Outcomes and adverse effects associated with stereotactic body radiation therapy in dogs with nasal tumors: 28 cases (2011–2016)

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OBJECTIVE
To assess outcomes, factors associated with survival time, and radiation-induced toxicoses in dogs treated for nasal tumors with curative-intent stereotactic body radiation therapy (SBRT).

DESIGN
Retrospective case series.

ANIMALS
28 client-owned dogs.

PROCEDURES
By use of a 6-MV linear accelerator, dogs were treated with SBRT (3 consecutive-day fractions of 9 or 10 Gy or once with 1 fraction of 20 Gy). Data regarding adverse effects, outcomes, and survival times were obtained from the medical records.

RESULTS
The median survival time to death due to any cause was 388 days. Of the 24 dogs known to be dead, 14 (58%) died or were euthanized because of local disease progression. Acute radiation-induced adverse effects developed in the skin (excluding alopecia) in 26% (6/23) of dogs and in the oral cavity in 30% (7/23) of dogs. Acute ocular adverse effects included discharge in 26% (6/23) of dogs and keratoconjunctivitis sicca in 4% (1/23) of dogs. Among the 22 dogs alive at > 6 months after SBRT, 4 (18%) developed a unilateral cataract; 4 (18%) developed other complications that may have been late-onset radiation toxicoses (excluding leukotrichia and skin hyperpigmentation).

CONCLUSIONS AND CLINICAL RELEVANCE
Results indicated that dogs treated with SBRT had outcomes comparable to those reported for dogs with nasal carcinomas and sarcomas that undergo conventionally fractionated radiation therapy. Administration of SBRT was associated with a comparatively lower frequency of acute radiation-induced adverse effects. For SBRT and conventionally fractionated radiation therapy, the frequencies of serious late-onset adverse effects appear similar. (*J Am Vet Med Assoc* 2019;254:602–612)

Stereotactic body radiation therapy is the treatment of tumors with 1 to 5 high-dose radiation fractions, whereas conventionally fractionated radiation therapy is the treatment of tumors with radiation fractions administered daily over a period of 3 to 4 weeks.[1,2] With regard to SBRT, the term body is used when tumors outside the brain are treated. Stereotactic body radiation therapy has been used with curative intent for treatment of canine nasal tumors.[3,4] The use of a low number of high-dose fractions with curative intent is a shift from the paradigm of administration of a high number of fractions to achieve differential sparing of normal tissues, such as brain and eyes. Advances in image guidance and radiation delivery techniques allow sparing of normal tissue through avoidance, so that high-dose fractions can be delivered to tumors with minimal radiation dosing of surrounding organs at risk.[1] These advances include imaging systems in the treatment room or mounted directly on the linear accelerator that allow radiation oncologists to obtain images of patients before treatment and adjust their position if needed, and delivery techniques that confine the high-dose radiation to the tumor through rapid dose falloff at the tumor margins.

In addition to avoidance rather than fractionation to spare normal tissues, it has been suggested that high-dose radiation fractions differ from low-dose radiation fractions in the mechanisms by which tumor cells are killed.[5] High-dose fractions (> 8 to 10 Gy) may cause apoptosis of tumor endothelial cells, thereby increasing the extent of tumor cell death, as well as increased antitumor immunity and vascular dam-

ABBREVIATIONS

GTV	Gross tumor volume
IMRT	Intensity-modulated radiation therapy
PTV	Planning target volume
SBRT	Stereotactic body radiation therapy

age that result in indirect tumor cell killing.[5] However, on the basis of preclinical and clinical human data, it has been argued that these additional biological mechanisms of tumor cell death do not contribute much to tumor control and that the clinical success of SBRT is a result of the equivalent or higher biologically effective radiation dose that can be delivered to the tumor while achieving normal tissue avoidance.[6]

Moderate to severe acute adverse effects in dogs with nasal tumors treated with conventionally fractionated radiation protocols for 3-D conformal radiotherapy are commonly reported.[7–9] Three-dimensional conformal radiotherapy refers to treatments that are based on 3-D anatomic information, such as CT images, with treatment fields that conform as closely as possible to the target volume to minimize the radiation dose applied to normal tissue.[10] Intensity-modulated radiation therapy is a treatment technique that uses beams of nonuniform fluences, thereby enabling even greater sparing of normal tissues than that achieved with 3-D conformal radiotherapy.[11] When used with conventionally fractionated radiation protocols, IMRT has been reported to result in fewer acute adverse effects in dogs with nasal tumors, compared with findings following 3-D conformal radiotherapy.[12,13] Although SBRT often involves IMRT to avoid normal tissues and therefore would be expected to induce less severe acute adverse effects, the term SBRT refers to a change in fractionation rather than to a treatment technique. An advantage of SBRT over conventionally fractionated IMRT is that fewer treatment episodes are required; nasal tumors in dogs have been treated with SBRT involving only 1 or 3 fractions.[3,4] Although development of fewer acute adverse effects and administration of a low number of radiation fractions are attractive potential advantages of SBRT, the decision to use SBRT with curative intent for treatment of canine nasal tumors should be based on the expectation that high doses per fraction provide comparable antitumor efficacy to that of conventionally fractionated radiation therapy. The first report[3] of the use of SBRT for dogs with nasal tumors described an overall median survival time of 13.3 months, supporting the aforementioned expectation. In that retrospective study[3] of 19 dogs with nasal sarcomas and carcinomas, treatment was comprised of 3 consecutive-day fractions of a prescribed radiation dose of 8 to 12 Gy administered by means of a linear accelerator-based stereotactic radiosurgery system. The authors reported that 6 of the 19 (32%) dogs had mild acute adverse effects. On the basis of the Veterinary Radiation Therapy Oncology Group scoring scheme,[14] 3 dogs had grade 1 or 2 oral toxicosis, 3 dogs had grade 1 skin toxicosis, and 1 dog had grade 1 ocular toxicosis (this dog had 2 adverse effects). In another study[4] of 57 dogs treated for nasal tumors with single-fraction SBRT, the median overall survival time was 8.5 months, with a median survival time of 10.7 months and 10.4 months for dogs with sarcoma or carcinoma, respectively. Tumor type in that study[4] included osteosarcoma and round cell tumor in addition to sarcoma and carcinoma, and dogs were prescribed a single radiation fraction of 12.5 to 28 Gy. Acute radiation-induced adverse effects developed in 13 of 57 (23%) dogs; 2 of those 13 dogs had grade 3 adverse effects as determined with the Veterinary Radiation Therapy Oncology Group scoring scheme.[14]

To date, there is limited information regarding outcomes for dogs with nasal tumors that receive SBRT. The objective of the study of this report was to assess outcomes, factors associated with survival time, and radiation-induced toxicoses in dogs treated for nasal tumors with curative intent SBRT, and to compare outcomes and radiation-induced toxicoses with those reported for dogs treated with conventionally fractionated radiation therapy.

