall survival time was analyzed in a similar manner. Death from any cause was considered an event, and living cats were censored at the time of Kaplan-Meier survival analysis. Toxicity was graded according to the criteria for acute and late radiation morbidity, as defined by the

Veterinary Radiation Therapy and Oncology Group.[19] Toxicity data were analyzed with descriptive statistics. All statistical analyses were performed with a commercial software package.[e]

Results

Eleven cats were treated with SBRT for ISS. Data on patient demographics, tumor locations, SBRT prescriptions, and outcomes were summarized (**Table 1**). Three of the 11 cats had received no tumor-specific treatment prior to SBRT, whereas surgery had been performed at least once before SBRT in 7 cases, and surgery had been combined with full-course adjuvant radiation therapy in 4 of those 7 cats. Graphic examples of typical dose distributions for SBRT and image guidance via kilovoltage cone-beam CT imaging are provided (**Figures 1 and 2**). Metastatic disease was not identifiable at the time of SBRT in any of the 11 cats. Changes in tumor volume during the irradiation protocol were evaluated by comparing the simulation CT image with each daily kilovoltage cone-beam CT image; clinically relevant changes in the volume of tumors (institutionally defined as a volume change exceeding 20%) were not observed for any of these cats. The mean value of the conformity index was 0.73 ± 0.14 (range, 0.40 to 0.85). There were no unplanned interruptions in treatment.

Computed tomography was repeated after SBRT in 2 cats to assess completeness of response. The objective response rate was 8 of 11 cats (patients had either a partial or complete response as measured by CT or physical examination). Potential clinical benefit (defined as those with a measurable response or stable disease) was realized in 10 of 11 patients. Each of the 7 cats that had died at the time of data analysis had been euthanized; 1 of these cats was euthanized because of pulmonary metastatic disease, another had pulmonary metastases and locally progressive disease, and the remaining cats were euthanized due to recurrent or progressive local disease. One additional cat was alive, with locally progressive disease, at the time of analysis. Overall, 7 of the 8 cats with progressive disease had progression of their primary tumor within the radiation treatment field. Median time to progression was 242 days, median overall survival time was 301 days, and the median follow-up time for censored subjects was 173 days (range, 126 to 1,208 days). One patient sequentially received carboplatin and toceranib phosphate for management of progressive local disease after failure of SBRT; this patient was still alive and was therefore censored from the analysis of overall survival time. Another patient received a second course of SBRT for management of progressive local disease, which was observed > 3 years after completing the initial course of SBRT; this cat was euthanized 4.5 months after receiving the second course of SBRT.

Acute toxicoses were noted in 4 of 11 cats. Grade 1 gastrointestinal toxicosis was observed in a cat in which the primary tumor was located near a hip joint and was characterized by mild, self-limiting diarrhea. Two cats had grade 1 integumentary toxicoses, characterized by mild erythema and dry desquamation multifocally within the irradiated field. Finally, 1 cat had grade 2 skin toxicosis, characterized by 2 foci (each < 2 cm in diameter) of superficial ulcers and moist desquamation within the radiation treatment field; these lesions arose in a region of thin, alopecic skin (grade 1 late skin toxicosis associated with a full course of intensity-modulated radiotherapy delivered 11 months prior to SBRT) and resolved with conservative management, consisting of oral administration of antimicrobials and analgesics and use of an Elizabethan collar to prevent self-trauma.

Table 1—Summary data for 11 cats that underwent SBRT for treatment of an ISS.

Variable	Cat 1	Cat 2	Cat 3	Cat 4	Cat 5	Cat 6	Cat 7	Cat 8	Cat 9	Cat 10	Cat 11
Demographics											
Age (y)	7	0.6	8	16	15	10	7	6	16	15	8
Sex	SIM	SIF	SF	SF	SF	CM	CM	SF	CM	CM	SF
Breed	MC	MC	DLH	DLH	DLH	SC	DSH	Himalayan	DSH	MC	DSH
Tumor											
Location	ISC	Thorax*	Flank	Hip area	Epaxial	Flank	Hip area	ISC	Inguinal	Lumbar	ISC
Grade	3	1	UK†	1	3	3	3	3	2	3	3
Volume (cm^3)	20.2	5.7	11.5	40.5	92.4	158.1	103.1	76.9	11.9	56.8	35.7
Prescription											
D/F (Gy)	5.4	6	6.5	6.25	8	10	10	10	10	10	10
Total (Gy)	27	30	32.5	31.25	24	30	30	30	30	30	30
DD to PTV											
95% (Gy)‡	24.5	29.3	30.3	30.4	22.1	24.8	23.5	28	23.9	18.8	29
Range (Gy)	21.3–27.8	13.7–32.0	25.9–34	13.7–33.5	11.1–29.5	12.7–39.9	11.6–36.3	16.0–39.0	13.2–38.4	11.0–43.0	23.5–37.4
Mean (Gy)	26.6	29.6	32.3	31.5	24.8	33.1	31.1	34.4	33.2	32.9	31.3
Follow-up											
Best response	Complete	Complete	Partial	Partial	Partial	Complete	Partial	Progressive	Stable	Stable	Partial
Progression	LR	No	PM	LR	LR	LR	LR	LR	No	No	LR and PM
PFI (d)	1,160	1,208	176	432	68	83	120	20	126	136	242
Deceased	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes
ST (d)	1,282	1,208	184	963	209	120	185	132	126	136	301

