Title

Long-term outcomes with conventional fractionated and stereotactic radiotherapy for suspected heart-base tumours in dogs

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Abstract:

Published radiotherapy results for suspected heart-based tumours in dogs are limited. In this retrospective longitudinal study (3/2014-2019), eight dogs with either clinical signs attributable to a heart-base mass (6), or asymptomatic with a progressively larger mass on echocardiogram (2), received conventional fractionated radiotherapy (CFRT) or stereotactic body radiotherapy (SBRT). Clinical findings in symptomatic cases included one or more of the following: retching/coughing (4), exercise intolerance (2), collapse (1), pericardial effusion (2), rare ventricular premature contractions (2), abdominal effusion (1), or respiratory distress due to chylothorax (1). CFRT cases received 50 Gray (Gy) in 20 fractions, and SBRT cases received 30 Gy in 5 or 24 Gy in 3 fractions. Two dogs received chemotherapy post-radiation. At analysis, 7/8 dogs were deceased and one was alive 684 days (d) post-treatment. The estimated median overall survival (MOS) from first treatment was 785 d (95% CI 114-868 d, [range 114-1492 d]). Five dogs received CFRT (MOS 817 d; (95% CI 155 d – not reached [range 155-1492 d])). Three dogs received SBRT with one alive at analysis (MOS 414 d, (95% CI, 114 d – not reached [range 114-414 d])). No statistically significant difference was found between survival for CFRT and SBRT. Of the symptomatic patients, 5/6 showed improvement. Mass size reduced in 4/5 cases receiving follow-up ultrasounds. Possible complications included asymptomatic radiation pneumonitis (4), atrial tachycardia/premature beats (4), and pericardial effusion with heart failure coincident with tumour progression (1). This study provides preliminary evidence that radiotherapy may impact clinically relevant or progressively enlarging heart-base masses.

Key Words: canine, chemodectoma, conformal radiotherapy, paraganglioma, SRS

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

Introduction:

Heart-base tumours refer to masses associated with the ascending aorta and pulmonary trunk. Chemodectomas are most common, although other tumours are also seen.[1,2] Heart-base tumours have a lower metastatic rate and are more common than carotid body tumours of the jugular groove.[3] Routinely dogs with heart-base masses are asymptomatic and diagnosed incidentally. Some dogs present with clinical signs, including exercise intolerance, dyspnoea, coughing, syncope, and/or signs related to blood flow obstruction or pericardial effusion (e.g., ascites, pleural effusion, tamponade, and heart failure).[4,5]

Pericardiectomy is the historical local treatment. Pericardiectomy can prolong survival (reported median survival times (MS) range from 661-730 days (d) with pericardiectomy vs. 42-129 d without) and can improve quality of life, but this procedure does not directly impact tumour volume/infiltration.[5,6] Toceranib phosphate (Palladia, Zoetis, Parsippany, New Jersey) was recently evaluated retrospectively; some cases had prior treatments, and a subset had clinical signs pre-treatment.[7,8] Signs improved in most clinically affected dogs; however, stable disease was the most common response, with MS=823 d (range 68-1190 d; n=27). In a case report of conventional fractionated radiotherapy (CFRT), one dog received 57.5 Gy in 23 fractions,

61 experienced tumour reduction, and was asymptomatic for 32 months.[9] A stereotactic body
62 radiotherapy (SBRT) case series is also reported, with six dogs receiving 10 Gy X 3 fractions. In
63 that study, there were two sudden deaths within 10 months post-radiation of unknown cause, but
64 the remainder lived >13 months.[10]
65
66 CFRT involves many radiation treatments, often requiring larger treatment volumes to account
67 for target uncertainties. Fractionating dose also allows normal tissues to recover while achieving
68 high target dose, which can allow for larger target volumes to include possible microscopic
69 disease within normal tissues. Access to on-board imaging (OBI), cone-beam computed
70 tomography (CBCT), and intensity-modulated radiotherapy (IMRT) have improved CFRT
71 delivery and reduced the organ at risk (OAR) volumes in the treatment field.[11,12] By comparison,
72 SBRT also utilizes these strategies, but higher dose treatments are delivered in 1-5 fractions, and
73 normal tissues are further spared by avoidance.[13] Heart-base tumours are attractive targets for
74 both CFRT and SBRT because: 1) surgically-curative options are limited[14]; 2) they have
75 somewhat well-defined edges, providing for a focused target region, although tumour infiltration
76 will not always correlate with imaging[15,16], and 3) endocrine tumours respond favourably to
77 various fractionation schemes.[17-19] However, lung/heart motion during treatment creates
78 uncertainty, necessitating target-volume expansion. This study assesses survival outcome in dogs
79 receiving definitive CFRT or SBRT for imaging-diagnosed heart-base masses with either 1)
80 tumour-related clinical signs or 2) asymptomatic but progressive tumours, and evaluates clinical
81 outcome and tumour response.
82
83 **Methods:**

This was a retrospective study at the University of California, Davis Veterinary Medical Teaching Hospital from 3/2014–3/2019. Cell lines were not used so no cell-line validation was performed. Electronic medical records were searched for dogs receiving a single CFRT or SBRT course for imaging-diagnosed heart-base masses with follow-up information. Dogs were included if they were intended to receive radiotherapy, and had attributable clinical signs and/or size progression of the mass as determined by serial echocardiogram. Other therapies such as corticosteroids, non-steroidal anti-inflammatories, and non-concurrent chemotherapy were permitted. Included dogs were retrospectively identified by a radiation oncologist.

