Journal of Veterinary Cardiology (2020) **27**, 62—77

Journal of Veterinary Cardiology
ESVC

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# A retrospective analysis of stereotactic body radiation therapy for canine heart base tumors: 26 cases☆

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Received 21 March 2019; received in revised form 21 January 2020; accepted 22 January 2020

**KEYWORDS**
Aortic body tumor;
Chemodectoma;
Paraganglioma;
Dog

**Abstract** *Introduction:* This study retrospectively evaluated outcomes and adverse radiation effects (AREs) associated with stereotactic body radiation therapy (SBRT) for canine heart base tumors (HBTs). A secondary aim was to identify any demographic or echocardiographic factors that might determine which dogs would most benefit from SBRT.
*Animals:* Twenty-six dogs that received SBRT for an imaging-based diagnosis of a HBT were evaluated.
*Methods:* Twenty-three dogs were treated with three fractions of 10 Gy delivered daily or every other day. The remaining 3 dogs received variable protocols of one to five fractions. Demographic, echocardiographic, and radiographic information, AREs, and treatment responses were collected. Correlations of these data with survival time were evaluated.

Data presented as a poster at the Radiation Research Society Annual Conference — September 23—26, 2018 in Chicago, IL.

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https://doi.org/10.1016/j.jvc.2020.01.002

*Results:* The median overall survival time was 404 days (95% confidence interval: 239—554 days). The majority of dogs experienced a partial response (25%) or stable disease (60%) for a median duration of 333 days (95% confidence interval: 94—526 days). Three dogs had progressive disease within six months of SBRT. Radiographic pneumonitis was identified in 7 of 23 dogs, and clinical pneumonitis was identified in 4 dogs. No other AREs were noted. The rate of distant metastasis was 13%. On multivariate analysis, it was found that vena caval obstruction, supraventricular and ventricular arrhythmias, clinical signs, and enlarged locoregional lymph nodes at presentation were negatively associated with survival time.
*Conclusions:* Stereotactic body radiation therapy was delivered with a low rate and degree of normal tissue complications. Asymptomatic dogs with confirmed, progressive growth of a HBT may most likely benefit from SBRT.


**Abbreviations**

| | |
|---|---|
| ARE | adverse radiation effect |
| CI | confidence interval |
| CIn | conformity index |
| CT | computed tomography |
| GTV | gross tumor volume |
| Gy | gray |
| HBT | heart base tumor |
| OST | overall survival time |
| PR | partial response |
| PTV | planned target volume |
| SBRT | stereotactic body radiation therapy |
| SD | stable disease |

## Introduction

Cardiac tumors are uncommon tumors in dogs, with an incidence of 0.19—3% [1—3]. The most common locations for primary cardiac tumors are the right atrium/auricle and the heart base [1]. Chemodectomas, or aortic body tumors, are the most common heart base tumors (HBTs) and originate in the wall of the ascending aorta, generally excluding involvement of the atria [1—10]. English bulldogs, boxers, and Boston terriers are reported to have an increased risk of developing HBTs [6,7,10—13]. Sporadic cases of other tumor types of the heart or heart base include ectopic thyroid carcinoma, lymphoma, myxoma, and sarcoma [14—20].

The majority of clinical signs secondary to HBT are location dependent and to a less extent dependent on histotype [5]. Respiratory compromise (coughing, exercise intolerance), signs of right-sided congestive heart failure (ascites, pleural effusion), weight loss, anorexia and inappetence, lethargy, collapse, pericardial effusion, and arrhythmias have been reported [4,6,8,9,13,21—23]. Heart base tumors are often incidentally found.

Characterizing a mass as a HBT is often based on imaging characteristics [1,12,24—26]. As sampling of HBTs has reported risk of complications (pneumothorax, hemorrhage, cardiac puncture, arrhythmias), antemortem definitive diagnosis is uncommon, and treatment is often pursued without a definitive diagnosis [23,24].

Complete surgical resection is often impossible. Radiation has been reported as a non-invasive, local treatment option. Case reports on radiation for HBTs are limited, and effects of radiation on survival in canine patients have not been previously analyzed [18—20]. The goal of this retrospective study was to evaluate clinical outcomes and adverse radiation effects (AREs) associated with stereotactic body radiation therapy (SBRT) for canine HBTs. A secondary aim was to identify any demographic or echocardiographic factors to determine which dogs would most benefit from SBRT.

## Animals, materials and methods

The medical records of dogs with an imaging-based (echocardiography and/or computed tomography [CT]), cytologic, or histologic diagnosis of a HBT treated with intensity-modulated SBRT at the Colorado State University Veterinary Teaching Hospital between November 2009 and November 2017 were retrospectively reviewed. Dogs were excluded if the clinical presentation was suggestive of hemangiosarcoma by having both hemorrhagic pericardial effusion and right atrial/auricular location of the mass. Information

relating to signalment, presenting clinical signs, imaging characteristics of the mass, details of radiation therapy, cytological or histopathologic diagnosis, presence of metastasis, use of surgical interventions or antineoplastic therapies, response to treatment, ARE development, follow-up imaging, and overall survival time (OST) or time until last follow-up were recorded. Echocardiographic parameters assessed before radiation therapy included peak pulmonary artery velocity, peak aortic velocity, mitral valve ratio of early (E) to late (A) ventricular filling velocities (MV E:A ratio), left atrium-to-aorta ratio by the Rishniw [29] or Swedish [30] method depending on the clinician's preference, subjective assessment of right heart size, systemic systolic blood pressure by the Doppler[c] method, tricuspid valve regurgitation pressure gradient by the modified Bernoulli formula, left ventricular fractional shortening (%), and left ventricular end-diastolic and end-systolic internal dimensions (LVIDd and LVIDs) normalized, as described by Cornell et al [31]. Evidence of radiographic, radiation-induced pneumonitis, fibrosis, or clinical signs relating to pneumonitis after radiation therapy was also extracted and recorded.

All dogs were immobilized in a Styrofoam bead-style cushion[d] in sternal or lateral recumbency. Computed tomography was performed using a Philips Gemini 16-slice scanner.[e] Precontrast and postcontrast helical scans were obtained through the thorax. Omnipaque™350[f] contrast media was used at a dose of 2 mL/kg. Images were reconstructed at 2.0-mm contiguous intervals with a 512 matrix.