*Lateral aspect of thorax. †Cytologic diagnosis. ‡Dose reported as 95% refers to the minimum dose delivered to 95% of the PTV.
CM = Castrated male. DD = Delivered dose. D/F = Dose per fraction. DLH = Domestic longhair. DSH = Domestic shorthair. ISC = Interscapular. LR = Local recurrence. MC = Maine Coon. PFI = Progression-free interval. PM = Pulmonary metastases. SC = Siamese cross. SF = Spayed female. SIF = Sexually intact female. SIM = Sexually intact male. ST = Survival time. UK = Unknown.

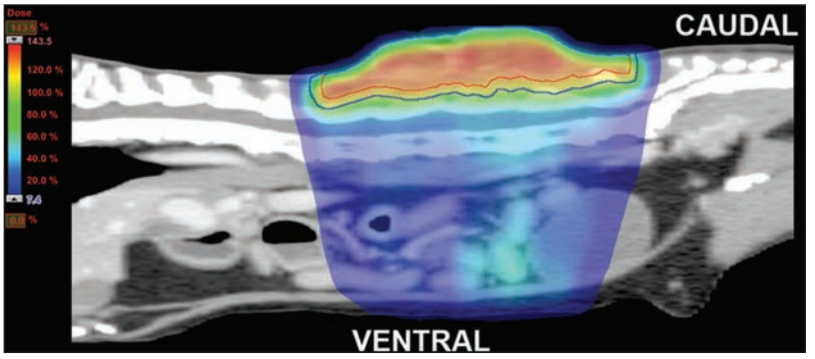

Figure 1—Representative parasagittal CT image of a dorsally located tumor in the lumbar area of a cat that underwent SBRT for an ISS. Dose distribution is depicted as a color wash superimposed over the simulation CT. A steep dose gradient between target volumes (the gross tumor volume is outlined in red, and the PTV is outlined in blue) and organs at risk is shown with areas of relatively high dose in red and orange and lower doses in yellow, green, and blue.

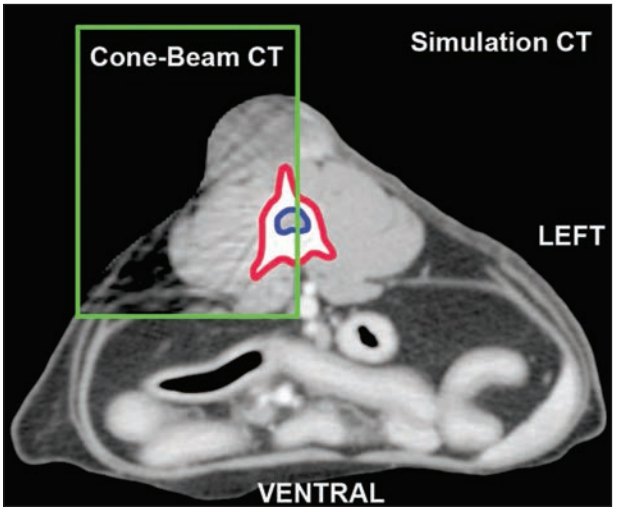

Figure 2—Representative transverse CT image of a dorsally located tumor in the lumbar area of a cat that underwent SBRT for an ISS. This image is derived from a simulation CT scan. The area within the green box is representative of a daily kilovoltage cone-beam CT for this cat. The vertebral body (red) and spinal cord (blue) are outlined. This demonstrates the high level of target and normal tissue reproducibility, which is possible when 3-D image guidance is used.

Grade 1 late skin toxicosis (leukotrichia or alopecia) was observed in 5 of 11 cases. No other late radiation-associated toxicoses were observed.