Signalment, including age, weight, sex, and breed were recorded. Diagnostic results (bloodwork, thoracic radiographs, abdominal ultrasound, echocardiogram, and CT imaging), clinical signs at diagnosis, radiotherapy parameters, follow-up visit information, and survival times were recorded. Response was assessed either by follow-up echocardiogram or thoracic radiographs by comparing images to pre-radiation diagnostics.

Prior to treatment, all cases had a simulation-CT scan with a helical scanner (Lightspeed 16 General Electric Co., Milwaukee, WI). All cases were anesthetized for imaging/treatment, and all SBRT dogs were jet-ventilated with 100% oxygen during imaging/treatments to minimize motion.[20] Patients were positioned head-first sternal in a vacuum-lock bag (SecureVac, Bionix Development Corporation, Toledo, OH). Non-contrast and contrast-enhanced series with 1.3-2.5mm collimation were acquired based on clinician preference.

All CT images were imported into the treatment planning system (Eclipse v. 11, Palo Alto, CA).[11,21] Relevant target volumes were contoured based on attending clinician recommendations which always includes a PTV, whereas the gross tumour volume (GTV) and clinical target volume (CTV) inclusion were clinician-dependent. The relevant OARs were contoured, commonly including the lungs (left, right, and/or both combined), spinal cord, trachea, and oesophagus.

3D-conformal calculations were performed with the anisotropic analytical algorithm (0.25 cm calculation grid) and DVO_11031 was utilized for IMRT, with tissue heterogeneity correction. Treatment plans were evaluated based on PTV dose-volume histogram (DVH) coverage and dose to OARs per clinician. When possible, 95% of the PTV was covered by the prescription dose, and standardized OAR constraints were not in place. All plans were assessed by a QA system (Mapcheck3, Sun Nuclear Corporation, Melbourne, FL) using standard techniques and gamma error.[21]

All treatments were delivered with 6 MV photons using a linear accelerator (TrueBeam, Varian Medical Systems, Palo Alto, CA) with the high-definition multi-leaf collimator (MLC). CBCT scans were acquired each treatment and matched digitally to the simulation-CT. Couch adjustments were automatically registered via software, and couch lateral, longitudinal, vertical, and rotational shifts were made after imaging approval by the clinician, and the dose delivered.

Recheck visits were recommended 2-3 weeks post-radiation, 8-12 weeks post-radiation to assess for pneumonitis, and thereafter every 3-6 months. Data from all rechecks were collected,

including acute side effects (defined as within 3 months post-radiation), late side effects, clinical signs, and survival. Tumour response was recorded based on radiographic/echocardiographic and cardiologist/radiologist assessment. Due to the retrospective nature, RECIST criteria were not applied to define size progression; rather progression was based on cardiologist measurements and written impressions based on comparison to the previous images.

All graphs and statistical analyses were made using software (STATA 14.2, Stata Corporation, College Station, TX; Microsoft Excel 2008 for Mac, Version 12.1, Microsoft Corporation, Redmond, WA). Due to the small sample size, non-parametric tests were used for continuous variables, and descriptive statistics are reported as medians/ranges. To evaluate for differences in age, weight, and PTV between treatment groups, a Mann-Whitney U test was used. To evaluate for differences between treatment protocol groups for categorical variables, a Fisher's exact test was used. The Kaplan-Meier method was used to estimate median overall survival times (MOS). Survival time was defined as between the first treatment day and death, or date of last contact. For censoring, all deaths were considered events, with dogs lost to follow-up or alive at analysis censored. Categorical values evaluated for survival included radiation protocol and brachycephalic breed. PTV volume was evaluated for effect on survival as a continuous variable. To identify differences in estimated survival times between categorical variables, a log rank test was used. To identify differences in survival times for continuous variables, a Cox regression with a Breslow method for ties was done. Due to the small sample size, only univariate testing was done. A p value <0.05 was considered statistically significant.

Results:

Eight dogs met the inclusion criteria (CFRT=5, SBRT=3, Table 1). In total, there were seven male castrates and one female spayed dog. The breeds were as follows: boxer, French bulldog, English Bulldog, pit bull mix, rough-coated collie, Labrador retriever, German shorthaired pointer, and dachshund, of which 4/8 were considered brachycephalic. There was no difference in sex distribution (p=0.63), presence of clinical signs at treatment (p=0.11), or proportion of brachycephalic dogs receiving SBRT vs. CFRT (p=0.50). There was no statistical difference in age (p=0.88), weight (p=0.23) or PTV volume (p=0.05) between dogs receiving SBRT vs. CFRT.