The 2-mm precontrast CT scans were imported into a Varian Eclipse™ treatment planning system[g] for 3D inverse planning. Normal structures and organs at risk (OARs) were contoured using the CT scan. Grossly evident tumor was delineated and defined as the gross tumor volume (GTV). There was no field expansion to account for potential subclinical disease. A uniform expansion of 2—5 mm was applied to the GTV to account for interfractional and intrafractional motion and setup inaccuracies (i.e., the planning target volume [PTV]). The PTV found to be overlapping sensitive OARs, including the esophagus, trachea, and mainstem bronchi, was cropped so as to limit dose delivery to these organs. Planning target volume varied based on the judgment of the prescribing radiation oncologist and attending medical physicist.

Most dogs were treated with a prescription of 30 Gray (Gy) delivered in three fractions on consecutive or alternating days. The remaining dogs were treated with variable protocols in one to five fractions (Supplemental Table B). The dosing goal was 100% of prescription to 99% of the GTV and to 95% of the PTV; however, $<$99% coverage of the GTV and $<$95% coverage of the PT at prescription was accepted to meet dose constraints for sensitive OARs, including the esophagus, trachea, mainstem bronchi, and lungs (Fig. 1; Supplemental Table A). Plans consisted of either 6 MV static beams or two 360° volumetric arcs. Conformity index (CIn) and homogeneity index were calculated as quantitative assessments of plan quality. Conformity index was calculated as the volume within the 100% isodose line divided by the volume of the PTV, as previously described for Varian systems. Homogeneity index was calculated as $D_5$-$D_{95}/D_p \times 100$, where $D_5$ and $D_{95}$ are the minimum dose in 5% and 95% of the PTV and $D_p$ is the prescribed dose [32].

All radiation plans were reviewed and approved by an American College of Veterinary Radiology board—certified radiation oncologist. A verification plan of the approved protocol was assessed for quality assurance before patient treatment for each radiation plan, as recommended by an American College of Radiology board—certified medical physicist. Quality assurance was carried out with gamma analysis using the Varian portal dosimetry system on individual fields. 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.

Dogs were anesthetized for CT image acquisition and treatment. Anesthetic protocols varied but in general consisted of an opioid premedication, followed by a propofol[h] induction and maintenance with isoflurane[i] gas and supplemental oxygen. Additionally, some dogs received atracurium and were treated at end-expiratory breath hold at the discretion of the attending radiation oncologist. Once anesthetized, the dogs were repositioned in immobilization devices used during their initial imaging. Daily patient position verification was performed by online registration

[c] Parks Medical Electronics, Inc, Aloha, Oregon, USA.
[d] Vac-Lok bag, Civco model MT-VL-37, Civco Systems, Orange City, IA, USA.
[e] Philips Gemini TF Big Bore 16-slice scanner, Philips Medical Systems, Nederland, B.V.
[f] GE Healthcare, Princeton, NJ, USA.
[g] Varian Eclipse™, Varian Medical Systems, Inc, Palo Alto, CA, USA.
[h] Dipravan, AstraZeneca, London, UK.
[i] Aerrane, Baxter, Haryana, India.

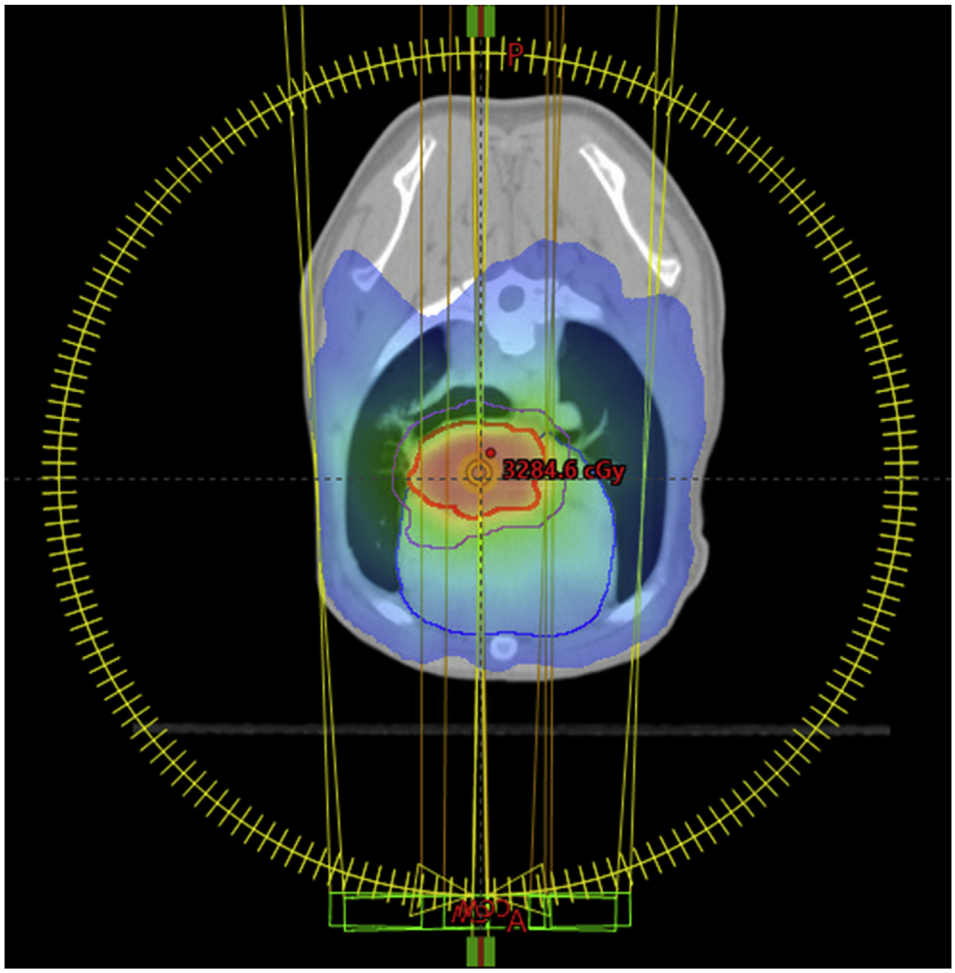


**Figure 1** Axial view of the thoracic radiation-planning computed tomography scan for a dog with a heart base tumor on Varian Eclipse™ planning software. The gross tumor volume (red outline) and the planning target volume (magenta outline) are overlaid by the estimated radiation dose in color wash. The red dot represents the maximum hot spot for this position. Blue color wash represents subclinical doses, progressing to red which represents the prescription dose (30 Gray). The yellow arcs around the thoracic scan represent the excursion of the 360° volumetric arcs used to deliver the radiation, one traveling clockwise and the second traveling counterclockwise.

of the simulation CT, with images of the daily setup obtained via a kilovoltage cone beam CT. Allowable setup inaccuracies corresponded to the planned PTV margin. Therapy was delivered using a Varian Trilogy™ linear accelerator.[j]

Follow-up physical examinations were recommended at 2 weeks after treatment and then as recommended by the referring cardiologist or if a patient presented with concerning clinical signs. A recheck CT scan was recommended 4—6 months after SBRT to assess the tumor volume. Adverse radiation effects were retrospectively evaluated using the toxicity criteria of the Veterinary Radiation Therapy Oncology Group [33]. Response to therapy was evaluated using the Veterinary Oncology Group consensus document for solid tumors [34]. If objective measurements were not available, subjective assessment of the images by the radiologist or cardiologist was accepted.