Discussion

Stereotactic body radiation therapy was well tolerated by and was associated with measurable responses in most cats with ISS. Limitations of this retrospective analysis include examination of a heterogenous patient population, a wide range in prescribed radiation dose and protocol, and lack of control of additional antineoplastic treatments following administration of SBRT, which could affect local tumor control or overall survival time. Another limitation is that biopsy specimens were not obtained in any of the cases in this series at the time of presumed disease progression. Without histologic evaluation to confirm disease progression or recurrence, processes such as necrosis, cystic degeneration, and hemorrhage cannot be definitively excluded as potential reasons for post-SBRT lesion enlargement. In fact, Miki et al[20] demonstrated that 31% of their patients' tumors increased in size following radiation therapy and that no size change was appreciated in the remainder of cases. Regardless of the measurable response, neither magnitude nor direction of size change appeared to affect either local control or overall survival time, and Miki et al[20] suggested that rather than tumor growth, size stability or growth could be attributed to edema and swelling secondary to the osmotic effects of tumor necrosis or that size increase could be due to intralesional bleeding or cystic degeneration. Excepting this possibility, presumed local tumor progression or recurrence was common in the present study of cats treated with SBRT for ISS.

Seven of the 8 cats with progressive ISS developed in-field recurrences or progression of their primary tumor. This suggests that treatment failure following SBRT occurs due to survival of tumor clonogenic cells within the irradiated field. Given that local tumor control following irradiation is probabilistic and follows a sigmoid dose-response relationship, the most logical strategy for improving the efficacy of SBRT in this setting of common in-field recurrences is therefore dose escalation.

The conformity index of cases in this series was relatively high; this index quantifies dose coverage of the delineated target volumes and the dose gradient outside that volume and is thereby complementary to dose-volume histogram and dose-distribution data used to judge overall quality of radiation therapy plans.[21,22] The primary reason for the value of this index to be < 1.0 was intentional use of intensity modulation to limit the radiation dose delivered to organs at risk. For example, the most commonly used prescription was 3 daily fractions of 10 Gy; although the goal in planning radiotherapy was to maximize the amount of the PTV receiving 30 Gy, the prescribing oncologists also limited dose delivered to overlying skin, such that no more than 1 cm^3 of skin received 24 Gy. Intentional sparing of organs at risk also explains why the minimum dose delivered to 95% of the PTV (Table 1) was less than the prescribed dose in each case. Skin was the most common organ at risk spared below the prescribed dose. Given the low incidence of clinically relevant acute and late radiation-associated toxicoses in this patient population, clinicians should consider modest increases in the total prescribed radiation dose. Our SBRT prescriptions for ISS evolved over time and generally became more aggressive with regard to dose per fraction as we became more comfortable with normal tissue tolerances in cats. Based on this experience, these authors feel it is reasonable to evaluate the efficacy and tolerability of an SBRT protocol that delivers 36 Gy in 3 fractions to the PTV, with no more than 1 cm^3 of skin exceeding 30 Gy.

Given the low metastatic rate of ISS, compared with the relatively high likelihood of locoregional tu-

mor recurrence even when aggressive local treatment is used, if such dose-escalation as described succeeds at decreasing the rate of in-field tumor progression or recurrence, clinicians will likely begin to observe marginal recurrences as the most common form of treatment failure. This is because SBRT fields are limited in size. Whereas a typical fractionated radiation therapy field would include a wide margin of normal tissue surrounding the grossly evident tumor to ensure coverage of subclinical or microscopic disease, normal tissues are not highly tolerant of the high total radiation dose and dose per fraction associated with SBRT protocols. As such, SBRT fields are typically limited such that there is no expansion of the clinical target volume beyond the margins of grossly evident disease. If this prediction comes to fruition, the risk for marginal recurrences following SBRT for ISS can be mitigated by following SBRT with a traditional course of fractionated radiation therapy or by performing wide resection following SBRT-associated downstaging of the primary tumor. Such wide resection may be better tolerated than surgery following conventional wide-field irradiation due to the fact that the surrounding tissues would have received comparatively less dose after SBRT and should therefore be able to heal better. If the prediction is wrong and higher-dose SBRT protocols result in long-term local tumor control, this may be related to out-of-field effects associated with such treatment.

In conclusion, SBRT could be completed in 3 to 5 treatment sessions and was well tolerated when used to treat cats with ISS. Measurable tumor responses can be expected in most affected cats. Stereotactic body radiation therapy, as prescribed and delivered in this study, may be a valid treatment option for downstaging disease prior to definitive surgery or palliation of ISS in cases of unresectable locally extensive disease or when owners decline more aggressive therapy. Methods deserving of further investigation via a well-organized prospective, controlled clinical trial have been proposed, which may improve the efficacy of SBRT in the setting of ISS.

a. Vac-Lok, CIVCO Medical Solutions, Orange City, Iowa.
b. Eclipse, version 8.6, Varian Medical Systems, Palo Alto, Calif.
c. Portal Dosimetry, Varian Medical Systems Inc, Palo Alto, Calif.
d. Trilogy, Varian Medical Systems Inc, Palo Alto, Calif.
e. SigmaStat, version 3.5, Systat Software Inc, San Jose, Calif.

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