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# Response of canine thyroid carcinomas to radioiodine

Running title: Radioiodine for canine thyroid carcinoma

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## Abstract

Radioactive iodine ($^{131}$I) has previously been reported to prolong survival in dogs with thyroid carcinoma. This study aimed to describe tumour response and progression-free interval (PFI) in dogs with thyroid carcinomas treated with $^{131}$I. Secondary aims were to describe overall survival time (OST) and prognostic factors. A bi-institutional retrospective review of records identified 66 dogs with thyroid carcinoma treated with $^{131}$I from January 2010–April 2020. Response was described using RECIST, or a subjective response assessment where specific tumour measurements were not available. Forty-eight dogs (72.7%) were treatment-naïve and 18 dogs (27.3%) had received prior therapy at the time of $^{131}$I treatment. Objective responses were available for 34 dogs and subjective responses for 58 dogs. The overall response rate (ORR) was 35.3% (4 complete and 8 partial responses). Improvement of clinical signs was seen in 76.2% of dogs (32/42). Kaplan-Meier-estimated median PFI (95%CI) was 301 (217-578) days and OST (95%CI) was 564 (421-865) days. Prior therapy was associated with a lower hazard for progression (HR 0.260 95%CI 0.123-0.548, *P*=0.0004). Treatment of thyroid carcinoma using $^{131}$I can effectively alleviate clinical signs and reduce disease burden in a proportion of dogs.

## 1. Introduction

Thyroid carcinomas are one of the most common endocrine malignancies in dogs.[1, 2] Approximately 60-90% of tumours originate from follicular cells, with most being iodine-trapping.[1, 3-5] Thyroid carcinomas have a high malignant potential, with between 16-38% of dogs reported to have metastatic disease at

diagnosis, most commonly affecting regional lymph nodes and lungs.[4, 6] Factors thought to contribute to increased metastatic potential include increased tumour size, macroscopic and histological evidence of vascular invasion and tumour location, with bilateral tumours being 16 times more likely to metastasise than unilateral tumours.[2, 6-8]

Surgical excision is the treatment of choice for non-metastatic, mobile tumours, however, only approximately 25-50% of cases are amenable to surgery, due to large tumour size and fixation to underlying tissues.[5, 9-11] Treatment with external beam radiation therapy (RT) has been reported for non-resectable, advanced stage thyroid carcinomas.[9, 12-14] Medical treatment for non-resectable tumours using platinum-based chemotherapy or doxorubicin results in variable outcomes, with 30-50% tumours showing some response.[15, 16] More recently, the tyrosine kinase inhibitor toceranib phosphate, has been reported in the management of unresectable thyroid carcinomas.[17, 18]

Radioactive iodine ($^{131}$I) has been utilised for the treatment of thyroid carcinoma in humans since the 1940s.[19] One study reported the outcomes of 31 dogs with thyroid carcinoma treated with $^{131}$I with a MST of 30 months, compared with 3 months for 7 untreated dogs.[20] In this study, one cohort was treated with a calculated dose of $^{131}$I, and another with a standard 1600Mbq dose - no difference in outcome was identified.[20] Another study reported outcomes of 39 dogs with nonresectable thyroid tumours treated with a calculated dose of $^{131}$I based on tumour size, results of thyroid scintigraphy and elevated thyroxine (T4), and reported a shorter MST for dogs with stage IV disease (i.e. with distant metastasis) compared with stage II or III.[21] $^{131}$I dose optimisation for the treatment of canine thyroid carcinomas is yet to be thoroughly investigated in veterinary oncology.

Although $^{131}$I may provide a survival benefit for dogs with thyroid carcinoma, tumour response following treatment has not been clearly described. Further, duration of tumour control has not been reported, and prognostic factors have not been clearly defined. Therefore, the aims of this retrospective study were to describe the response and duration of control of thyroid carcinomas in dogs treated with $^{131}$I. Secondary aims were to identify prognostic factors, adverse events (AEs) and assess survival outcomes.