## Statistical analysis

Survival time (in days) was calculated as the time between the first day of treatment and date of death. Survival analysis was performed on an intent-to-treat basis; events included death from any cause. Dogs were censored if they were still alive at the time of statistical analysis or lost to follow-up. The continuous data on survival time (days) was evaluated for normality distribution. If normality was not met, the data were converted to

[j] Varian Trilogy™ linear accelerator, Varian Medical Systems, Inc., Palo Alto, CA, USA.

log scale for analysis using a t-test to compare 2 categories of a variable. Kaplan-Meier curves were calculated and compared between groups using a log-rank test. The analysis of 2 categorical variables was performed using a Fisher's exact test if any of the variable categories had <5 data points. If normality was met, correlations between 2 continuous variables were performed using a Pearson correlation. If not, Spearman nonparametric statistics was calculated. A t-test was used to evaluate significance of a continuous variable between 2 categories, if normality was met. If the normality was not met, a Wilcoxon nonparametric 2-sample test was used. A *p*-value of 0.05 was used to determine significance of all analyses. Each factor was evaluated for significant association with the outcome. The factors that met the criteria of *p*-value of 0.25 were selected to be included in the multivariable Cox proportional hazard regression analysis. The main factor of interest was fixed in the multivariable model, and other confounding variables were all entered in the initial full model. A backward elimination process was used with *p*-value <0.1 to retain the factors to build the final model. A *p*-value of 0.05 was used to determine significance in the final model. Adjusted hazard ratios were reported for the final model. SAS version 9.4[k] was used for all statistical analyses.

## Results

Twenty-six dogs met the inclusion criteria. Dog demographics, clinical and treatment data, supplemental therapies, and post-SBRT sequelae were analyzed for an association with survival time (Table 1).

The median OST was 404 days (95% confidence interval [CI]: 239—554 days; Fig. 2). Two dogs never improved clinically after therapy and were euthanized 1 and 3 months later. Of the 10 dogs that presented with heart failure, 7 dogs represented for recurrent heart failure (with ascites, pleural effusion, syncope, pericardial effusion, pulmonary edema requiring furosemide) between 1 and 9 months after treatment. The remaining 3 dogs had no further episodes of heart failure recorded. None of the echocardiographic parameters investigated were significantly associated with survival (Supplemental Tables C and D).

[k] SAS Institute Inc., Cary, NC, USA.

The median follow-up time for all dogs was 359 days (95% CI: 206—534 days). Six dogs were alive at the time of data analysis, and 2 dogs were lost to follow-up. The median follow-up time for the 8 censored dogs was 571 days (95% CI: 102—1,113 days). The cause of death could be determined in 16 of 18 deceased dogs. Eleven (69%) dogs died of tumor-related causes, whereas 5 (31%) dogs died of unrelated causes.

Table 2 summarizes the dog breed, tumor type, CT findings of tumor compression/invasion, arrhythmias before and after SBRT, heart failure characteristics, chemotherapy protocols, lung toxicity, tumor response and time to response, and OST for each dog. A cytological or histologic diagnosis of the HBT was available in 11 dogs, five of which were obtained at necropsy. One dog had a mass sampled via fine-needle aspirate, and the result was non-diagnostic. The majority of this group (7/11 dogs, 64%) had neuroendocrine tumors. Two dogs had ectopic thyroid tumors, and one dog had myxosarcoma. One dog had a histologically confirmed, well-differentiated hemangiosarcoma on necropsy, with the tumor located at the base of the heart.

Presence of clinical signs at time of treatment was negatively associated with survival (*p*-value = 0.0059). Nineteen (73%) dogs had clinical signs at the time of treatment, and 7 (27%) were free of signs. Ten (38%) dogs had heart failure before treatment, 7 dogs had right-sided failure (ascites, non-hemorrhagic pericardial effusion, pleural effusion), 2 dogs exhibited low output or forward failure resulting in syncopal episodes, and 1 dog had both left-sided heart failure (pulmonary edema, dyspnea) and right-sided failure (ascites). Four (15.4%) dogs had evidence of a heart murmur at the time of treatment, 5 (19.2%) dogs had evidence of pericardial effusion before treatment, and 10 (38%) dogs had a supraventricular and/or ventricular arrhythmia noted on the electrocardiogram before treatment (Table 2). There was a significant correlation between dogs with tumor compression/invasion of any cardiac or vascular structures and being symptomatic before therapy ($p = 0.0023$); however, there was no significant effect of tumor compression/invasion on survival time ($p = 0.3361$; Table 1).

Four dogs presented with pre-SBRT supraventricular arrhythmias, 5 dogs presented with ventricular arrhythmias, and 1 dog presented with both (Table 2). The arrhythmia resolved in 6 of 10 dogs after SBRT. The original arrhythmia persisted in 4 dogs, and a new arrhythmia was diagnosed in 9 dogs. Two dogs had both a persistent arrhythmia after SBRT and developed a new arrhythmia. Six

**Table 1** Demographic, clinical signs, treatment, supplemental therapies, and postradiation sequelae variables analyzed for association with overall survival time on univariate analysis.