Materials and Methods

Case selection criteria

The 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. Medical records of all dogs with nasal tumors treated with curative-intent SBRT at the Western Veterinary Specialist and Emergency Centre (Calgary, AB) and at the Veterinary Medical Centre of the Western College of Veterinary Medicine (Saskatoon, SK) in October 2011 through April 2016 were examined. Dogs were eligible for inclusion in the study if the medical records were complete. Dogs without a cytologic or histologic diagnosis of tumor type (n = 3) or with a diagnosis of round cell tumor (1) were excluded from the survival time analysis but were not excluded from assessments of radiation-induced toxicoses.

Medical records review

Medical records for the dogs were used to collect demographic data (age, breed, sex, and weight), tumor information (histologic type and systemic staging), details of the radiation treatment plan, and adjuvant treatments. For each dog, survival time, disease progression information, and the nature and time to development of radiation-induced adverse effects were obtained from the medical record and through follow-up contact with the owner and referring veterinarian.

Tumor staging, including thoracic radiography, thoracic CT, clinicopathologic analyses, urinalysis, and cytologic examination of fine-needle lymph node aspirate specimens, was performed at the discretion of each dog's primary clinician. A CT report by a board-certified veterinary radiologist was available for all dogs; however, for the purpose of the study, pretreatment CT images were rereviewed by a board-certified veterinary radiation oncologist or radiologist to stage each dog's tumor with a modified Adams staging scheme.[15] In this scheme, TI = tumor is confined to 1 nasal passage, paranasal sinus, or frontal sinus with no bony involvement; TII = tumor has

bony involvement (including bilateral nasal passage involvement), but with no evidence of an orbital, subcutaneous, or submucosal mass; TIII = tumor has involvement with the orbit or a subcutaneous or submucosal mass; TIV = tumor has extension into either the nasopharynx or cribriform plate; and TIVa = tumor has invaded into brain tissue. Mandibular and retropharyngeal lymph nodes were evaluated on CT images and considered enlarged if the maximum width was > 10 mm or > 20 mm, respectively.[16,17] Dogs with lymph nodes that were enlarged (as determined on CT examination) were categorized as having regional metastasis unless a cytology report of normal or reactive lymphoid tissue was available.

Dogs were treated by use of a 6-MV linear accelerator.[a] Inverse radiation treatment planning was performed by 1 of 2 board-certified veterinary radiation oncologists using treatment planning software.[b] The GTV was calculated on the basis of all contrast-enhancing mass tissue detected on CT images, including contrast-enhancing mass tissue that extended outside of the nasal cavity. The PTV included a 3- to 5-mm isotropic expansion from the GTV. In 1 dog, the ipsilateral mandibular lymph nodes were irradiated prophylactically, and the nodes were included in the GTV. The PTV in this dog included a 5-mm isotropic expansion from the nodes. The goal of planning was for 100% of the PTV to receive ≥ 95% of the prescribed dose. Organs at risk that were contoured included the eye (globe), lenses, and optic nerves ipsilateral and contralateral to the tumor and the brain, oral mucosa, and skin. The brain was contoured from the most rostral CT slice on which it was visible to the most caudal CT slice on which the connection to the spinal cord was still visible. Oral mucosa was contoured from the most rostral CT slice on which it was visible to 1 CT slice caudal to the PTV. Both brain and oral mucosa contours excluded GTV. Skin was defined as the 2-mm-wide strip of tissue immediately adjacent to the outer body contour. The right and left optic nerves were contoured from the nerve head through the bony margins of the optic canal to the first intracranial CT slice. The dose constraints for critical organs suggested by the American Association of Physicists in Medicine Task Group 101[18] were used in planning.

Data regarding tumor radiation dose collected from the radiation treatment plans were as follows: prescription dose, number of treatment fractions, total treatment delivery period, volume of GTV and PTV, target coverage (the volume of PTV receiving < 95% of the prescribed dose and the volume of GTV receiving < 100% of the prescribed dose), plan conformity (ratio of 100% of the prescription isodose volume to PTV volume), dose falloff (ratio of 50% of the prescription isodose volume to PTV volume), and dose heterogeneity (ratio of biologically effective maximum and minimum doses within the PTV). The biologically effective maximum and minimum doses were used in assessment of the dose heterogeneity to account for the different fractionation protocols. The biologically effective maximum and minimum doses were calculated with an equation as follows:

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

where n is the number of fractions, d is the dose per fraction, α is the $\log_e$ number of cells killed per Gy, and β is the $\log_e$ the number of cells killed per Gy squared. An α/β of 10 Gy was used for effect on tumor.[19] As suggested in the American Association of Physicists in Medicine Task Group 101 report,[18] the data collected for all organs at risk from the SBRT plans used for initial treatment were as follows: dose to 1% of volume, dose to 5% of volume, mean dose, and maximum dose. The volume of brain receiving radiation exposure > 24 Gy was also calculated, because a relationship between the volume of brain receiving > 24 Gy and increased risk of death within the first 6 months after radiation treatment has been suggested by results of a previous study.[20]