## 2. Methods

### Patient selection

This bi-institutional retrospective study reviewed the medical records for dogs treated with $^{131}$I between January 2010 and April 2020. Eligible cases included: (a) diagnosis of thyroid neoplasia by cytology or

histology, and positive radiotracer uptake on scintigraphy, or high serum total thyroxine (T4) concentration with a tissue diagnosis of thyroid neoplasia; (b) measurable disease at the time of treatment, and (c) details of prior, concurrent, or subsequent therapies. Increased radiotracer uptake was determined by subjective assessment of the tumour site or site of previous surgery relative to salivary glands and compared with the contralateral thyroid lobe, or by calculating the thyroid:salivary gland ratio > 1.12:1+/-0.13 (mean+/-SD).[22] To be included in the response analysis, cases required at least one documented response assessment post-$^{131}$I. All dogs were retrospectively staged according to the modified WHO classification for tumours of domestic animals.[23] Metastatic or multicentric disease was classified by presence of pulmonary nodules on imaging, cytologically or histologically confirmed metastasis from enlarged regional lymph nodes, or non-physiological uptake of radiotracer in the area of regional lymph nodes, thorax or abdomen. For dogs with eutopic thyroid tumours, radiotracer uptake in areas other than the neck were presumed to be metastasis, though ectopic disease could not be excluded. In cases of dogs with increased radiotracer uptake in abdominal organs, cytological confirmation of metastasis was required for inclusion. Cytology was not required to confirm pulmonary metastasis based on thoracic radiographs, computed tomography (CT) or scintigraphy. Additional information collated from the records included: signalment, tumour location, clinical signs at diagnosis, longest diameter of tumour measurement (mm), baseline clinicopathologic testing, total T4 values, staging information, AEs following $^{131}$I, date of disease progression, treatment for thyroid carcinoma prior to and following $^{131}$I, duration of follow-up, concomitant medications, and date and cause of death. Referring veterinarians were contacted for additional follow-up details where required. Tumour size was based on recorded calliper measurements, cervical ultrasound measurements, or CT measurements. Adverse events were retrospectively graded according to the Veterinary Radiation Therapy Oncology Group (VRTOG) and Radiation Therapy Oncology Group (RTOG) radiation morbidity scoring scheme.[24, 25]

Thyroid scintigraphy involved administration of intravenous sodium pertechnetate ($Na^{99m}TcO_4$; 40-279 MBq) and, within 30 minutes, left and right lateral and ventral-dorsal images were captured of the neck and thorax using a gamma camera† with all-purpose collimator and 256 X 256 X 16 matrix, for a total of 400 kcounts. Treatment with $^{131}$I was administered either orally or subcutaneously, with a prescribed dose of 1600 Mbq (43.2 mCi) per dog.[20] Dogs were housed in a nuclear medicine ward for a minimum of 7 days (range 7 – 15 days), and were discharged from hospital once the ambient dose measured at a distance of 1 metre from the dog was below 25 µSv/hour, per the Australian Radiation Protection and Nuclear Safety Agency (ARPANSA) radiation safety guidelines.[26]

## Response assessment

Tumour response was reported using the response evaluation criteria for solid tumours in dogs v1.0 (cRECIST v1.0) based on records of calliper or imaging measurements of the primary tumour.[27] Progressive disease (PD) was defined as an increase in the longest diameter of the tumour size of at least 20%, appearance of new lesions i.e. new pulmonary nodules, enlarged regional nodules or other lesions cytologically confirmed as metastasis, or worsening of associated clinical signs. Dogs with disappearance of all lesions were designated a complete response (CR). Subjective response criteria were also applied for dogs with clinical signs, or that did not have consistent tumour measurements recorded. Dogs that showed improvement in clinical signs, subjective reduction in the tumour size, or stable tumour size were designated a 'non-complete response clinical benefit' (non-CR CB). Responses were maintained for at least 90 days or were designated PD. Dogs that received prior therapy were required to have measurable local or metastatic disease based on physical examination or imaging at the time of $^{131}$I treatment.