| Variable | Number of dogs | Median survival time (days) | 95% confidence interval (days) | *p*-value |
|---|---|---|---|---|
| **Gender** | 24 | | | 0.7733 |
| Male (castrated) | 17 | 404 | 206—1794 | |
| Female (spayed) | 7 | 476 | 35-NR | |
| **Brachycephalic breed** | 26 | | | 0.9278 |
| No | 9 | 388 | 64—1794 | |
| Yes | 17 | 453 | 193—554 | |
| **Bulldog breed** | 26 | | | 0.6445 |
| No | 18 | 388 | 206—554 | |
| Yes | 8 | 494 | 30-NR | |
| **Clinical signs at time (before SBRT)** | 26 | | | **0.0059** |
| Asymptomatic | 7 | 1794 | 388—1794 | |
| Symptomatic | 19 | 279 | 157—453 | |
| **Heart failure/syncope (before SBRT)** | 26 | | | 0.0915 |
| No | 16 | 505 | 279—1794 | |
| Yes | 10 | 206 | 30—453 | |
| **Tumor compression/invasion of cardiac structures (before SBRT)** | 26 | | | 0.3361 |
| No | 4 | 554 | 388-NR | |
| Yes | 22 | 404 | 193—588 | |
| **Vena caval compression (before SBRT)** | 26 | | | 0.0696 |
| No | 18 | 476 | 254—1794 | |
| Yes | 8 | 206 | 30—404 | |
| **Pulmonary artery compression (before SBRT)** | 26 | | | 0.6645 |
| No | 10 | 479 | 153-NR | |
| Yes | 16 | 453 | 157—919 | |
| **Supraventricular arrhythmias (before SBRT)** | 26 | | | 0.2888 |
| No | 21 | 476 | 206—1794 | |
| Yes | 5 | 279 | 193—453 | |
| **Ventricular arrhythmias (before SBRT)** | 26 | | | **0.0076** |
| No | 20 | 534 | 239—1794 | |
| Yes | 6 | 230 | 30—453 | |
| **Pericardial effusion (before SBRT)** | 26 | | | 0.9849 |
| No | 21 | 404 | 239—554 | |
| Yes | 5 | 453 | 153-NR | |
| **Pleural or peritoneal effusion (before SBRT)** | 26 | | | 0.4957 |
| No | 18 | 440 | 239—1794 | |
| Yes | 8 | 254 | 153-NR | |
| **Locoregional lymphadenomegaly (before SBRT)** | 26 | | | 0.1866 |
| No | 11 | 534 | 153—453 | |
| Yes | 15 | 388 | 239—1794 | |
| **Daily vs. every other day (EOD) fractions** | 26 | | | 0.1819 |
| Daily | 15 | 453 | 206-NR | |
| EOD | 8 | 289 | 35—534 | |
| **Breath hold for respiratory management during SBRT** | 26 | | | 0.4549 |
| No | 14 | 333 | 64—1794 | |
| Yes | 12 | 453 | 157—534 | |
| **Pericardiectomy** | 26 | | | 0.1215 |
| No | 17 | 534 | 157—1794 | |
| Yes | 9 | 299 | 153—476 | |

(*continued on next page*)

Table 1 (*continued*)

| Variable | Number of dogs | Median survival time (days) | 95% confidence interval (days) | *p*-value |
|---|---|---|---|---|
| **Chemotherapy** | 26 | | | 0.5732 |
| No | 20 | 404 | 206—554 | |
| Yes | 6 | 388 | 153—1794 | |
| **Response to therapy** | 20 | | | **0.0289** |
| Partial response | 5 | 1794 | 254—1794 | |
| Stable disease | 12 | 476 | 193-NR | |
| Progressive disease | 3 | 157 | 153—388 | |
| **Arrhythmias (after SBRT)** | 26 | | | 0.1264 |
| No | 16 | 279 | 157—476 | |
| Yes | 9 | 534 | 153-NR | |
| **Pneumonitis (grade 1)** | 23 | | | 0.9621 |
| No | 16 | 404 | 206—1794 | |
| Yes | 7 | 388 | 153-NR | |
| **Pneumonitis (grade 2)** | 23 | | | 0.9506 |
| No | 19 | 388 | 206—1794 | |
| Yes | 4 | 394 | 193-NR | |
| **Distant metastasis** | 23 | | | **0.0356** |
| No | 20 | 453 | 239—1794 | |
| Yes | 3 | 157 | 153—388 | |

SBRT, stereotactic body radiation therapy.
Bold p-values indicate a statistically significant value (< or = to 0.5). NR: not reached.

dogs that developed a new arrhythmia had no evidence of an abnormal heart rhythm before therapy; however, only two dogs underwent a 24-h continuous electrocardiogram evaluation.

On univariate analysis, it was found that symptomatic dogs ($p = 0.0059$) and dogs with a pretreatment ventricular arrhythmia ($p = 0.0076$) had a shorter survival than dogs who did not have these risk factors (Table 1). After controlling for multiple factors including sex and brachycephalic breed, dogs with pretreatment symptoms, heart failure, vena caval obstruction, supraventricular and ventricular arrhythmias, or locoregional lymphadenomegaly showed a higher risk of death than dogs without these factors (Table 3).

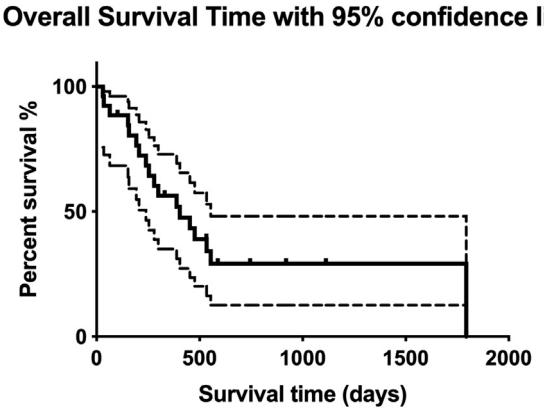


**Figure 2** Kaplan-Meier graph of overall survival time of dogs that received treatment with stereotactic body radiation therapy (solid line). The dotted lines represent the 95% confidence interval (CI). The median survival time was 404 days (95% CI: 239—554 days). Censored cases are indicated by tick marks.

Response to therapy was predictive of the outcome. Dogs with a partial response (PR; at least 30% reduction in the sum of tumor diameters) had significantly longer survival than dogs with stable disease (SD; less than 30% reduction or 20% increase in the sum of tumor diameters) or progressive disease (PD; appearance of 1 or more new lesions or at least 20% increase in the sum of tumor diameters), and dogs with SD had significantly longer survival than dogs with PD ($p = 0.0289$; Table 1). Four of the 5 dogs with a PR had a cytological or histologic diagnosis; of which, two were ectopic thyroid tumors, one was a well-differentiated hemangiosarcoma, and one was a neuroendocrine tumor.