Each dog was immobilized in sternal recumbency for the radiation planning CT imaging and radiation treatment by use of a vacuum deformable body cushion,[c] a thermoplastic neck cushion,[d] a custom-made bite block stand, thermoplastic bite block,[e] and head mask[f] (at the Western College of Veterinary Medicine) or a custom head immobilization stand, a foam immobilization system,[g] and head mask[h] (at the Western Veterinary Specialist and Emergency Centre). Planning CT slice thickness was 2.0 mm for all dogs, and pre- and postcontrast scans were obtained. For dogs treated prior to May 2013 at the Western Veterinary Specialist and Emergency Centre, megavoltage portal films were compared side by side with digitally reconstructed radiographs to verify patient position before treatment. From May 2013 to May 2015, megavoltage portal films and a patient position verification and correction system[i] were used at this site. After May 2015, cone-beam CT and on-board imaging software[j] were used to verify and correct patient position. For all dogs treated at the Western College of Veterinary Medicine, kilovoltage portal films or cone-beam CT images (or both) with on-board imaging software[j] were used to verify and correct patient position. For each dog, plan verification was performed with a 2-D multidetector array[k] and γ analysis criteria of 3% and 3 mm. Machine quality assurance included a daily output check with an ion chamber-based device[l] that had a tolerance limit of 2% and accuracy of a 2-D to 2-D match based on orthogonal kilovoltage images taken with the on-board imager of the treatment unit. Monthly quality assurance included isocenter verification of gantry, maintenance of collimator and couch rotations within a tolerance of 1 mm, and verification of the coincidence of the on-board imager x-ray beam axis with the treatment beam axis.

Radiation toxicosis scores determined by use of the Veterinary Radiation Therapy Oncology Group scoring scheme[14] were reported when available in the medical records. When scores were not available, adverse effects were scored retrospectively from follow-up data in

the records, if sufficient information was included to allow a score to be assigned. Acute effects were defined as those occurring within the first 2 months after completion of SBRT, whereas late effects were defined as those occurring > 6 months after completion of SBRT. For the brain only, adverse effects were classified as acute delayed if they developed from 2 weeks to 6 months after completion of SBRT.

As part of the follow-up for the study, owners were invited to complete a questionnaire by telephone or electronically by means of the University of Saskatchewan's fluid survey tool.[m] Data obtained included response to treatment (ie, were any clinical signs improved by radiation therapy) and level of response to treatment (ie, were clinical signs completely resolved, much improved, somewhat improved, the same as before radiation therapy, or worse than before radiation therapy). Owners were asked about the perceived discomfort of their dog that resulted from acute radiation-induced adverse effects in the skin, eyes, and oral cavity during the first 2 months after radiation treatment (ie, there was no effect on the dog's apparent comfort, the dog appeared uncomfortable, the dog appeared very uncomfortable, or I do not remember). Owners were also asked how satisfied they were with their decision to use radiation therapy for their dog's nasal tumor (ie, very satisfied, satisfied, neutral, unsatisfied, or very unsatisfied).

Statistical analysis

Dogs without a cytologic or histologic diagnosis of tumor type (n = 3) or with a diagnosis of round cell tumor (1) were excluded from the survival time analysis but were not excluded from assessments of radiation-induced toxicoses. All analyses were completed by an analytic epidemiologist (CLW) using a commercial software program.[n] Survival time was calculated as the interval from the first day of treatment to the day of death or euthanasia, and an estimate of survival over time was obtained by Kaplan-Meier analysis. Survival analysis was used to explore the bivariate associations between potential risk factors and survival time with adjustment for differences by site. The log-rank test stratified by site was used for categorical variables, and Cox proportional hazards regression analysis was used for continuous variables with robust cluster variance accounting for site. The proportional hazards assumption was tested with Schoenfeld residuals. Dogs that were still alive or lost to follow-up were censored from the analysis. Patient-related risk factors examined in the analysis included age, weight, sex, tumor histologic type (carcinoma or sarcoma), and tumor stage. Tumor-dose risk factors included radiation dose protocol, reirradiation, target coverage, plan conformity, dose falloff, and dose heterogeneity. A value of $P < 0.05$ was considered significant.

Results

Twenty-eight dogs met the inclusion criteria. All of the dogs were client owned. Types of dog represented included mixed-breed (n = 8), Shetland Sheepdog (3), Golden Retriever (2), Labrador Retriever (2), and Miniature Dachshund (2); Australian Shepherd, Boston Terrier, Cane Corso, English Springer Spaniel, German Shepherd Dog, Siberian Husky, Vizsla, Weimaraner, Western Siberian Laika, Soft Coated Wheaton Terrier, and Yorkshire Terrier were each represented once.

Histologic diagnosis of the tumor was available for 22 of the 28 dogs and included adenocarcinoma (n = 6), carcinoma (5), squamous cell carcinoma (2), chondrosarcoma (3), sarcoma (2), transitional cell carcinoma (1), myxosarcoma (1), osteosarcoma (1), and mast cell tumor (1). For 3 dogs, carcinoma was diagnosed on the basis of cytologic findings. Two dogs underwent biopsy but examination of the collected specimen did not confirm neoplasia, and 1 dog did not undergo biopsy and no cytologic examination of a tumor sample was performed; these 3 dogs were treated with SBRT because of the high index of suspicion of nasal tumor (as determined from CT findings). Data from the 3 dogs without a cytologic or histologic diagnosis of a nasal tumor and the dog that had a mast cell tumor were excluded from the survival analysis but were not excluded from assessment of radiation toxicoses.

Patient characteristics for all 28 dogs and for the 24 dogs with cytologic or histologic diagnosis of the nasal tumor that were included in survival analysis were summarized **(Table 1)**. Pretreatment tumor staging included results of thoracic radiography (n = 20) or thoracic CT with or without thoracic radiography (6), a CBC and serum biochemical analysis (28), urinalysis (15), and cytologic examination of mandibular lymph node aspirate specimens (6). Four dogs did not have a record of thoracic radiographic or thoracic CT imaging findings during the 4 weeks prior to treatment. All thoracic radiographs and CT scans were interpreted by 1 of 4 board-certified veterinary radiologists, and no metastases to the lungs were reported. Of the 6 dogs that underwent cytologic examination of mandibular lymph node aspirate specimens, 5 had no cytologic evidence of lymph node metastasis; for 1 dog, the sample was nondiagnostic. Two dogs had enlarged lymph nodes as revealed by CT. One of the 2 dogs had 1 enlarged retropharyngeal lymph node that was not aspirated; this dog was excluded from the survival analysis because examination of the nasal mass biopsy specimen did not confirm neoplasia. The other dog had enlarged left mandibular and left retropharyngeal lymph nodes unilaterally; aspiration of the mandibular lymph nodes yielded nondiagnostic samples. However, in this dog, the enlarged mandibular lymph nodes were prophylactically irradiated with the same dose as the primary tumor (3 fractions, each 9 Gy) because of possible regional metastasis; data from this dog were included in the survival analysis. This was the only dog in which regional lymph nodes were irradiated.