## Data analysis

Patient and tumour characteristics were described by frequency tables and summary statistics. Progression-free interval (PFI) and overall survival time (OST) were described using the Kaplan-Meier estimator in the 'survival' package in R version 4.0.3 (R Foundation). Dogs that were alive, or had died, without PD were censored in progression analysis. Dogs that were alive at last contact or lost to follow-up were censored in survival analysis. Dogs that received more than one treatment with $^{131}$I were censored for survival at the time of the second treatment. Dogs that received external beam radiation <8 months prior to $^{131}$I progression were excluded from the response analysis, given the potential for ongoing antitumour effect.[14] Dogs that received other treatment for thyroid carcinoma after $^{131}$I but prior to documented progressive disease were censored from the PFI and response analysis at the time of the other treatment. Evaluation of prognostic factors was conducted with an illness-death model (a state-transition model).[28] The subject states were treated (1), progressed (2), and deceased from any cause (3). Transitions were allowed from state 1 to 2 (disease progression), state 1 to 3 (death before progression), and state 2 to 3 (death after progression). The transition dataset was prepared using the 'mstate' package.[29, 30] A Cox proportional-hazards model was fitted for each transition using R package 'survival'.

Candidate predictors included age at diagnosis, tumour stage, clinical signs at diagnosis, hyperthyroidism, presence of hypercalcemia, subjective response, prior therapy, treatment following progression, and dose of $^{131}$I (MBq/kg). Precision of the estimates was assessed using 95% confidence intervals. Age was

nominated as a confounding variable, and other predictors were age-adjusted. Predictors were assessed in a univariable fashion as the available data were not sufficient to support multivariable modelling.

## 3. Results

### Patient and tumour characteristics

Seventy-four dogs were diagnosed with thyroid carcinoma and treated with radioactive iodine between January 2010 - April 2020. Eight dogs were excluded due to insufficient follow up. Of the 66 included cases, 14 (21.2%) were from one institution, and 52 cases (78.8%) were from the second. Table 1 summarises the patient and tumour characteristics.

Forty-four dogs (66.7%) presented with clinical signs, including polydipsia/polyuria and weight loss (suspected to be due to hyperthyroidism), increased upper respiratory tract noise, dysphagia, coughing, lethargy, or dysphonia. The remaining 22 dogs (33.3%) had a palpable mass as the only clinical sign. Of 59 dogs with pre-treatment T4 available, T4 was elevated in 11 (18.6%), normal in 33 (55.9%) and decreased in 15 (25.4%). Two dogs with low T4 had thyroid stimulating hormone (TSH) evaluated, which was consistent with hypothyroidism. None of the dogs with low T4 displayed clinical signs of hypothyroidism. Nine dogs had an elevated total calcium. Three of these had ionised calcium assessed, which was elevated in all three.

Histology reports were available for 22 dogs and confirmed follicular cell thyroid carcinoma in 21 cases, of which seven were described as follicular cell of compact subtype, and well-differentiated adenocarcinoma in one. This dog had a CT confirming a cervical mass originating from the right thyroid gland (Figure 1). Immunohistochemistry was not performed.

Staging: Twenty-two dogs had a CT and scintigraphy, 29 dogs had thoracic radiographs and scintigraphy, 14 dogs had scintigraphy alone, and one dog, which had an elevated T4, had thoracic radiographs alone. All CT scans were reviewed by a board-certified radiologist. Thoracic radiographs were reviewed by a board-certified surgeon or radiologist. Metastatic disease was diagnosed in 32 dogs (table 1). Two dogs had regional lymph node metastasis on imaging and confirmed histologically, and one dog had two ventral peritoneal nodules identified on CT, which were cytologically consistent with neuroendocrine carcinoma, and presumed to be thyroid carcinoma metastasis.

Of the 10 dogs with stage II disease, three had incompletely excised tumours with residual disease on scintigraphy, three dogs had non-resectable ectopic tumours - owners of one dog declined surgery, and the reason for not pursuing surgery was not recorded for three dogs.