Distant metastasis to the lungs was identified in one dog before treatment, and two dogs had metastasis to the kidneys or both lung and kidneys after SBRT. Metastasis was confirmed cytologically or histologically in both dogs with kidney involvement to be neuroendocrine in origin and was assumed as the most likely differential in the dogs with pulmonary nodules on imaging. The presence of distant metastases before or after treatment ($p = 0.0356$) was associated with a significantly shorter survival time.

**Table 2** Summary of tumor and patient characteristics at presentation, chemotherapy protocols, acute lung toxicity, response and time to response, and overall survival times.

| Dog | Breed | Tumor type | Clinical signs | Tumor comp. vs. invasion (CT) | Arrhythmia | Heart failure status (Y/N) | Chemotherapy | VRTOG Lung Toxicity (grade) | Response; Duration of response (days) | Survival time (days) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | GSD | Ectopic thyroid tumor | Incidental finding | Right PA comp. | None | N | Cyclophosphamide (metronomic) | 0 | PR; 353 | 1794 |
| 2 | Boston terrier | n/a | Exercise intolerance | LA comp., right PA comp. | **Before SBRT**: APCs (4 d) | N | None | 0 | n/a | 239 |
| 3 | Boston terrier | n/a | Cough | Left PA comp. | None | N | None | 0 | SD; 369 | 476 |
| 4 | Boxer | Neuroendocrine carcinoma | Lethargy, diarrhea, abd distention | CrVC comp. | **Before SBRT**: rare VPCs (15 d) | Y: right-sided failure | None | 0 | n/a | 206 |
| 5 | Labrador retriever | n/a | Cough, exercise intolerance, voice change, stridor | CrVC, RA, PA comp. | None | N | None | 0 | n/a | 64 |
| 6 | French bulldog | n/a | Cough, vomiting, weight loss | LA, RA, MPA comp. | **After SBRT**: SVT, sinus arrest (1 mo) | N | None | 2 | SD; 460 | 534 |
| 7 | Boxer | n/a | Incidental finding | None | **After SBRT**: VPCs (9 mo) | N | None | 0 | SD; 526 | 533* |
| 8 | Boston terrier | n/a | Cough | RA, right PA comp., CrVC invasion | **Before SBRT**: intermittent VPCs (3 mo) | N | None | 0 | SD; 285 | 299 |
| 9 | German shorthaired pointer | Neuroendocrine tumor | Lethargy | RA invasion, right PA comp. | **Before SBRT**: single VPC (4 d) **After SBRT**: SVT, sinus arrest (7 wk) | Y: right-sided failure | Doxorubicin; toceranib | 1 | PD | 153 |
| 10 | Miniature pinscher | Myxosarcoma | Cough, weight loss, inappetence, exaggerate swallowing | CrVC, azygos comp. | None | N | None | 0 | SD; 333 | 404 |
| 11 | Boston terrier | n/a | Incidental finding | None | None | N | None | 0 | n/a | 554 |
| 12 | English bulldog | Well-differentiated hemangiosarcoma | Lethargy, gagging, respiratory distress, mucoid nasal discharge | RV and IVS invasion | **Before SBRT**: sinus arrest with junctional escape, rare VPCs, atrial flutter (versus focal atrial tachycardia) and variable AV conduction (3 wk) **After SBRT**: same as mentioned for Before SBRT (3 d) | Y: right-sided failure | None | n/a | PR; 94 | 453 |

(*continued on next page*)

Table 2 (*continued*)

| Dog | Breed | Tumor type | Clinical signs | Tumor comp. vs. invasion (CT) | Arrhythmia | Heart failure status (Y/N) | Chemotherapy | VRTOG Lung Toxicity (grade) | Response; Duration of response (days) | Survival time (days) |
|---|---|---|---|---|---|---|---|---|---|---|
| 13 | Border collie-mixed breed | n/a | Diarrhea, vomiting, stranguria, abd distention | RA invasion, LA, CrVC, CVC comp. | None | Y: right-sided failure | None | 0 | SD; 77 | 102* |
| 14 | Boston terrier | Neuroendocrine tumor | Cough, restlessness | Right PA comp. | **Before SBRT**: VPCs (1 wk) **After SBRT**: SVT, VPCs (5 mo), 2nd deg. AV block, Afib (8 mo) | Y: right-sided failure | None | 2 | PR; 63 | 254 |
| 15 | American bulldog | Malignant chemodectoma | Collapse | MPA invasion, LV free wall and IVS invasion, right and left PA comp. | None | Y: forward failure | None | 0 | n/a | 157 |
| 16 | Boston terrier | n/a | Cough, gagging | Right PA comp. | None | N | None | 0 | SD; 1,004 | 603* |
| 17 | English setter | n/a | Incidental finding | RA invasion | **After SBRT**: rare VPCs (4 mo) | N | Carboplatin | 1 | SD; 587 | 588* |
| 18 | Poodle (toy) | n/a | Cough | LA comp. | **Before SBRT**: APCs (3 wk) **After SBRT**: APCs (3 mo) | N | None | 0 | SD; 109 | 279 |
| 19 | Boston terrier | n/a | Weight loss, slow eating | CrVC, RA, MPA comp. | None | N | None | 0 | SD; 27 | 35 |
| 20 | French bulldog | Malignant chemodectoma | Vomiting, ataxia, collapse | CrVC, LA, right PA comp. | **Before SBRT**: rare VPCs (4 d) | Y: forward failure | None | n/a | n/a | 30 |
| 21 | Bernese mountain dog | Neuroendocrine tumor | Incidental finding | None | **After SBRT**: P mitrale (12 mo) | N | Mitoxantrone; dacarbazine; carboplatin; toceranib | 1 | PD | 388 |
| 22 | English bulldog | Non-diagnostic | Incidental finding | Right PA comp. | **After SBRT**: APCs (1 mo) | N | None | 2 | PR; 589 | 410* |
| 23 | Labrador retriever | Ectopic thyroid tumor | Lethargy, weight gain, abd distention | RVOT, MPA intraluminal obstruction | **Before SBRT**: APCs (2 mo) | Y: right-sided failure | Toceranib | 0 | PR; 294 | 330* |
| 24 | French bulldog | n/a | Weight gain, abd distention | RA, CVC invasion, CrVC, LA comp., PA obstruction | None | Y: right-sided failure | None | 0 | SD; 745 | 138* |
| 25 | English bulldog | Chemodectoma, aortic body | Cough, tachycardia | Right PA, left PV comp. | **Before SBRT**: APCs (6 mo), Afib (3 wk) **After SBRT**: APCs, SVT, VPCs, atrial flutter (2 mo) | Y: left-sided failure | CHOP-based protocol; lomustine | 2 | SD; 77 | 193 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 26 | French bulldog | n/a | Incidental finding | None | **After SBRT:** APCs, SVT, sinus arrest with junctional escape, VPCs (4 mo) | N | None | n/a | n/a | 105* |