Ninety-three percent (26/28) of the dogs received no adjuvant chemotherapy. One dog received masitinib (12.75 mg/kg [5.8 mg/lb]) orally every 24 hours for 6 months starting 1 month after SBRT. Another dog received doxorubicin (27 mg/m^2) IV at 4 and 10 weeks after SBRT and carboplatin (275 mg/m^2) IV at 7 weeks after SBRT. Among the 28 dogs at

Table 1—Patient details for 28 dogs treated with curative-intent SBRT for presumed or confirmed nasal tumors and for 24 of those dogs with cytologic or histologic diagnosis of a nasal tumor that were included in the survival time analysis.

Variable	All dogs (n = 28)	Dogs included in survival time analysis (n = 24)
Median (range) age (y)	9.8 (3.1–14.3)	9.8 (3.1–14.3)
Median (range) weight (kg)	23.2 (3.1–41.8)	23.8 (3.1–41.8)
Sex		
No. (%) of neutered males	15 (54)	14 (58)
No. (%) of neutered females	9 (32)	6 (25)
No. (%) of sexually intact males	3 (11)	3 (13)
No. (%) of sexually intact females	1 (4)	1 (4)
Tumor characteristics (No. [%] of dogs)		
Histologic classification		
Carcinoma	17 (61)	17 (71)
Sarcoma	7 (25)	7 (29)
Other tumor type	1 (4)	0 (0)
No definitive diagnosis	3 (11)	0 (0)
Stage		
I	7 (25)	5 (21)
II	6 (21)	6 (25)
III	7 (25)	5 (21)
IV	5 (18)	5 (21)
IVa	3 (11)	3 (13)

Dogs were treated at 1 of 2 veterinary hospitals in October 2011 through April 2016. Tumor stage was classified by use of a modified Adams staging scheme.[14] In this scheme, TI = tumor is confined to 1 nasal passage, paranasal sinus, or frontal sinus with no bony involvement; TII = tumor has bony involvement (including bilateral nasal passage involvement), but with no evidence of an orbital, subcutaneous, or submucosal mass; TIII = tumor has involvement with the orbit or a subcutaneous or submucosal mass; TIV = tumor has extension into either the nasopharynx or cribriform plate; and TIVa = tumor has invaded into brain tissue. Dogs received SBRT as either 3 consecutive-day fractions of 9 or 10 Gy or 1 fraction of 20 Gy.

the time of SBRT, 19 (68%) were receiving meloxicam (0.1 mg/kg [0.05 mg/lb]) orally every 24 hours, 3 (11%) were receiving prednisone (0.38 mg/kg [0.17 mg/lb], 0.42 mg/kg [0.19 mg/lb], or 0.54 mg/kg [0.25 mg/lb]) orally every 24 hours, and 6 (21%) were not receiving a corticosteroid or NSAID.

The CT scans used for treatment planning were performed a median of 1 day (range, 1 to 6 days) before start of treatment. For all 28 dogs, radiation dose protocols included 3 consecutive-day fractions of 10 Gy (n = 15), 3 consecutive-day fractions of 9 Gy (9), or 1 fraction of 20 Gy (4). The dose per fraction for the 3-fraction protocols was increased from 9 to 10 Gy in 2013 on the basis of the outcomes for dogs treated prior to that date. For the 24 dogs with cytologic or histologic diagnosis of a nasal tumor that were treated with SBRT and included in the survival analysis, 7 (29%) received 3 consecutive-day fractions of 9 Gy, 14 (58%) received 3 consecutive-day fractions of 10 Gy, and 3 (13%) received 1 fraction of 20 Gy. The median volume of PTV receiving < 95% of the prescribed dose was 2.3 cm^3 (range, 0.0 to 15.9 cm^3). The median volume of GTV receiving < 100% of the prescribed dose was 12.7 cm^3 (range, 0.0 to 83.4 cm^3). The median plan conformity was 0.5 (range, 0.1 to 1.1). The median dose falloff outside the target and dose heterogeneity was 3.9 (range, 2.6 to 8.2) and 1.4 (range, 1.2 to 1.9), respectively.

The median survival time to death attributed to any cause was 388 days, with a range of 4 to 1,422 days **(Figure 1)**. Risk factors that were not associated with survival time included age (P = 0.32), weight (P = 0.14), sex (P = 0.13), and tumor histologic type (carcinoma or sarcoma; P = 0.13). Tumor stage was associated with survival time (P = 0.02). Dogs with stage TIVa tumors (those invading into the brain tissue)

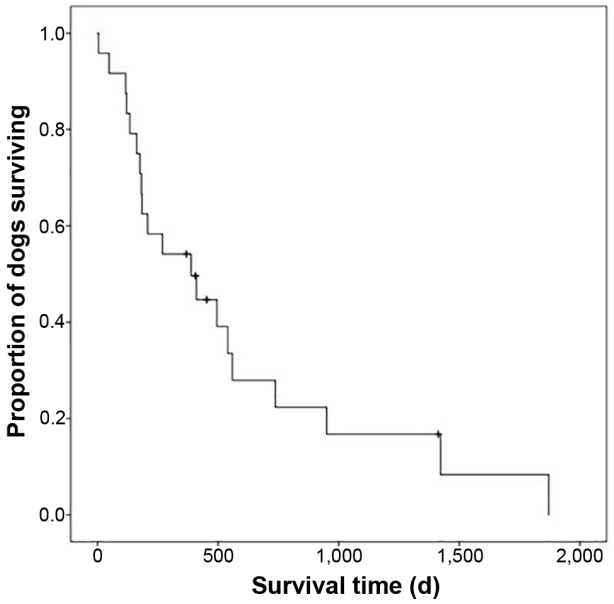

Figure 1—Kaplan-Meier curve for survival time among 24 dogs with nasal tumors that were treated with curative-intent SBRT. Dogs received SBRT as either 3 consecutive-day fractions of 9 or 10 Gy or 1 fraction of 20 Gy. Dogs that were alive (n = 3) or lost to follow-up (1) at the time of analysis were censored from the analysis.

had a shorter survival time than did dogs with stage TI ($P = 0.03$), stage TII ($P = 0.03$), or stage TIII ($P = 0.04$) tumors. The survival times for dogs with stage TIVa tumors did not differ from the survival times for dogs with stage TIV tumors ($P = 0.13$). There was no association between survival time and reirradiation at the time of tumor regrowth ($P = 0.65$), the volume of PTV receiving < 95% of the prescribed dose ($P = 0.11$), the volume of GTV receiving < 100% of the prescribed dose ($P = 0.17$), or plan conformity ($P = 0.96$). Radiation dose protocol was associated with survival time ($P = 0.04$); dogs treated with 3 fractions of 10 Gy had a shorter survival time than did dogs treated with 3 fractions of 9 Gy ($P = 0.02$). A decrease in dose falloff and an increase in dose heterogeneity were associated with shorter survival time (both $P < 0.001$).