Thoracic scintigraphy was interpreted as stage IV disease without corresponding lesions on CT in four dogs, and without corresponding lesions on radiographs in 10 dogs (table 2). Of the dogs where scintigraphy detected lesions not seen on radiographs, there was uptake in the caudal thorax in three dogs, in the region of the cranial mediastinum in two, the right thorax in three, and generalised patchy uptake in two. In one case, enlargement of the cranial mediastinum was detected on thoracic radiographs without radiotracer uptake in this region on scintigraphy. Five dogs had lesions on CT not detected with scintigraphy. One had enlarged retropharyngeal lymph nodes and confirmed metastasis on histopathology, one had a cranial mediastinal mass, one had ventral peritoneal nodules and two had pulmonary nodules. In one dog with pulmonary nodules, the failure of scintigraphic detection was suspected to be due to interference from iodinated contrast given 6 days prior. For all other dogs there was a minimum of four weeks between CT scan with iodinated contrast and scintigraphy and $^{131}$I treatment.

Prior therapy: Forty-eight dogs (72.7%) were treatment naïve, and 18 (27.3%) had received therapy prior to $^{131}$I (Table 1). Of the ten dogs that had had prior surgery, on scintigraphy four dogs had no residual local disease but did have distant metastasis, four had residual local disease only, and two dogs had both residual local disease and distant metastasis. Four dogs had received cytotoxic chemotherapy prior to $^{131}$I. Carboplatin was given in two dogs as the sole chemotherapy agent. One of these dogs had an ectopic heart base thyroid carcinoma and received stereotactic radiation (SRT) (3x7.5 Gy) followed by a single dose of carboplatin one month prior to $^{131}$I – this dog was excluded from the response and censored from PFI and OST analysis. Two doses of doxorubicin were administered in one dog, and one dog received three doses each of carboplatin and doxorubicin, followed by a single dose of toceranib, which was discontinued due to gastrointestinal toxicity. Three dogs received toceranib without cytotoxic chemotherapy prior to $^{131}$I. No dogs received additional therapy within two weeks of $^{131}$I treatment. The median number of days between diagnosis and $^{131}$I treatment was 35 days (range 7-318).

Concurrent medications included non-steroidal anti-inflammatories in thirteen dogs and prednisolone in eight dogs.

## Response to radioactive iodine ($^{131}$I) treatment

Radioiodine was administered subcutaneously (SQ) in 52 dogs (78.8%) and orally in 14 dogs (26.9%). The median dose (range) of orally treated dogs was 1767.5MBq (1409-2053.9 MBq). The median dose (range) of subcutaneously treated dogs was 1600 MBq (800-1600 MBq). There were 34 (51.5%) evaluable responses using RECIST, and 58 (87.9%) using the subjective response criteria, summarized in Table 3. All cases with a RECIST response also had a subjective response assessment. The ORR according to RECIST was 35.3%. Progressive disease was local in three dogs, with five developing presumed metastasis. The location of the presumed metastasis included development of pulmonary lesions in two, an aggressive bony lesion in the right proximal humerus (cytologically suspicious for neuroendocrine metastasis) in one, an aggressive bony lesion affecting the cervical vertebral body causing neck pain and neurological signs, as well as progression of local disease in one, and progression of ventral peritoneal nodules in one.

The median time to maximal reduction in tumour size for all dogs was 116 days (range 7-379). Of the 44 dogs with clinical signs, clinical responses were recorded for 42, and 32 (76.2%) showed improvement in clinical signs within 4.5 months post-treatment.

Of the 11 dogs with elevated T4, 10 were euthyroid within 10 weeks of $^{131}$I treatment. One dog had surgery prior to $^{131}$I and T4 was normal at the time of $^{131}$I. Two dogs with elevated total calcium had calcium reassessed post $^{131}$I and it was normal in both.

Restaging was performed in 4 dogs. One dog had resolution of scintigraphic uptake in the thorax 383 days post-treatment, one dog had resolution of radiographic pulmonary nodules after 154 days, one dog had progressive pulmonary nodules on CT 72 days after treatment, and one dog had progressive abdominal nodules 49 days after treatment.