CT, computed tomography; Y, yes; N, no; GSD, German shepherd dog; comp., compression; PA, pulmonary artery; LA, left atrium; QRS, QRS complex; APC, atrial premature contraction; d., day; RA, right atrium; CrVC, cranial vena cava; abd, abdominal; RV, right ventricle; MPA, main pulmonary artery; mo., month; SVT, supraventricular tachycardia; VPC, ventricular premature contraction; * - dog censored from survival analysis; wk., week; AV, atrioventricular; CVC, caudal vena cava; Afib, atrial fibrillation; LV, left ventricle; IVS, interventricular septum; SV, supraventricular; RVOT, right ventricular outflow tract; PV, pulmonary vein; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; SD, stable disease; PD, progressive disease; PR, partial response; VRTOG, Veterinary Radiation Therapy Oncology Group; SBRT, stereotactic body radiation therapy.

**Table 3** Final multivariable models using Cox proportional hazard regression analysis.

| Factor | Categories | Model 1 | | Models 2—4 | |
|---|---|---|---|---|---|
| | | Hazard ratio (95% CI) | *p*-value | Hazard ratio (95% CI) | *p*-value |
| Which pretreatment variables have a significant association with survival time in a multivariable model? | Symptomatic vs. no symptoms | 5.776 (1.477—22.59) | 0.0117 | | |
| | Enlarged LN vs. normal LN | 3.668 (1.033—13.03) | 0.0445 | 15.59 (2.404—101.1) | 0.004 |
| | Heart failure vs. none | 9.294 (1.037—83.27) | 0.0463 | 98.59 (4.41-2,204) | 0.0038 |
| | Supraventricular arrhythmia vs. none | | | 405.2 (11.64—14,103) | 0.0009 |
| | Ventricular arrhythmia vs. none | 5.41 (1.053—27.79) | 0.0432 | 44.99 (3.587—564.1) | 0.0032 |
| | Vena caval obstruction vs. none | | | 6.623 (1.078—40.68) | 0.0412 |
| | Pleural or peritoneal effusion vs. none | 0.034 (0.003—0.357) | 0.0048 | 0.002 (0—0.072) | 0.0009 |
| | Brachycephalic breed vs. non-brachycephalic breed | 0.304 (0.092—1.003) | 0.05 | | |
| | Castrated male vs. spayed female | | | 0.086 (0.016—0.466) | 0.0045 |

CI, confidence interval; LN, lymph node.

Locoregional lymphadenomegaly on CT before treatment was identified in 15 (58%) dogs, including the sternal, cranial mediastinal, and tracheobronchial lymph nodes. The enlarged lymph nodes were included within the radiation treatment in 13 of 15 dogs. None of these lymph nodes were sampled. On univariate analysis, it was found that lymphadenomegaly before SBRT was not significantly associated with survival ($p = 0.1866$; Table 1), but on multivariable hazard regression analysis, it was found to be a significant factor (Table 3).

On multivariate analysis (Table 3), it was found that the following factors continued to negatively impact survival: symptoms at time of presentation ($p = 0.0117$), presence of lymphadenopathy ($p$-value $= 0.0445$), congestive heart failure ($p$-value $= 0.0463$), presence of supraventricular or ventricular arrhythmias ($p$-value $= 0.0009$ and 0.0032, respectively), vena caval obstruction ($p$-value $= 0.0412$), lack of pleural or peritoneal effusion ($p$-value $= 0.0009$), being a non-brachycephalic breed ($p$-value $= 0.05$), and being a castrated male ($p$-value $= 0.0045$).

Radiation planning parameters were analyzed; however, none of the factors were significantly associated with survival (Supplemental Tables C). The CIn was significantly and negatively associated with survival time ($p = 0.0041$); however, when an outlier (dog 1) was removed from analysis, the CIn was no longer significant ($p = 0.1004$).

Several dogs received adjuvant surgical procedures. Eight dogs underwent a pericardiectomy before radiation; of which, only 3 had pericardial effusion, and 1 dog received a pericardiectomy 7 months after radiation for scant, de novo transudative pericardial effusion. Pericardiectomy was not significantly associated with survival ($p = 0.1215$; Table 1).

One dog had a pacemaker placed for previously diagnosed complete atrioventricular block. Three dogs required intraluminal stent placement (dog 15 in branch pulmonary arteries; dog 13 and 24 transatrial from the cranial to caudal vena cava) before SBRT to address external compression of these vessels by the HBT. Survival analysis could not be performed owing to the fewer number of dogs that received a stent or a pacemaker.

Six dogs received adjuvant chemotherapy (Table 2). Chemotherapy was not statistically associated with survival ($p = 0.5732$; Table 1).

Follow-up imaging was available for 19 dogs. Recheck CT was available for 10 dogs, and the remaining 9 dogs had a recheck echocardiogram or chest radiographs. The median time to initial recheck imaging was 63 days (95% CI: 44—77 days). Eleven dogs had routine, follow-up imaging, whereas 8 dogs had imaging performed to investigate a problem, including melena, right-sided heart failure, cough, pleural effusion, vomiting, and inappetence. There were no complete responses. A PR was observed in 5 (25%) dogs, and 12 (60%) dogs had SD. Three (15%) dogs had PD at initial recheck. The PD was noted at 3, 4, and 6 months after SBRT for dogs 15, 9, and 21, respectively, and occurred both inside the radiation field (dogs 9 and 21) and outside the field (dogs 9, 15, and 21). Dog 21 developed tracheobronchial lymphadenomegaly outside the field 6 months after radiation (PD); however, the irradiated lymph nodes and tumor decreased in volume by 77% compared with the original CT. After a PR at 3 months, dog 12 went on to develop in-field progression of the primary mass and regional lymphadenomegaly 8 months after SBRT. Dog 10 had SD with routine imaging rechecks every 6 months until he developed in-field PD of the primary mass 13 months after SBRT. The median duration of tumor response for the 17 dogs with SD or PR, based strictly on objective tumor sizes from imaging rechecks, was 333 days (95% CI: 94—526 days).