Six dogs underwent reirradiation following tumor recurrence (as confirmed by CT examination) after SBRT. Radiation dose protocol, time to retreatment, survival time, and delayed toxicoses for these dogs were summarized **(Table 2)**.

Twenty-four dogs were known to have died or been euthanized; 14 (58%) of those dogs died or were euthanized because of local disease progression. Local disease progression was diagnosed on the basis of clinical signs (n = 12) or CT examination findings (2). The remaining 10 dogs died or were euthanized because of loss of hind body motor function (n = 3), osteoarthritis (1), progressive neuromuscular weakness (1), aggression (1), seizures with no evidence of nasal tumor progression on CT images (1), mandibular osteosarcoma (1), unknown cause (death occurred at home [1]), and splenic metastases (as determined from results of abdominal ultrasonography and CT examination and cytologic findings [1]). The dog with splenic metastases was irradiated for treatment of a nasal adenocarcinoma. The splenic lesions were diagnosed cytologically as carcinoma (suspect transitional cell carcinoma); however, no primary tumor was identified. At the time when the splenic metastases were detected, CT examination indicated possible progression of the nasal tumor. The CT examination report was not available for review, and tumor measurements were not available in the radiologist's report. Distant metastases from the nasal adenocarcinoma could not be ruled out. One dog developed histologically confirmed metastasis to the right ipsilateral mandibular lymph node, which was detected 462 days after radiation treatment.

Radiation dose details for organs at risk for the 28 dogs included in the radiation-induced adverse effect assessment were summarized **(Table 3)**. One dog died prior to the acute adverse effect period (on day 4 after the first SBRT treatment). Four dogs had no assessment of acute adverse effects documented in medical records, and there was no information available from owner questionnaires. Among the remaining 23 dogs, 18 (78%) developed hair loss, 6 (26%) developed erythema or dry desquamation, and 1 (4%) developed patchy swelling. Thirteen of the 23 (56%) dogs developed acute adverse effects in the oral cavity; there were grade 1 effects (injection without mucositis)[14] in 6 (26%) dogs and grade 2 effects (patchy mucositis)[14] in 7 (30%) dogs. Acute ocular adverse effects developed in 7 of the 23 (30%) dogs; 6 dogs had ocular discharge and 1 had keratoconjunctivitis sicca. The acute adverse effects reported after reirradiation of 6 dogs included grade 1 oral effects in 2 dogs, grade 2 oral effects in 2 dogs, and ocular discharge in 1 dog. One dog had no recorded assessment of acute adverse effects after reirradiation.

Seventy-nine percent (22/28) of dogs survived > 6 months and were considered at risk for late-onset radiation-induced effects. Of these 22 dogs, 10 (45%) developed leukotrichia and 2 (9%) developed skin hyperpigmentation. Four (18%) dogs developed a cataract. In 3 dogs, the eye ipsilateral to the tumor was affected; in 1 dog, the eye contralateral to the tumor was affected (in this dog, the ipsilateral eye had been enucleated prior to SBRT). Four of the 22 (18%) dogs developed other complications that may have been attributable to radiation. One dog had vision loss in the eye contralateral to the tumor at 461 days after initial SBRT (3 fractions of 9 Gy) and 54 days after SBRT retreatment. Findings of an ophthalmic examination were normal other than an absent menace response, and a late-onset adverse effect in the optic apparatus was suspected. A second dog developed

Table 2—Radiation dose details and reported late-onset radiation-induced adverse effects for 6 of the 28 dogs in Table 1 that were treated for presumed or confirmed nasal tumors with curative-intent SBRT and were subsequently retreated with SBRT because of tumor regrowth.

Dog	Initial SBRT protocol	Time to reirradiation (d)	Reirradiation protocol	Survival time (d)	Late-onset adverse effect
1	3 fractions of 9 Gy	238	2 fractions of 10 Gy	540	No
2	3 fractions of 9 Gy	916	2 fractions of 10 Gy	944	No
3	3 fractions of 9 Gy	771	2 fractions of 10 Gy	1,422	No
4	3 fractions of 9 Gy	407	2 fractions of 10 Gy	465	Vision loss[a,b]
5	3 fractions of 10 Gy	212	2 fractions of 10 Gy	388	No[b]
6	1 fraction of 20 Gy	163	1 fraction of 20 Gy	426	Seizures[b]

[a]Vision loss in the contralateral eye (with regard to tumor location). [b]Leukotrichia was also reported as a late-onset adverse effect.

Time to reirradiation was the interval from the end of the initial SBRT protocol to commencement of the reirradiation protocol. Survival time was the interval from the first day of treatment to the day of death or euthanasia. Late-onset radiation-induced adverse effects were those that became clinically evident 6 months or later after completion of treatment.

Table 3—Median (range) radiation dose details for organs at risk for the 28 dogs in Table 1 with presumed or confirmed nasal tumors that were treated with 1 or 3 fractions of curative-intent SBRT.