Diagnoses were based on imaging. Thoracic radiographs were available within 4 months pre-radiotherapy (range 26-106 d) for all dogs, revealing: a suspected heart-base mass (8), with tracheal deviation (3), widened cranial mediastinum (2), and cardiomegaly (3). All dogs had echocardiograms identifying the mass within 4 months pre-radiotherapy (range 10-102d), and revealed: pericardial effusion (2), compressed main or branch pulmonary artery (2), obstructed cranial vena cava inflow (1), pleural effusion (1), and elevated right ventricular pressure from pulmonary artery obstruction (1). In 5/8 cases, serial echocardiograms were performed pre-radiotherapy showing no change from baseline (2), progressive enlargement (3), improved systolic function after concomitantly diagnosed taurine deficiency and supplementation (1), and newly developed pericardial effusion (1). Electrocardiograms (ECG) leads were reported for 4/8 cases pre-radiotherapy, revealing normal rhythm (2) and rare ventricular premature contractions (VPC) (2).

Abdominal ultrasound was performed within 4 months (range, 0-120 d) pre-irradiation in 6/8 dogs revealing: thickened gall bladder wall (1), asymptomatic but possible biliary duct dilation (1), hyperechoic liver nodule (1), splenic nodules (2), unremarkable abdomen (2). Routine bloodwork was available within seven weeks (range 0-47 d) of starting radiotherapy, and no results were considered clinically significant.

Three dogs were previously diagnosed with other cardiovascular-related conditions: 1) a taurine-responsive cardiomyopathy with resolved congestive heart failure; 2) a chylothorax secondary to the heart-base mass treated with lung lobectomy, pericardiectomy, and caval stent placement; and 3) partial seizure vs. syncopal events. Other notable historical diseases included cutaneous hemangiosarcoma with doxorubicin administration four years prior to heart-base radiotherapy, and suspected nodular liver hyperplasia ultimately reassigned as liver carcinoma.

Six dogs had clinical findings attributed to their mass, including: retching/coughing (4), exercise intolerance (2), pericardial effusion (2), rare VPCs (2), collapsing episodes (1), ascites from caval obstruction (1), and respiratory distress with chylothorax (1). Both asymptomatic dogs received SBRT, and due to small sample size, statistics were not performed regarding clinical signs and outcome. The two asymptomatic dogs had progressive tumour enlargement on serial echocardiograms (tumour diameter measured on both axes increased by 60% over 5 months, and by 69% over 6 months pre-radiotherapy, respectively).

All dogs had a CT-scan for radiotherapy planning. The CT characteristics were as follows: all masses were round/lobular, soft-tissue attenuating, contrast-enhancing (heterogeneously, n=6),

and involving the heart-base. Cardiac or vascular compression was observed as follows: pulmonary artery (3), cranial vena cava (1), right atrium (1). Effusions were noted: pleural (1), pericardial (2), ascites (1). Caudal vena cava distension was appreciated in the dog with ascites.

GTVs included all contrast-enhancing tumour; CTV was not contoured. The PTV was a 3 or 5 mm isometric expansion around the GTV for both SBRT and CFRT cases (Figure 1A); 3 mm margins were used for smaller dogs.[11,22,23] For one SBRT case with PTV overlapping oesophagus and trachea, these OARs were specifically cropped for IMRT-optimization. For all other cases, no OAR cropping was performed. A summary of PTV volumes is shown in Table 2.

All cases used a single isocentre IMRT technique (7-11 field, sliding window; n=7) or 3D-conformal, 12 isocentric static fields (n=1) (Figure 1B). Bolus was not used. The dose was prescribed to 95% of the PTV, except one SBRT target was prescribed to 90% of the PTV due to concern for oesophageal dose. The target and OAR doses are described in Tables 3-5. The median dose to all PTVs was 105.2% (range [103.8-109.4%]), and an isodose colourwash and DVH are shown in Figure 1C-D.

Oesophageal median dose was 3.6% of prescription, with maximum doses not exceeding 4.2 Gy/ fraction for SBRT. Heart dose was within accepted limits, with maximum dose <113% of prescription for all cases, median < 5 Gy for SBRT cases, and < 14 Gy for CFRT cases, although one SBRT case did exceed the human recommended volume-dose[24]. D2 and D98 are values that may better represent dose heterogeneity, with D2 representing the hottest 2% of the contour and D98 representing the coldest 2%. The median D2=109% of prescription (range 106-112%),

median D98=97% (range 73-98%), and PTV median dose ranged from 103.8-109.4%. Other recommended reporting data are located in Tables 3-4.[25]

Conformity Index (CI) describes how dose conforms to the PTV, with values < 2 recommended, values closer to 1 ideal, and two different common equations utilized. CI does not account for whether the dose is in the same location at the target.[26-28] Gradient index (GI) describes how quickly the dose drops outside the PTV, with smaller values representing steeper gradients.[29] Heterogeneity index (HI) describes PTV dose variation, and can be calculated with the simpler Radiation Therapy Oncology Group (RTOG) calculation where < 2 is ideal, or with a more strict calculation using D98 and D2 (this calculation reveals more heterogeneity; values will vary widely by plan although the ideal value is 0) .[28] Table 6 shows that all CI were reasonably close to unity (median CI=0.81 and 1.10, based on two different equations, respectively[26,28]), GI was similar to the Paddick study for stereotactic wherein GI values were 2.4-3.3[27] (median GI=3.35 in the current study), all cases had acceptable RTOG HI (median HI=1.12), and 7/8 cases had alternate HI values ≤ 15 suggesting some heterogeneity in the approved plans.[29] Values for CI, GI, and HI were only evaluated retrospectively and were not used in plan approval.