## Treatment outcomes

Fifty-six dogs were included in the PFI analysis, and ten were censored within the studied sample. Three dogs are alive without progression at the time of writing, six died of other causes without tumour progression: two euthanised due to osteoarthritis, one euthanised due to congestive heart failure, one euthanised due to presumed radiation pneumonitis secondary to $^{131}$I, one died of multicentric lymphoma 956 days following $^{131}$I, and one died at home 11 days after $^{131}$I for an unknown reason. One dog was censored from the progression analysis when toceranib was started without tumour progression. The

median PFI (95% CI) was 301 (217-578) days (Figure 2). Thirty-four dogs (64.2%) progressed locally, fifteen (26.3%) developed distant metastasis, and seven (13.2%) experienced local progression and metastasis to lymph nodes. Following tumour progression, sixteen dogs started toceranib and four received a second treatment with $^{131}$I. In those four dogs, PFI in three was approximately half that of the first treatment, and in the fourth dog second PFI was longer than after the first treatment (Table S1).

Fifty-five dogs died during the study period. Eight dogs are still alive at the time of writing (survival range 226 – 2416). Five of these dogs have disease progression (, two are receiving toceranib, and three are not receiving any treatment. Three dogs were lost to follow-up (follow-up range 210-1209 days). The median OST (95% CI) was 564 (421-867) days (Figure 3). Median duration of follow up was 569 days (range 10-2585). Death attributable to the tumour occurred in 49 (74.2%) dogs. Cause of death was not clear from the medical records in six dogs.

The estimated median PFI for dogs with stage II disease was 821 days (95%CI 299-∞), compared with dogs having stage III (212 days 95%CI 160-578) or stage IV (301 days 95%CI 166-637) disease. The estimated median overall survival for dogs with stage II, III and IV disease were 643 days (95%CI 414-∞), 527 days (95%CI 210-1020) and 469 days (95%CI 364-1075) respectively.

## Prognostic factors

Dogs that received prior treatment for thyroid carcinoma showed a 74% lower hazard for progression compared with treatment naïve dogs (HR 0.260 95%CI 0.123-0.548, *P*=0.0004) and this effect persisted after controlling for the effect of age (Figure 4). A weak effect of age was seen affecting PFI (HR 1.016 95%CI 1.006-1.027, *P*=0.003) but not survival post-progression. Having stage III disease compared with stage II impacted PFI (HR 3.143 95%CI 1.179-8.38, *P*=0.02), however an effect was not seen for survival post-progression (table 4). None of the other factors analysed showed an association with disease progression or death (Table 4).

## Adverse events

Serum T4 was measured prior to discharge in 18 dogs, and was low (grade 2) in all (Table 5). Fifty-three dogs were supplemented with levothyroxine at discharge. TheT4 was below the reference range in five dogs 4 weeks later and the thyroxine dose was increased; the T4 for all other dogs was within reference range at the next recheck. Haemogram results from between 1-11 weeks post treatment were available for 39 (59.1%) dogs. Two dogs developed neutropenia, one grade 1 neutropenia (2.6 cells x $10^9$/L, reference 3.5 - 12.0 x $10^9$/L) documented 53 days which had resolved at next recheck 5 months later, and

one grade 4 neutropenia (0.4 x $10^9$ cells/L, reference 3.0-11.5) and grade 1 anaemia (haematocrit 0.35, reference 0.37-0.55) 4 weeks post treatment that resolved 15 days later. Two dogs with cervical thyroid tumours developed grade 1 bruising and erythema of the ventral cervical region 31- and 50-days post $^{131}$I. In one dog, coagulation factors were not evaluated, but a hemogram was unremarkable and changes were resolved at the next recheck 15 weeks later. In the second dog, a haemogram, PT and aPTT were normal and changes resolved within 2 weeks. One of these two dogs achieved a CR following $^{131}$I and the second dog had SD. One dog with extensive pulmonary nodules on thoracic radiographs and increased uptake of $Na^{99m}TcO_4$ throughout the lung fields developed presumed grade 5 radiation pneumonitis. Nine days following $^{131}$I, whilst in isolation, the dog developed respiratory distress. Prednisolone was administered to reduce airway inflammation however the dog become cyanotic, developed haemoptysis and was euthanised the following day. No necropsy was performed.