Acute lung AREs were limited to radiographic (7/23 dogs, 30%) or mildly clinical (4/23 dogs, 17.4%) pneumonitis, Veterinary Radiation Therapy Oncology Group grade 1 or grade 2, respectively [33]. Postradiation radiographs were available for 23 dogs. All of the dogs that developed clinical pneumonitis had evidence of radiographic pneumonitis on thoracic radiographs. None of the dogs exhibited grade 3 acute lung toxicity. The median time to development of grade 1 and grade 2 pneumonitis was 62 days (95% CI: 22—106 days) and 57 days (95% CI: 22—78 days), respectively. All clinical dogs were treated with corticosteroids and had improvement in their cough. Bulldogs were significantly more likely to develop clinical pneumonitis than other breeds ($p = 0.021$). Neither the lung volume of the dog nor the dose delivered (Gy) to a certain percentage of the lung correlated with development of pneumonitis (Supplemental Figures I and II). There was no correlation between survival and developing grade 1 or grade 2 pneumonitis (Table 1).

## Discussion

This population of 26 dogs received SBRT without severe complications. Multiple negative prognostic and predictive factors for OST were identified.

The majority of tumors were located at the heart base. There was some variability or

uncertainty in determining tumor origin owing to tumor size and invasion of cardiac structures. Dogs with variable tumor locations were included in the study because of the breed (bulldog) and the absence of pericardial effusion and/or because paragangliomas have been confirmed in atrial locations [35–37]. The accuracy of echocardiography to correctly determine the cardiac tumor type is relatively modest (50–78%). Visualization of the right atrium can be improved by the presence of pericardial effusion; however, few dogs in the present study presented with pericardial effusion [25,26]. Sampling of HBTs has not been attempted with high frequency in the literaturliterature because of risk of adverse events [27,28]; however, with technological advancements in imaging modalities, it may be reasonable to attempt cytological sampling of HBT performed by an experienced radiologist [38,39].

Seventy-three percent of dogs presented with signs related to the obstructive (infiltration or tumor thrombus) or extraluminal compressive nature of the HBT. On both univariate and multivariate analyses, it was found that asymptomatic dogs had longer survival times ($p$-value = 0.0059 and 0.0117 respectively). Because chemodectomas can be slow growing, it cannot be said with confidence that asymptomatic dogs required therapy. However, 6 of the 7 asymptomatic dogs either had concerning imaging changes at presentation (elevated aortic velocity, elevated left atrium/aorta ratio, dilated hepatic veins, and hepatomegaly) or a large tumor relative to the size of the dog. For these reasons, it was considered reasonable to pursue therapy in the absence of tumor-related clinical signs.

Ehrhart et al [21] found an improved survival in dogs with a HBT that received a pericardiectomy (median survival time (MST): 730 days) compared with dogs that did not receive (MST: 42 days), regardless of whether or not the dog presented with pericardial effusion. Similarly, Vicari et al [4] noted a longer mean survival time (661 days) for dogs that received a pericardiectomy than for dogs that were treated medically (129 days). Pericardiectomy did not improve survival in this study ($p$-value = 0.1215). The discrepancy between outcomes could reflect the different patient populations. The cohort in this study had a heterogenous group of tumors, whereas the majority of subjects in the previous 2 reports had aortic body tumors [4,21]. In addition, more than half of our cohort consisted of brachycephalic breeds, which was not the case in the study by Ehrhart et al [21]. The current cohort may have been more severely affected; however, comparison with previous studies is difficult owing to lack of descriptive information on presenting clinical signs. Both previous reports had similar limitations as the present study, including being retrospective, having few definitive diagnoses at the time of therapy [4], and including <30 dogs in survival analysis. Future, prospective, case-control studies are needed to elucidate which outcomes are most representative of the general population.

For the 3 dogs with severe effusions or syncope refractory to medical therapy, stenting was recommended to achieve immediate symptom relief before radiation. Another differential to consider in dogs presenting with recurrent cavitary effusions or refractory syncope is right ventricular dysfunction. Bulldogs, which accounted for 30% of this study population, are predisposed to primary right ventricular cardiomyopathy [40]. Right ventricular dysfunction due to cardiomyopathy or secondary to tumor effects and decreased cardiac output could primarily explain or exacerbate signs of cavitary effusion or syncope. It could also explain the ventricular arrhythmias in dogs with tumors arising from the heart base that have little local tumor effect on the ventricles. It is difficult to objectively evaluate the function of the right ventricle on the echocardiogram, so systolic dysfunction could easily be misinterpreted as compressive/infiltrative effects of the HBT [41]. Neither the size of the tumor nor the radiation dose to the target volumes was associated with survival (Supplemental Table C). Actual dose to 95% of the PTV almost invariably fell below the dosing goal because priority was given to sparing the adjacent OARs. Neither was determination of intrafractional respiratory motion consistently evaluated for each patient nor was respiratory management used for every dog, so PTV margins may have been suboptimal. These factors could result in underdosing the GTV, in-field recurrences, and therefore shorter survival times. That being said, two of the 4 dogs with in-field PD had gross sarcomas (myxosarcoma, hemangiosarcoma) known to be radioresistant, and the remaining two dogs had biologically aggressive, neuroendocrine tumors with distant metastasis. Respiratory management using breath holding did not significantly impact survival ($p$ = 0.4549; Table 1).

The CIn was the only radiation-planning parameter that significantly correlated with survival. Although it makes more logical sense for a more conformal plan to positively correlate with survival, this association was negative. Possible explanations include a trend toward more conformal radiation plans over time as dosimetrists gained experience with treatment planning for this

tumor and location, while in parallel, the dogs presenting for therapy were more severely symptomatic. Prescribing radiation oncologists may have become less stringent on dose constraints to adjacent OARs over time as AREs reported were uncommon and not severe. The CIn and homogeneity index are great examples of objective, quantitative planning parameters; however, there is little information regarding the correlation between these theoretical parameters and clinical data. A non-homogenous dose with a higher central dose may improve local tumor control and may be safely achievable with intensity-modulated radiation therapy [32]. Regardless, when the most dramatic outlier was removed from analysis, the CIn was no longer significant. The dose restrictions to OARs for this dog, the first dog treated chronologically, were markedly more conservative than for subsequently treated dogs.