Seven dogs began treatment within 7 months of diagnosis (median time from diagnosis=3.1 months [range 0.9-33.3 months]). One initially asymptomatic patient commenced radiation 33 months post-diagnosis, but after subsequent progression, mild pericardial effusion, and collapse episode.

Three dogs received SBRT (30 Gy in five fractions (2), or 24 Gy in 3 fractions (1), on consecutive days), while five dogs received 50 Gy in 20 fractions. There were no treatment interruptions or protocol deviations, and no early adverse effects recorded. In total 3/5 dogs receiving CFRT commenced 0.4-0.5mg/kg per os daily prednisone halfway through treatment, and tapered off 2-5 weeks post-radiation. All cases were rechecked within 10 weeks. After radiation, one dog received metronomic chlorambucil to address another concurrent neoplasia. Another dog began toceranib phosphate after progressive atrial invasion was noted 4 months post-radiation.

All dogs had at least one post-radiation imaging study. Six dogs had at least one follow-up echocardiogram 1-11 months post-irradiation for comparison to pre-radiotherapy echocardiogram. Response was observed in 4/6 dogs with follow-up: one dog had steady tumour shrinkage with a complete response and no tumour visible on echocardiogram by 16 months post-irradiation, and 3/6 had tumour volume reduction, ranging from 8-75% reduction based on the longest axis measurements recorded, within 3.5-11 months post-irradiation. One dog had static disease for 11 months, but tumour progression by 25 months. One dog had tumour progression by 3 months post-irradiation. The remaining two dogs had follow-up thoracic radiographs: one dog at 2 months post-irradiation (static compared to previous radiographs, without further imaging performed) and one dog after developing clinical signs 1-year post-irradiation with a progressive tumour. In summary, in our small dataset, 4/8 dogs had some degree of response with tumour volume reduction via follow-up echocardiogram, and 2/8 dogs had static masses reported 2 and 11 months post-radiation. Mass progression was noted at 3 months and 1 year post-radiation in the other 2/8 dogs.

Subjective clinical improvement was reported in 5/6 symptomatic dogs. The dog requiring abdominocentesis pre-radiotherapy had reduced procedure frequency from weekly pre-irradiation to 1-2 monthly post-radiotherapy. Of the clinically improved cases during the first-year post-treatment: 2/5 had tumours shrink, 2/5 had static tumours, and 1/5 did not have follow-up imaging within a year.

Seven dogs were deceased at analysis (follow-up period 114-1492 d), and one dog remained alive 684 d, with a 1-year echocardiogram revealing 75% diameter reduction. One dog had a necropsy-confirmed malignant paraganglioma; this dog had the shortest outcome and also cranial cava invasion pre-treatment. No dogs were lost to follow up, and one living dog was censored from MOS. The MOS=785 d (95% CI 114-868 d; range 114-1492 d) (Figure 2). For the five CFRT cases, the MOS=817 d (95% CI 115 d – upper limit not reached), and for the three SBRT cases, the MOS=414 d (95% CI 114 d – upper limit not reached). Although the MOS for CFRT was nearly twice that of SBRT-treated dogs, the difference was not statistically significant ($p=0.22$). The MOS for the six symptomatic dogs=817 d (95% CI 155 d – upper limit not reached; range 155-1493 d). The two asymptomatic dogs had survival times of 114 d and 414 d. Statistical differences in survival were not found between brachycephalic vs. non-brachycephalic ($p=0.16$). Weight ($p=0.31$) and PTV ($p=0.56$) were not significant prognostic factors.

Because there were eight cases, minimal necropsies, and cause of death confounded by the heart-base mass itself, cause-specific survival was not assessed. Still, one dog was euthanized due to progressive orthopaedic disease (1,492 d), one died from metastatic bladder carcinoma (817 d),

and one had suspected disseminated cancer from another location at euthanasia (785 d). A fourth dog was diagnosed with primary liver carcinoma with suspected metastasis coincident with right heart failure and heart-base mass progression, so both disease processes contributed to euthanasia. Interestingly, the dog still alive at 684 d post-radiotherapy was the only case with right atrial involvement, and eventually received toceranib phosphate following atrial invasion 4 months post-irradiation.