## 4. Discussion

This is the first study to describe the response and durability of tumour control for a large cohort of dogs with measurable thyroid carcinomas treated with $^{131}$I. The ORR in our study was 34.3%, which were largely partial responses. In contrast, the ORR with definitive external beam RT has been reported to be between 70-100%, suggesting that this approach is more likely to cytoreduce tumours than $^{131}$I.[9, 12, 13, 31] Toceranib is reported to provide an ORR of between 26.7-46.1%, which is comparable to the response rates in our study.[17, 18] The median time to maximal tumour reduction following $^{131}$I was 116 days (3.9 months), which is favourable compared with external beam RT, for which the reported range is 6-22 months.[9, 12-14] Follow-up visits were not consistent therefore this time may be an overestimation.. Despite the modest effect on tumour size, improvement in associated clinical signs was seen in the majority (76.2%) of dogs, which is similar to that reported with SRT (81%).[13] All dogs with functional tumours became euthyroid following $^{131}$I. A recent study of 5 dogs with ectopic functional thyroid carcinomas treated with $^{131}$I also described normalisation of T4 in all dogs.[32] This raises a question around the importance of achieving a measurable response. Turrel et al found no difference in the MST of dogs treated with $^{131}$I that had subsequent tumour resection compared with $^{131}$I alone, postulating no benefit in reducing tumour burden.[21] However, these conclusions were based on a small number of cases, so any true benefit of adjuvant surgery may have been missed due to type II error. In our cohort, dogs receiving treatment prior to $^{131}$I presumably had a lower disease burden than treatment naïve dogs, and this could explain the reduced risk of disease progression compared with treatment naïve dogs. Similarly, Sheppard-

Olivares et al reported a HR of 17.2 for death in treatment-naïve asymptomatic dogs treated with toceranib, compared with dogs that received prior therapy.[17] Residual macroscopic disease following surgery and $^{131}$I has been shown to be an independent negative prognostic factor in people.[33] Neoadjuvant chemotherapy, sorafenib and external beam RT are utilised to cytoreduce tumours, prior to surgery and adjuvant $^{131}$I.[34, 35] Prospective studies evaluating the effects of neoadjuvant cytoreductive treatment on outcome for dogs with nonresectable thyroid carcinoma treated with $^{131}$I are warranted to evaluate this further.

The overall median PFI for dogs treated with $^{131}$I was 301 days, which is comparable to both hypofractionated and stereotactic body radiation, and medical treatment. The median progression free survival (PFS) reported following SRT was 315 days and the mean time to progression was 490 days following hypofractionated RT.[12, 13] In contrast, one study treated 25 dogs with unresectable thyroid carcinoma using conventionally fractionated megavoltage radiation, and reported a 3-year PFS rate of 72%.[14] The median PFI with toceranib ranges from 206 days in treatment naïve dogs to 1015 days in previously treated dogs, and with cytotoxic chemotherapy from 202-480 days.[15-17] This suggests $^{131}$I may provide similar tumour control comparable to other non-surgical treatment modalities.

Our study did not observe an effect of response to treatment on outcome. Lee *et al*. (2020) reported that dogs who responded to SRT showed a longer median PFS and median OST, with non-responders (SD + PD) having a 4.3-fold greater hazard for progression.[13] The prognosis is worse for people with thyroid carcinoma that do not respond to $^{131}$I and alternative local and systemic treatments are warranted.[13, 36, 37] It is possible that small numbers of dogs that developed PD limited our ability to detect an effect of treatment response on PFI and survival, and ultimately larger prospective studies will be required to assess this.

We report the outcomes of four dogs retreated with $^{131}$I at progression (Table S1) which suggest that repeated $^{131}$I can be effective in some cases. These data were not statistically evaluated as they are structurally not compatible with the current analyses; a frailty-type model with more complex transition structure would be needed, which was beyond the scope of this study.