	Group	
Organ at risk	**1 fraction (n = 4)**	**3 fractions (n = 24)**
Brain		
Dose to 1% of volume (Gy)	19.6 (2.2–20.6)	28.6 (0.2–31.1)
Dose to 5% of volume (Gy)	15.0 (0.6–19.0)	22.0 (0.1–29.4)
Mean dose (Gy)	2.14 (0.2–7.1)	3.1 (0.0–11.6)
Maximum dose (Gy)	20.2 (15.4–21.3)	29.7 (0.3–32.6)
Volume > 24 Gy (cm^3)	0.0	3.1 (0–11.0)
Oral mucosa		
Maximum dose (Gy)	20.5 (19.8–21.0)	29.5 (22.7–31.3)
Skin		
Dose to 1% of volume (Gy)	13.4 (10.5–15.8)	18.4 (12.6–25.1)
Dose to 5% of volume (Gy)	7.2 (4.9–11.8)	10.3 (2.0–18.0)
Mean dose (Gy)	1.3 (0.8–2.3)	1.9 (0.5–3.4)
Maximum dose (Gy)	18.4 (16.9–18.6)	25.7 (23.1–31.6)
Eye		
Ipsilateral to tumor		
Dose to 1% of volume (Gy)	18.2 (17.5–19.5)	25.1 (0.5–30.7)*
Dose to 5% of volume (Gy)	16.9 (14.9–19.1)	22.6 (0.4–30.4)*
Mean dose (Gy)	11.2 (5.7–16.4)	12.8 (0.3–24.6)*
Maximum dose (Gy)	19.1 (18.7–20.0)	28.1 (0.6–31.2)*
Contralateral to tumor		
Dose to 1% of volume (Gy)	8.4 (6.1–15.6)	11.5 (0.4–26.3)
Dose to 5% of volume (Gy)	7.4 (5.0–13.4)	9.5 (0.3–22.5)
Mean dose (Gy)	5.4 (2.7–9.2)	6.0 (0.2–11.0)
Maximum dose (Gy)	9.3 (7.0–17.9)	13.6 (0.4–29.4)
Lens		
Ipsilateral to tumor		
Dose to 1% of volume (Gy)	13.8 (8.2–17.8)	13.8 (0.4–28.4)
Dose to 5% of volume (Gy)	12.6 (7.0–17.6)	11.9 (0.4–28.1)
Mean dose (Gy)	10.0 (3.9–15.6)	8.9 (0.3–25.9)
Maximum dose (Gy)	14.6 (8.8–18.0)	14.8 (0.4–28.6)
Contralateral to tumor		
Dose to 1% of volume (Gy)	5.9 (3.4–9.0)	6.4 (0.3–12.8)
Dose to 5% of volume (Gy)	5.7 (3.1–8.4)	6.0 (0.3–12.1)
Mean dose (Gy)	4.9 (2.3–7.6)	4.2 (0.2–9.7)
Maximum dose (Gy)	6.0 (3.5–9.3)	6.7 (0.3–13.2)
Optic nerve		
Ipsilateral to tumor		
Dose to 1% of volume (Gy)	18.0 (1.9–20.7)	26.0 (0.2–31.4)
Dose to 5% of volume (Gy)	17.5 (1.8–20.6)	25.2 (0.2–31.3)
Mean dose (Gy)	13.9 (11.0–18.3)	17.0 (0.2–30.3)
Maximum dose (Gy)	18.2 (2.0–20.7)	26.3 (0.2–31.5)
Contralateral to tumor		
Dose to 1% of volume (Gy)	10.5 (0.8–19.8)	14.4 (0.2–30.0)
Dose to 5% of volume (Gy)	10.1 (0.8–19.7)	13.7 (0.2–29.5)
Mean dose (Gy)	8.0 (0.6–15.0)	9.1 (0.1–20.9)
Maximum dose (Gy)	10.7 (0.9–19.9)	14.6 (0.2–30.2)

*Data are from 27 dogs; 1 dog in the 3 fraction group underwent orbital enucleation prior to SBRT.

seizures 259 days after initial SBRT (1 fraction of 20 Gy) and 96 days after SBRT retreatment. A CT examination performed at that time revealed no evidence of tumor progression, an intact cribriform plate, and a contrast-enhancing region in the olfactory lobe. Differential diagnoses for the brain lesion included a tumor unrelated to the nasal tumor, metastasis from the nasal tumor, and radiation damage. This dog developed progressive seizures and died at 426 days after initial SBRT; no necropsy was performed. In a third dog, an oronasal fistula was detected at 366 days after SBRT (1 fraction of 20 Gy), at the same time as identification of local tumor regrowth. The oronasal fistula was located in the region of the tumor. Finally, 1 dog developed behavioral changes (aggression toward people and other dogs) 178 days after SBRT (3 fractions of 10 Gy). Cross-sectional imaging of the dog was declined by the owner, and no necropsy was

performed at the time of its death. The cause of the behavioral change by a late-onset effect in the brain could not be ruled out.

Twenty of 28 (71%) owners completed the questionnaire. Of the 20 owners who responded, 18 (90%) reported that their dog's clinical signs were improved following radiation therapy. Among the 18 owners reporting improvement, 9 reported that the clinical signs were much improved, 5 reported that the clinical signs were somewhat improved, and 4 reported that the clinical signs were completely resolved. Two owners reported no improvement in their dog's clinical signs following radiation therapy; 1 indicated that the clinical signs were the same as before radiation therapy, and 1 indicated that the clinical signs were worse than before radiation therapy. With regard to acute radiation-induced adverse effects, 16 of 20 (80%) owners reported no effect of skin changes on their dog's comfort during the first 2 months after radiation therapy, 3 (15%) owners reported their dog appeared uncomfortable, and 1 (5%) owner did not remember whether any discomfort had occurred. No owners reported discomfort from eye changes during the first 2 months after radiation therapy. Fifteen of 20 (75%) owners reported no effect of oral cavity changes on their dog's comfort during the first 2 months after radiation therapy, 3 (5%) owners reported that their dog appeared uncomfortable or very uncomfortable, and 2 (10%) owners did not remember whether any discomfort had occurred. Eighty percent (16/20) of owners reported being satisfied or very satisfied with their decision to use radiation therapy, whereas 20% (4/20) were neutral or unsatisfied. Of the owners who were neutral (n = 3) or unsatisfied (1), 3 owners commented on a short survival time after treatment and 1 owner commented on cost of treatment.