Acute adverse effects included non-clinical, radiographically-diagnosed pneumonitis in 4/8 dogs (SBRT=1/3, CFRT=3/5), all imaged within 10 weeks post-radiation. No overt signs of tracheitis or esophagitis were reported. A total of 4/8 dogs (SBRT=2/3, CFRT=2/5) developed atrial arrhythmias post-irradiation. Occasional VPCs were noted in 3/4 dogs that developed atrial arrhythmias, and 2/3 also had VPCs pre-radiotherapy. Atrial tachycardia was identified 8-13 weeks post-radiotherapy in 3/4 dogs with arrhythmias; 2/3 had weakness or collapse coinciding with arrhythmia onset, 1/3 had no referable signs, and all were clinically managed with sotalol (Bayshore Pharmaceuticals, Short Hills, NJ). Of these acute onset arrhythmias, 2/3 dogs had progressive masses at arrhythmia diagnosis (SBRT (1), CFRT (1)), with one dog having static disease (SBRT). The CFRT case with an acute arrhythmia also developed concurrent right-sided congestive heart failure from pulmonary arterial obstruction, received a pericardiectomy, but was euthanized for disseminated liver carcinoma and congestive heart failure 3 months post-irradiation. The remaining dog with a late-onset arrhythmia (CFRT) was diagnosed 11 months post-radiotherapy. This dog did not have recorded clinical signs, but the arrhythmia coincided with increased, chronic ascites.

Discussion:

This study provides preliminary evidence that CFRT and SBRT may be effective treatments for canine heart-base tumours, with MOS=785 d. In total, 5/6 cases with clinical signs pre-radiation had clinical improvement post-irradiation, and 4/8 had some degree of tumour size reduction. Half of dogs developed cardiac-related complications either related to the tumour or complicated by radiotherapy, including new atrial arrhythmias. Metastasis from heart-base tumours was not definitively identified; however, three were diagnosed with other neoplasia, making it impossible to elucidate origin without necropsy.

In this study, no survival difference was found between CFRT vs. SBRT. The Biologically Effective Dose (BED) for 8 Gy X 3 (BED_{10} 43.2, BED_3 88), and 6 Gy X 5 (BED_{10} 48, BED_3 90), have lower BED_{10} tumour-efficacy values than our CFRT protocol (BED_{10} 62.5, BED_3 91.7). Likewise, for the Biologically Equivalent Dose in 2-Gy fractions ($EQD2_{a/b}$): for 8 Gy X 3 ($EQD2_{10}$ 36, $EQD2_3$ 52.8) and 6 Gy X 5 ($EQD2_{10}$ 40, $EQD2_3$ 54), the $EQD2_3$ are similar to slightly lower for these SBRT protocols than for the CFRT protocol ($EQD2_{10}$ 52.1, $EQD2_3$ 55). This $EQD2_3$ value may be more relevant for normal tissue damage than BED_3. Importantly, EQD2 and BED values are somewhat controversial in terms of applicability to SBRT protocols, but one would expect our CFRT to have superior cell kill and similar to slightly worse normal-tissue effects than our SBRT based on these calculations. T_{pot} is the time required for a tumour to double in size and considers both the number of cells cycling and how quickly they progress through the cycle. Accounting for T_{pot} may result in similar tumour-efficacy values between the different protocols. Although CFRT provided longer survival times, the survival difference was not statistically significant. Additional cases would help determine a difference.

SBRT and CFRT may differ in side effects and tumour kill, such that higher dose per fraction may result in more effective cell kill or more side effects. Our BED values are somewhat lower than others published.[9,10] Still, all studies (inclusive of this one) of heart-base radiation report long-term survivors. Like other endocrine tumours, heart-base tumours may respond to a variety of protocols/doses.[17-19] Importantly, whenever a protocol offered has fewer treatments, one introduces impactful case-selection bias as owners with sicker animals may pursue SBRT where they otherwise would not pursue weeks of treatments. These animals might have worse outcomes regardless of protocol, which is not easily assessed in pet dogs because of owner-input. There may also be clinician bias in offering SBRT for smaller or less symptomatic tumours, and we may see such a trend when Tables 1-2 are analysed in combination: smaller tumours and asymptomatic dogs are in the SBRT group. Regardless, these expedient SBRT protocols remain an attractive option for owners despite potential differences in risks/outcomes.

SBRT PTVs are minimized to reduce unnecessary normal-tissue dose from the high dose per fraction. Target location is known with greater certainty using on-board CBCT imaging and/or jet ventilation to reduce lung motion, so only 3-5 mm PTV expansions were used for the TrueBeam linear accelerator.[12,30,31] Even with image guidance, narrow PTV expansion may lead to geographic misses, especially with sharp dose gradients. The utilized PTV margin may have been inadequate for some cases. Planning constraints may ultimately influence outcome, but are difficult to study in small cohorts. Our median PTV dose was between 100-110% of prescription. The global dose maximum was <113%, which is acceptable at this institution. Additionally, the CI, GI, and HI indices for nearly all plans were within limits. However, minimum dose ranged