One dog presented with two ventral peritoneal nodules identified on CT, cytologically diagnosed as a neuroendocrine carcinoma. The nodules were not reported on the initial CT, but were detected at a follow-up scan, and on review of the initial scan were noted to be present. These lesions were suspicious for metastatic or ectopic disease but did not uptake with radiotracer when the scintigraphy images were

reviewed. The lesions continued to grow following $^{131}$I treatment, however completely responded to toceranib. In people, ectopic thyroid tissue has been reported in the abdomen, however to date, there are no reports to date of ectopic thyroid carcinoma within the abdomen.[38, 39] However, abdominal metastasis to the adrenal glands, liver, stomach, pancreas and kidneys have been reported in people with thyroid carcinoma.[40-43] In many cases, lesions are amenable to $^{131}$I treatment, however in the presented case there was no radiotracer uptake on scintigraphy, and progression occurred following $^{131}$I. In people, responses to $^{131}$I are reported to be less effective in non-$^{99m}$Tc-pertechnetate avid metastasis, thus this treatment modality is not strongly recommended in canine patients with non-functional thyroid tumours that lack radiotracer uptake.[44] Without histology, it remains possible that the abdominal lesions represented *de novo* development of an unrelated neuroendocrine tumour.

There were five dogs with suspected cranial mediastinal involvement based on CT or scintigraphy. It is unclear whether these lesions represent true metastasis of the tumour to lymphatic tissue, or multicentric disease with ectopic thyroid tissue, and the significance of these two classifications to prognosis is unknown in canine patients.[7]

This study reports a greater number of presumed metastatic lesions identified by scintigraphy than thoracic radiographs. There were four presumed metastatic lesions noted on scintigraphy not seen on CT, and five lesions detected on CT that were not seen on scintigraphy. A previous report found scintigraphy to be less sensitive than thoracic radiography for detection of lung nodules, however no data exists comparing CT with planar scintigraphy for staging dogs with thyroid carcinoma.[45]Whilst scintigraphy is considered a specific method of assessing iodine-trapping thyroid tumours, false positive results can occur secondary to nonthyroidal masses, swallowed saliva and skin contamination.[46] An interpretation scheme for reporting of canine thyroid tumours using scintigraphy has been proposed, assessing pattern of tumour circumscription and heterogeneity of the tracer uptake, however has not been widely utilised.[22] Modification of the scheme to include standardised reporting of metastatic lesions and further validation would help to reduce inter-reporter variation in assessment of scintigraphic images.[22]In people, the CT component of SPECT/CT detects smaller lesions than planar scintigraphy, which might explain why some lesions were visible on CT but not scintigraphy in this study.[47] Use of $^{123}$I is thought to be superior in the detection of intrathoracic disease compared with $Na^{99m}TcO_4$, however due the long half-life and cost, this agent is not widely utilised for clinical diagnostic purposes in veterinary oncology.[22] Because of small case numbers and the lack of standardised staging and review of imaging reports by board-certified radiologists, we are unable to draw any conclusions on the sensitivity of staging between these imaging

modalities.[45] Further investigation, with the aim of comparing the sensitivity and specificity of advanced imaging and planar scintigraphy for the diagnosis and staging of canine thyroid neoplasia is warranted.

We observed an effect of stage III disease on the PFI compared with stage II disease, however an effect on PFI or survival for dogs with stage IV disease was not detected in this study. Turrel *et al.* (2006), reported a worse OST in dogs with stage IV disease compared with II/III (MST 366 days vs 839 days, 95% CI not reported).[21] Other veterinary studies using radiation to treat canine thyroid carcinomas have not found an effect of stage on outcome.[7, 12-14, 20] This raises the question as to whether metastatic disease warrants treatment with $^{131}$I or other systemic therapy, or whether the local disease should be the focus of treatment. In people with follicular thyroid carcinoma, lymph node and distant metastasis are known negative prognostic factors, and treatment with radioactive iodine independently predicts a longer survival.[33, 48, 49] Furthermore, veterinary studies assessing prognostic factors for canine thyroid carcinomas are typically small and retrospective, which may limit the ability to detect an effect of stage on survival. A limitation in our study is that we included dogs with presumed stage IV disease based on scintigraphy alone, without analogous changes on CT or radiographs, and without histology. Thus, we may have included dogs with less advanced disease in the stage IV group, which may have affected our outcome analysis. Ultimately, use of a validated reporting scheme for canine scintigraphy scans, and prospective trials with standardised staging will be required to investigate this further in dogs.