Discussion

In the present study, the median survival time of dogs treated for nasal tumors with curative-intent SBRT was 388 days (12.9 months), which was comparable to the previously reported median survival time of 13.3 months following 3-fraction SBRT in 19 dogs with nasal carcinomas and sarcomas.[3] Similar to the conclusion of that previous study, findings of the present study also have suggested that survival times following SBRT are within the range of survival times reported for dogs receiving conventionally fractionated megavoltage radiation therapy as a single therapy (ie, 10.5 to 21.4 months).[7–9,15,21–23] In another study,[4] median survival time following single-fraction SBRT for dogs with nasal sarcoma (n = 9) was 10.7 months; for dogs with nasal carcinoma (40), survival time was 10.4 months. The results of the present study were similar, although the median survival time in that previous study[4] was 8.5 months when all tumor types were considered. Those authors suggested that the inclusion of 7 dogs with osteosarcoma may have contributed to the lower overall median survival time, but a shorter median survival time for SBRT, compared with that for conventionally fractionated radiation therapy, was also considered. In both previous studies,[3,4] dogs were treated for nasal tumors with curative-intent SBRT. Although achievement of a cure is rare following radiation therapy for canine nasal sarcomas and carcinomas, we consider SBRT (as prescribed in the present study) to be of curative intent, because the goal of treatment was to achieve local tumor control and extend survival time. In contrast, the goal of palliative radiation therapy is to improve a patient's quality of life through amelioration of signs, not to extend a patient's survival time.[24]

Three of the dogs in the present study received SBRT without cytologic or histologic confirmation of neoplasia. This is not standard of care at either hospital participating in this study because there is a risk of severe adverse effects associated with radiation therapy as well as a high cost of treatment. The 3 dogs that were treated without a diagnosis of neoplasia each had a nasal cavity mass detected during CT or rhinoscopic examination and had undergone a biopsy procedure; however, examination of the biopsy specimen did not confirm a neoplastic disease. The owners of these dogs declined a second biopsy procedure and elected to treat their dog on the basis of a high index of suspicion of neoplasia.

A limitation of the present study was the use of overall survival time as an outcome measure. Progression-free interval would be better suited for assessment of the impact of risk factors, because survival times are affected by owners' decisions regarding euthanasia. Survival time was also extended for the 6 dogs with owners who elected reirradiation. However, progression-free interval was not evaluated in this study because of the lack of regular postradiation therapy examinations and cross-sectional imaging needed to accurately determine the date of tumor regrowth. Factors that were associated with overall survival time in the present study included brain invasion by the tumor, radiation dose protocol, dose heterogeneity (ratio of biologically effective maximum and minimum doses within the PTV), and dose falloff (ratio of 50% of the prescription isodose volume to PTV volume). Although previous studies[8,15] have identified that survival time for dogs with nasal carcinomas treated with conventionally fractionated radiation therapy was shorter than that for treated dogs with nasal sarcomas, we did not find an association between survival time and histologic tumor type in the present study. The ability to detect a difference, if one existed, was limited by the low sample size. Dose per fraction was escalated from 9 to 10 Gy at both treatment facilities as outcome data became available for the dogs initially treated with SBRT. The shorter survival time for dogs undergoing 3 fractions of 10 Gy than for dogs undergoing 3 fractions of 9 Gy was unexpected and difficult to explain. A higher tumor dose would be expected to increase the tumor response duration, leading to increased survival time, unless the higher dose resulted in an increased frequency

of radiation-related complications, which was not apparent in the dogs that received 3 fractions of 10 Gy. It is possible that late-onset radiation-induced adverse effects were misdiagnosed as tumor regrowth by family veterinarians, because most dogs did not have cross-sectional imaging performed at the time that tumor regrowth was diagnosed. It may be that the difference in survival time was attributable to other differences between the 3 consecutive-day treatment groups. Six of the 14 dogs that received 3 fractions of 10 Gy had stage IV or IVa tumors, whereas 2 of the 7 dogs that received 3 fractions of 9 Gy had stage IV tumors. This difference in tumor stage may have contributed to the shorter survival time in the dogs that received 3 fractions of 10 Gy. A type 1 error is also possible; in the present study, a value of $P < 0.05$ was used to determine significance, which indicates a 5% probability of incorrectly rejecting the null hypothesis. Total prescribed dose was not associated with survival time in the 2 previous studies[3,4] of canine nasal tumors treated with SBRT.

The shorter survival times with increased dose heterogeneity identified in the present study could have been influenced by the presence of lower-dose areas within the target volume that resulted in earlier tumor recurrence. Nasal tumor recurrence after conventionally fractionated radiation therapy most commonly occurs in the irradiated volume within the nasal cavity and is thought to be attributable to an inadequate dose.[25] Dose heterogeneity within the tumor volume may be less important than the minimum biologically effective dose within the tumor volume. This is supported by results of a study[26] that explored the calculated tumor control probability in a hypofractionated radiation protocol for canine nasal tumors with a simultaneously integrated boost delivered to areas of gross disease. The estimated tumor control probability increased with increasing dose boost, despite the accompanying increase in dose heterogeneity that would be expected with a boost. The maximum and minimum biologically effective doses were used in the calculation of dose heterogeneity to account for the different fractionation protocols used in the present study. There are data to suggest that at dose fractions > 8 to 10 Gy, novel biological processes that do not play a role in conventionally fractionated protocols contribute to tumor cell killing; hence, it has been argued that use of a linear-quadratic model to calculate isoeffect doses for different SBRT fractionation schemes is not appropriate.[27] However, although the linear-quadratic model would be expected to be less accurate at doses > 10 Gy than would be conventionally fractionated protocols, there is evidence indicating that the linear-quadratic model is still acceptable to use.[6,27] The association between a shorter survival time and a more rapid dose falloff could be a result of underdosing of tumor cells located outside the targeted volume, and suggests that adding a wider treatment planning margin to gross tumor could be considered. A clinical target volume to account for subclinical disease that is not visible on diagnostic images is generally added to the GTV when conventionally fractionated radiation therapy is used.[28] In many instances of SBRT planning, the clinical target volume is kept equal to the GTV to allow for greater normal tissue sparing.[1] No clinical target volume was added to the GTV in the present study, and it is possible that this practice could lead to disease progression attributable to tumor cells located outside the treated area. A change in planning practice is not warranted given the lack of information on progression-free interval provided by the present study. However, on the basis of the associations between survival time and both dose heterogeneity and dose falloff identified in the present study, these relationships should be evaluated in future studies of SBRT for treatment of canine nasal tumors.