357 from 43.9-86.5%, demonstrating that cold spots were permitted, especially near the oesophagus
358 for SBRT.
359
360 Table 5 shows recommended OAR dose limits for stereotactic (6-8 Gy fractions, 5-doses) and
361 conventional (2-Gy fractions) protocols for humans alongside our values.[24] We met human
362 constraints for spinal cord and oesophagus. For SBRT, one trachea volume exceeded
363 recommendations; however, the point maximum dose was 6.3 Gy/fraction, and the canine
364 trachea can tolerate more radiation than some structures.[32] One SBRT case had 25cc of heart
365 receive 32 Gy, although the median/maximum doses were within tolerance. Lung volumes
366 remain difficult to compare in humans vs. dogs. The dog lung volume is 30-50% of humans;
367 therefore, we have 1/3 of the lung volume receiving the human-recommended dose. The largest
368 volume receiving 13.5 Gy was only 161.2cc in our study. Overall, the doses delivered to normal
369 tissues were acceptable, albeit with limited follow-up, and noting that half of cases developed
370 new arrhythmias post-radiotherapy, possibly related to radiation or to the tumour itself.
371
372 Regarding side effects, pneumonitis is expected when treating lung-adjacent targets. In our
373 clinical experience, most dogs with radiographically-diagnosed pneumonitis have no referable
374 signs. In contrast, the atrial tachycardia seen in our cohort, and reported in one other published
375 study, could be of concern, as arrhythmias can lead to exercise intolerance, weakness, heart
376 failure, or sudden death.[10] It is difficult to elucidate radiation vs. tumour-related effects, as up to
377 43% of heart-base tumours are locally infiltrative; therefore, the tumour itself can lead to
378 arrhythmias and effusions, in addition to mechanical flow obstruction.[4] Our heart doses were
379 mostly within human recommendations, and humans may have comorbidities of heart-disease

and lifestyle that increase complication risks. Still, the studied tumour herein arises from heart structures, so these hearts may be more susceptible to radiation complications. The canine heart may also be more inherently vulnerable, or the tumour itself may have caused arrhythmias.

Based on our experience and other reports, we recommend following cases with ECG and echocardiograms to assess for arrhythmias, heart function, and tumour size. Specifically, an ECG pre-radiation, and at regular intervals starting 1-2 months post-radiotherapy, may be warranted, as some arrhythmias may require treatment, and assessing how commonly these arrhythmias are clinically relevant will be useful information to collect. Finally, based on our observation of arrhythmias as a potential clinically-relevant complication, at our institution we currently recommend radiotherapy for newly diagnosed heart-base tumours when they have 1) clinical signs referable to the mass, and/or 2) documented tumour growth on subsequent imaging. There are many dogs diagnosed incidentally that may not develop clinical signs or appreciable growth for years, and the limited data from this study and the previous SBRT study[10] may be early evidence of potential radiation-related complications. For progressive, but non-clinical, heart-base tumours, it is unclear if/when they will be clinically affected by their tumour without treatment; therefore, one might inform owners of the limited data regarding acute and late arrhythmia complications with radiotherapy. A larger study with frequent follow-up with EKG, echocardiogram, and tumour measurements is warranted.

Our survivals are similar to those seen with toceranib phosphate alone.[7] However, 21% of dogs in that study had no pre-treatment signs and achieved only SD, so it is warranted to further investigate toceranib phosphate in a population similar to our study with progressive

403 asymptomatic tumours, or tumours causing signs. The upfront cost and anaesthesia associated
404 with radiotherapy are significant compared to short-term toceranib phosphate administration;
405 however, the long-term financial costs of the two options may be similar over the lifetime of a
406 dog. Knowing more clearly whether toceranib phosphate is comparable to radiation for
407 clinical/progressive cases is valuable. Only one case in our study received toceranib phosphate,
408 and this patient was still alive at 684 days.
409
410 It is not possible to unequivocally determine whether radiotherapy improved pericardial effusion
411 that was present pre-radiotherapy. Although radiotherapy may improve effusions, it can cause
412 effusions (though rarely acutely, more commonly months to years post-radiation).[9,33] Importantly,
413 protracted survivals have been reported with pericardiectomy alone.[6]
414
415 There are limitations to this study. There are few dogs in this series, which limited our
416 assessment of prognostic factors. There was no control group to indicate the disease course in
417 untreated dogs with similar clinical signs. Moreover, all cases had a heart-base tumour on
418 echocardiogram; however, location is not pathognomonic for tumour type.[34] Complete staging
419 was not always performed, as is common in retrospective veterinary studies. There was not
420 consistent imaging follow-up or consistent timing for imaging after treatment. In some cases, the
421 pre-radiation echocardiogram was months before treatment, and post-radiation imaging was
422 months after treatment, so partial responses may have occurred while stable disease was recorded
423 because of the limited time points. Mass reduction was not based on RECIST criteria, rather on
424 echocardiographic assessment and clinical judgement. Additionally, stable disease could be
425 related to radiotherapy, or the nature of slow progression, so stable disease is difficult to

426 accurately capture in this population. Furthermore, different protocols, treatment planning
427 approaches and delivery techniques limit this study. Finally, lack of statistical differences
428 between some groups could be due to low power or a type II error.
429
430 In conclusion, IMRT-based and 3D-conformal SBRT and CFRT appear to be effective treatment
431 options for clinically relevant heart-base tumours with MOS=785 d , and they may also provide
432 clinical improvement. The role of radiation therapy for static, asymptomatic heart base tumours
433 still needs to be determined. Short-term and late-term side effects cannot be ruled out in those
434 that had cardiovascular clinical signs at death, and arrhythmias were seen in a high proportion of
435 dogs in this study. Further assessment of SBRT and CFRT techniques for heart-base tumours is
436 warranted, and fractionation may need modification to maximize benefit and minimize late side
437 effects.