About one-third of the dogs developed grade 1 pneumonitis. In the 17.4% of dogs that developed grade 2 pneumonitis, there was a diffuse interstitial pattern primarily localized in the cranial lung fields up to the level of the carina, consistent with the known radiation fields. Given the distribution, clinical signs, and response to treatment in these dogs, radiation-induced pneumonitis was suspected. Clinical signs occurred between 3 weeks and 2.6 months. Given the low incidence of this ARE and the response to prednisone, the authors at this point have not elected to preemptively treat dogs with anti-inflammatories before radiation therapy considering the potential side-effects (gastric ulceration, iatrogenic hyperadrenocorticism, immunosuppression). Lung volume did not correlate with development of grade I ($p = 0.7637$) or grade II ($p = 0.2735$) pneumonitis. Bulldogs were found to have a significantly higher risk of developing clinical pneumonitis ($p = 0.021$). One hypothesis for this predisposition is their 'barrel-chested' conformation; a higher percentage of the lung is distributed to the cranial thorax (radiation field) than that found in other dog breeds. However, there was no apparent differences in the dose received at any relative lung volume between the dogs that developed grade 1 or grade 2 pneumonitis and those that did not develop (Supplemental Figures I and II). The small population and the predilection for bulldogs to develop HBTs could have overemphasized the importance of the breed on pneumonitis.

Both supraventricular and ventricular arrhythmias documented before treatment were negatively associated with survival time. Subclinical or intermittent arrhythmias likely went underdiagnosed. Ventricular tachyarrhythmias are a major contributor to sudden cardiac death in humans and probably dogs, although Holter recordings proceeding sudden cardiac death in dogs are scarce [42,43]. The arrhythmias before radiation can be attributed to the local infiltrative properties or ischemic effects of the primary tumor or unidentifiable myocardial metastases [1]. While effacement and disruption of the atrioventricular node leading to 3rd-degree atrioventricular blockade has been reported, many other arrhythmias have been documented with cardiac tumors [4,13–15,22]. Most HBTs affect atria and the great vessels; however, two dogs in this study had tumor invasion of ventricular structures (Table 2). Case reports of functional, catecholamine-secreting paragangliomas of the right atrium have been reported [35,36]. Tachyarrhythmias could be attributed to episodic catecholamine release from a functional tumor, both before and after radiation therapy. In addition, pericardial effusion and non-cardiac neoplasia should be differentials for arrhythmias in dogs without obvious local tumor effects.

Radiation-induced arrhythmias have been documented in healthy dogs receiving fractionated radiation protocols with doses of 2–4 Gy per fraction to total doses of 35–80 Gy [44]. Radiation injury to the heart was attributed to damage to the vasculoconnective tissues, evidenced by increases of connective tissue and perivascular fibrosis and decreases in capillary volume by 6 months after treatment [44]. These changes are compatible with ischemic damage to the heart, leading to further myocardial damage and conductive disturbances. The reported low alpha-beta ratios of the cardiac microvasculature and connective tissue that predispose these structures to late radiation effects may indicate higher concern for myocardial injury at high doses per fraction, such as that seen with SBRT. Therefore, we cannot rule out that arrhythmias after SBRT were not in some way induced/exacerbated by radiation. Conversely, image guidance and conformal dosing used with SBRT should limit high radiation doses to the heart and pericardium, especially the ventricles. This may explain why only one dog had evidence of scant pericardial effusion after SBRT (dog 21). No dogs, including dog 21, presented for any clinical signs consistent with pericarditis.

Eight dogs had obstruction of the cranial and/or caudal vena cava. Chronic or severe vena caval obstruction can decrease preload to the right side of the heart and increase systemic vascular resistance, ultimately causing cavitary effusions and reduced cardiac output. The degree of vena

caval obstruction was not quantified for this study, although 3 of these dogs had cavitary effusions presumed to be due to right-sided congestive heart failure. When vena caval compression was noted, other critical structures were often compressed or invaded (Table 2), so the significance of this prognostic factor could be related to size and general invasiveness of the tumor and not specifically to impairment of venous return.

The median duration of tumor control in responsive dogs is almost 1 year and likely a conservative estimate. This strongly suggests that radiation can confer a survival benefit in dogs with rapidly growing tumors. Six of the 7 dogs with 'incidentally' found HBTs in this study had relatively large tumors concerning changes on the echocardiogram secondary to the expansile nature of their tumor. The outcome of dogs with HBTs could be optimized by selecting for asymptomatic dogs with documented, rapid tumor progression. Findings on echocardiographic assessment that may warrant treatment in the absence of overt clinical signs include increased right ventricular outflow tract/transpulmonary/pulmonary branch velocities (supportive of external compression), dilated hepatic veins (in the absence of pericardial effusion could be due to right ventricular dysfunction from compression/obstruction), and pericardial effusion (not yet causing tamponade). Serial CT scans or echocardiograms every 3—6 months to assess the rate of tumor growth are warranted for asymptomatic dogs.

On multivariate analysis, there were several factors that significantly impacted survival that seem contradictory at first glance. This includes the positive influence of pleural or peritoneal effusion on survival. Dog 12, that survived 453 days, was an outlier in this category and may have influenced these results. Given the retrospective nature of this study and the small sample size, these statistics need to be taken into consideration but viewed with caution, and further research is needed for validation.

Limitations of this study include the small sample size, a limited number of definitive diagnoses, and the heterogeneity of neoplasms. It is extremely likely that many pretreatment factors are interrelated and strongly associated with the 'aggressiveness' of a tumor. This may explain why many factors were found to be significant. Reported hazard ratios were accompanied by broad CIs, likely reflective of the small sample sizes in each group. Therefore, these findings should be considered exploratory, and interpretation should be done with caution. The inability to distinguish a radiation-induced side-effect (i.e., arrhythmia) from preexisting cardiac damage is an additional limitation. A 24-h continuous electrocardiogram is recommended before initiating radiation therapy and will likely help improve the distinction between a tumor-induced and a radiation-induced arrhythmia.

## Conclusions

In summary, this retrospective study shows that SBRT can be used as a safe treatment for canine HBTs, with the majority of dogs experiencing SD or PR of their tumor. Response to radiation therapy was positively associated with survival in both univariate and multivariate analysis. While a handful of dogs had PD within 1 year of treatment, another subset of dogs experienced durable tumor control that lasted many months to years. On multivariate analysis, the potential negative prognostic factors with an adverse effect on OST included vena caval obstruction, enlarged regional lymph nodes, and a supraventricular or ventricular arrhythmia at presentation. Prospective, case-control investigations are needed to further elucidate the clinical benefit of SBRT for dogs presenting with and without clinical signs and to document the profile of radiation-induced AREs.

## Conflict of interest statement

The authors do not have any conflicts of interest to disclose.

## Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jvc.2020.01.002.

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