The frequency of acute skin and oral adverse effects that would be expected to cause discomfort was lower in the present study than in most studies of conventionally fractionated 3-D conformal radiation therapy.[7–9] This was consistent with the findings of the 2 previous studies[3,4] of SBRT for treatment of dogs with nasal tumors. In contrast to conventionally fractionated radiation therapy, the acute adverse effect period starts when SBRT is completed, and the assessment of most acute effects in the present study was performed by referring veterinarians, who were likely unfamiliar with acute radiation-induced adverse effects, or was based on owners' observations. This may have led to underreporting of acute adverse effects in the present study. Lower frequency and severity of acute radiation-induced adverse effects have also been reported for conventionally fractionated IMRT because of normal tissue avoidance.[12,13] An advantage of SBRT over conventionally fractionated IMRT is the reduced number of treatment fractions and anesthetic episodes. The method used to contour the oral mucosa was a limitation of the present study because it did not allow reporting of dose details to the full organ. Entire organs at risk should be contoured in future SBRT studies so that toxic effect data can be used to develop dose constraints, given that SBRT uses relatively novel dose fractionation and there are currently limited data on appropriate dose constraints.[29]

In contrast to findings of the present study, no cataract development was evident in the 2 previous studies[3,4] of SBRT used for treatment of canine nasal tumors. However, not all dogs in those studies had regular posttreatment ophthalmic examinations, and it is possible that radiation-induced cataracts were present but not diagnosed. The frequency of cataract formation in the present study was comparable to that associated with conventionally fractionated, 3-D radiation therapy.[7,9] In contrast to results of conventionally fractionated 3-D radiation therapy, cataract formation was limited to the ipsilateral eye in dogs of the present study, with the exception of 1 dog in which the tumor had close proximity to the contralateral eye. Cataracts restricted to the ipsilateral eye

in dogs with nasal tumors treated with conventionally fractionated IMRT have also been reported.[12] Two of the 4 dogs with possible late-onset effects of radiation therapy other than cataracts, which included vision loss, seizures, oronasal fistula, and aggression, had been treated with a second course of radiation therapy. Three of the dogs in the present study were euthanized because of possible late-onset effects of radiation, which is comparable to the percentage of possible late-onset effects that has been reported for conventional radiation therapy.[7] Late-onset radiation-induced effects in these dogs could not be confirmed because of a lack of follow-up imaging and necropsy at the time of clinical sign development. The lack of regular follow-up with veterinarians experienced with late-onset radiation-induced adverse effects and lack of regular ophthalmic examinations may have resulted in underreporting of late-onset effects in the study dogs. In addition, the clinical signs associated with some late-onset radiation-induced adverse effects, such as chronic rhinitis, are similar to signs associated with disease progression; it is possible that some of the dogs considered to have progression of disease (based on clinical signs) could actually have had a late-onset radiation-induced adverse effect.

The overall survival time in the present study supported a comparable outcome of SBRT with that of conventionally fractionated radiation therapy for treatment of dogs with nasal tumors. Moreover, SBRT had a lower frequency of acute radiation-induced adverse effects and required fewer treatment episodes. Although a risk of serious late-onset adverse effects with SBRT exists, the risk appears to be comparable to that of conventionally fractionated radiation therapy. The equipment and personnel required to perform SBRT and the increased treatment planning time may result in comparable or higher costs than conventionally fractionated 3-D conformal radiation therapy, despite the lower number of treatment episodes. Nevertheless, most owners involved in the present study were satisfied with their decision to treat their dog's nasal tumor with SBRT.

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Dr. G. Neal Mauldin was involved in collection of data and approval of the manuscript and is Chief Medical Officer for PetCure Oncology.

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Footnotes

a. Eclipse, Varian Medical Systems, Palo Alto, Calif.
b. Clinac 2100C or Clinac 2100EX (Calgary), Clinac 2100EX (Saskatoon), Varian Medical Systems, 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 Profile Frame 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, Palo Alto, Calif.
k. MapCheck 2, Sun Nuclear Corp, Fla.
l. CheckMate 2, Sun Nuclear Corp, Fla.
m. FluidSurveys, University of Saskatchewan, Saskatoon, SK, Canada.
n. Stata SE, version 14, StataCorp LP, College Station, Tex.

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From this month's *AJVR*

Evaluation of diagnostic coelioscopy in koi (*Cyprinus carpio*)

Brittany N. Stevens et al

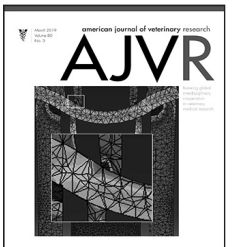
OBJECTIVE
To describe a technique for endoscopic evaluation of the coelomic viscera of koi (*Cyprinus carpio*) and to evaluate the ability to visually examine coelomic structures by use of an approach cranial or caudal to the pelvic girdle.

ANIMALS
16 subadult koi.

PROCEDURES
Koi were anesthetized with buffered tricaine methanesulfonate. Coelioscopic examination was performed via a ventral midline incisional approach cranial or caudal to the pelvic girdle. A 2.7-mm X 18-cm 30° oblique endoscope within a 4.8-mm operating sheath and infusion of saline (0.9% NaCl) solution was used. Ease of entry into the coelomic cavity and visual examination of structures were scored for each fish. Fish were euthanized 2 or 8 weeks after the procedure, and necropsy was performed.

RESULTS
The coelioscopic procedure was tolerated well, and all koi recovered uneventfully. For all fish, ease of entry and visual examination scores of the liver, intestines, gonads, heart, and anterior kidney were satisfactory to excellent. Visual examination of the posterior kidney and swim bladder was satisfactory to difficult, whereas the spleen and gallbladder were not visually identified. No significant differences were noted in entry or visual examination scores between the cranial and caudal approaches or between sexes. Minor complications included mild hemorrhage, rupture of the gonadal capsule, formation of adhesions between the viscera and incision site, and delayed healing of the incision.

CONCLUSIONS AND CLINICAL RELEVANCE
Diagnostic coelioscopy of koi appeared to be safe and effective. This procedure could have potential for use in examination of coelomic structures and disease diagnosis. (*Am J Vet Res* 2019;80:221–229)



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