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Table 1: Patient Population Description

		Median age (years) Range [6.0-13.5]	Median weight (kg) Range [7.4-40.7]	Clinical signs at the time of radiation[§]	
				Yes	No
All dogs (n= 8)		9.7	22.3	6	2
By Treatment Scheme	**SBRT[†] (n= 3)**	10.1	39.0	1	2
	CFRT[‡] (n= 5)	9.2	21.3	5	0

[†] Stereotactic Body Radiotherapy (SBRT). One patient received 8 Gy X 3 doses, two patients received 6 Gy X 5 doses.
[‡] Conventional Fractionated Radiotherapy (CFRT).
[§] Tumour-attributed clinical signs included respiratory distress (n= 1), coughing or retching (n= 4), lethargy (n= 2), collapse (n= 1). Clinical findings in this group also included pericardial effusion (n= 2) and abdominal effusion (n= 1).

Table 2: Mean, Median, and Range for Planning Target Volumes in Centimetres Cubed (cc)

	PTV† Total Volume (cc)		
	All Dogs (n= 8)	**SBRT‡ (n= 3)**	**CFRT§ (n= 5)**
Mean	172.9	80.6	228.2
Median	152.4	84.4	191.3
Range	35.5-403.1	35.3-122.2	88.7-403.1

† Planning Target Volume (PTV)
‡ Stereotactic Body Radiotherapy (SBRT)
§ Conventional Fractionated Radiotherapy (CFRT)

Table 3: Dose Characteristics for All Planning Target Volumes Relative to Prescribed Dose

	All Dogs (n= 8)			SBRT [§§] (n= 3)			CFRT [¶¶] (n= 5)		
	Overall Mean	**Overall Median**	**Overall Range**	**Overall Mean**	**Overall Median**	**Overall Range**	**Overall Mean**	**Overall Median**	**Overall Range**
Min[†]	0.71	0.77	0.44-0.87	0.70	0.80	0.44-0.86	0.71	0.77	0.54-0.87
Max[‡]	1.11	1.12	1.10-1.12	1.11	1.11	1.10-1.12	1.12	1.12	1.11-1.12
Mean[§]	1.05	1.05	1.02-1.08	1.05	1.05	1.02-1.08	1.05	1.05	1.03-1.08
Median[¶]	1.06	1.05	1.04-1.09	1.06	1.05	1.04-1.09	1.06	1.05	1.04-1.09
D2[††]	1.09	1.09	1.06-1.12	1.09	1.08	1.07-1.11	1.09	1.09	1.06-1.12
D98[‡‡]	0.94	0.97	0.73-0.98	0.89	0.96	0.73-0.97	0.97	0.97	0.96-0.98

[†] Minimum dose to the planning target volume (PTV) relative to prescribed dose
[‡] Maximum dose to PTV relative to prescribed dose
[§] Mean dose to PTV relative to prescribed dose
[¶] Median dose to PTV relative to prescribed dose
[††] D2= dose to 2% of PTV (i.e., highest dose to PTV) relative to prescribed dose
[‡‡] D98= dose to 98% of PTV (i.e., lowest dose to PTV) relative to prescribed dose
[§§] Stereotactic Body Radiotherapy (SBRT)
[¶¶] Conventional Fractionated Radiotherapy (CFRT)

Table 4: Dose Characteristics for Select Organs at Risk, Relative to Prescribed Dose for All Cases

	Oesophagus (n= 3)			**Heart (n= 7[†])**			**Spinal Cord (n= 8)**		
	Overall Mean	**Overall Median**	**Overall Range**	**Overall Mean**	**Overall Median**	**Overall Range**	**Overall Mean**	**Overall Median**	**Overall Range**
Min[‡]	0.005	0.006	0.004-0.006	0.01	0.006	0.005-0.035	0.001	0.001	0.000-0.003
Max[§]	0.74	0.7	0.42-1.10	1.1	1.1	1.07-1.12	0.46	0.36	0.22-0.95
Mean[¶]	0.16	0.14	0.08-0.26	0.30	0.33	0.20-0.37	0.09	0.08	0.02-0.20
Median[††]	0.04	0.04	0.03-0.04	0.17	0.16	0.04-0.28	0.02	0.02	0.00-0.06

[†] The remaining dog had Heart minus Planning Target Volume (PTV) contoured for the Heart organ at risk (OAR), with values slightly lower when compared to the other cases with heart data

[‡] Minimum dose to the OAR relative to prescribed dose

[§] Maximum dose to OAR relative to prescribed dose

[¶] Mean dose to OAR relative to prescribed dose

[††] Median dose to OAR relative to prescribed dose

570 Table 5: Dose Limit: Human Recommendations versus Current Study Population

		Recommended	Current Study
Oesophagus	**SBRT**[‡] **(n= 2)**	Max[¶] < 35 Gy	Max 12.5 & 20.9 Gy
		< 5 cc 19.5 Gy	< 0.01 cc 19.5 Gy
	CFRT[§] **(n= 1)**	Mean < 35 Gy	Mean 13.1 Gy
		Recommended	**Current Study**
Lung	**SBRT (n= 3)**	1500 cc receives 13.5 Gy	24.7-161.2 cc received 13.5 Gy
	CFRT (n= 5)	V20[††] < 37%	V20 0-24.5%
		Mean < 20 Gy	Mean 1.3-12.8 Gy
		Recommended	**Current Study**
Trachea	**SBRT (n= 3)**	Max < 40 Gy	Max 31.6 Gy
		< 4 cc 16.4 Gy	*27.2 cc 16.4 Gy in one case*[‡‡]
	CFRT (n= 5)	N/A	Max 53 Gy
		Recommended	**Current Study**
Heart[†]	**SBRT (n= 3)**	Max < 38 Gy	Max 26.3-33.7 Gy
		< 15 cc 32 Gy	*25 cc 32 Gy in one case*[§§]
	CFRT (n= 4)	67% < 45 Gy	Max 11.9 % 46 Gy
		33% < 60 Gy	Max dose 55.95 Gy

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572 [†] The remaining dog had 'Heart minus Planning Target Volume (PTV)' data, with lower values compared to cases with 'Heart' data
573 [‡] Stereotactic Body Radiotherapy (SBRT)
574 [§] Conventional Fractionated Radiotherapy (CFRT)
575 [¶] Maximum dose to organ
576 [††] Volume receiving 20 Gy less than 37%

577 ‡‡ Trachea recommended dose not met in one SBRT case
578 §§ Heart recommended dose not met in one SBRT case
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Table 6: Conformity, Gradient, and Heterogeneity Indices for All Cases, SBRT, and CFRT

		Overall Mean	Overall Median	Overall Range
CI[†]	**All Dogs (n= 8)**	1.08	1.10	0.99-1.17
	SBRT[‡‡] **(n= 3)**	1.09	1.10	1.03-1.13
	CFRT[§§] **(n= 5)**	1.08	1.10	0.99-1.17
CI[‡]	**All Dogs**	0.82	0.81	0.72-0.91
	SBRT	0.79	0.79	0.72-0.86
	CFRT	0.83	0.81	0.77-0.91
GI[§]	**All Dogs**	3.34	3.35	2.98-3.78
	SBRT	3.51	3.60	3.16-3.78
	CFRT	3.24	3.33	2.98-3.53
HI_{RTOG}[¶]	**All Dogs**	1.12	1.12	1.10-1.20
	SBRT	1.11	1.11	1.10-1.12
	CFRT	1.13	1.12	1.11-1.20
HI[††]	**All Cases**	14.84	12.90	9.92-33.23
	SBRT	19.68	15.00	10.79-33.23
	CFRT	11.94	12.58	9.92-13.54

[†] Conformity Index (Volume of 100% isodose line / PTV volume)

[‡] Conformity Index (PTV volume getting Rx)^2 / (PTV volume * volume of 100 % isodose line)

[§] Gradient Index (Volume of 50% / Volume of 100%)

¶ RTOG Heterogeneity Index (PTV Maximum / Rx)

†† D2-D98 Heterogeneity Index (PTV D2 – PTV D98 / Rx * 100)

‡‡ Stereotactic Body Radiotherapy (SBRT)

§§ Conventional Fractionated Radiotherapy (CFRT)

Figures Legends:

Figure 1: Representative planning for a CFRT heart-base radiation case. A, Contouring for the heart (magenta), Gross Target Volume (pink), and planning target volume (PTV) expansion (red). B, Field distribution for a 7-field IMRT. C, Dose cloud showing 50% of prescription dose (blue) through 100% dose and higher (red). D, Dose-Volume Histogram demonstrating the dose to targets and organs at risk, with PTV (red), heart (magenta), lung lobes (yellow and light green), oesophagus (brown), and body (bright green) shown.

Figure 2: Kaplan Meier survival curves. A, Median overall survival (MOS) for all cases, and B, Stereotactic Body Radiotherapy (SBRT, dotted line) vs. Conformal Radiotherapy (CFRT, solid line) survival for dogs receiving radiation therapy for suspected heart-base tumours. Eight dogs were treated with radiation, resulting in a MOS of 785 days (95% CI 114-868 days, range 114-1492) for all cases. The MOS for CFRT cases was 817 days, and the MOS for SBRT cases was 414 days, which were not found to be statistically different ($p= 0.22$). One dog was still alive at 684 days at the time of manuscript preparation, and had been treated with SBRT. Censoring is indicated by a hash mark.