Other than transient reduction in T4 recorded in 18/18 dogs assessed following $^{131}$I, toxicity was observed in less than 10% of dogs following $^{131}$I. The high rate of low T4 in treated dogs was expected, and has been previously reported by Turrel et al, where 29/30 dogs treated with $^{131}$I had serum $T_4$ levels below the reference range post-treatment.[21] Myelosuppression was noted in 2 dogs in this study, however haemograms performed after $^{131}$I were recorded for only 39 dogs, so the true prevalence may have been underestimated. Turrel et al reported three cases of severe myelosuppression leading to death. In contrast, the two dogs that developed a grade 1 and 4 neutropenia and grade 1 anaemia in our study had no clinical signs, and these changes self-resolved. This may relate to the lower $^{131}$I doses used in our study. Turrel et al administered calculated doses, with a median dose of 3700 MBq, compared with our study where 1600 MBq standard doses were used.[20, 21] Further prospective trials are warranted to determine optimal dosing strategies in dogs.

We report the second suspected case of radiation pneumonitis in a dog following $^{131}$I, which was the only dog in the series with moderate diffuse thoracic uptake on scintigraphy and a nodular pulmonary pattern on thoracic radiographs. The first report described a dog with high pulmonary metastatic burden that died secondary to radiation pneumonitis 15 days after $^{131}$I, a similar timeframe to the presented case.[50] A case series reporting pneumonitis and pulmonary fibrosis in 15 people with diffuse lung metastasis following $^{131}$I treatment led to a recommendation that whole-body retention doses be less than 2960 MBq (80 mCi) in cases of diffuse pulmonary metastasis.[51] Absorbed dose assessments in blood and tissues have not been performed in dogs treated with $^{131}$I so veterinary recommendations to this effect cannot be made. Although these occurrences are rare, the possibility of pneumonitis or pulmonary fibrosis developing in dogs with moderate diffuse radiotracer uptake on scintigraphy should be discussed with owners prior to treatment.

Two dogs developed suspected radiation-induced bruising/erythema, which has been reported following external beam RT but not following $^{131}$I.[9] These changes could represent damage to regional blood vessels, reported in people receiving $^{131}$I; or could relate to tumour necrosis and cell death.[52]

There were several limitations of this study, largely related to the retrospective design. We included dogs with a presumed diagnosis of thyroid carcinoma based on scintigraphic uptake of $^{99m}$Tc pertechnetate or elevated T4 in combination with a measurable mass. It is possible that some of the treated dogs had thyroid adenomas rather than carcinomas, however clinically appreciable adenomas are rare and typically small and mobile, so this is considered less likely.[4] Five dogs with cranial mediastinal nodules as seen on CT or scintigraphy were designated stage IV disease without additional lesions, however it is unknown whether the mediastinal changes represented metastasis, or rather local extension of disease or neoplastic ectopic foci. Furthermore, normal ectopic tissue in this area can show radiotracer uptake as a result of elevated endogenous TSH.[22] Thus, this may overestimate the PFI and OST in dogs with stage IV disease by including dogs with less advanced disease. A standard dose of $^{131}$I was utilised, however whether an individualised dose leads to superior outcomes is yet to be determined. Staging tests varied and images were not consistently reviewed by a board-certified radiologist, which may have led to over- or underestimation of tumour stage. Calliper measurement of tumour size was inconsistent, and few patients had follow-up scintigraphy scans, which would have been useful for cases with residual disease following thyroidectomy. Cytology was not mandatory for classification of metastatic disease, which may have led to overestimation of clinical stage in this cohort.

Five dogs included in the response analysis received prior medical therapy, which was discontinued 2 weeks prior to $^{131}$I. No further treatment was administered until documented progression, though it remains possible that prior therapy may have contributed to the responses. The inclusion of a subjective response assessment in conjunction with RECIST provided an overview of response in a larger number of dogs, as the data for dogs with a RECIST response is susceptible to missing data bias.[53] Whilst subjective responses are prone to misinterpretation, reporting of reduction tumour shrinkage or progression without specific measurements can still provide an indication of treatment benefit.[54]

## 5. Conclusions

Radioactive iodine provides effective management of clinical signs associated with thyroid carcinomas and can provide prolonged survival, however most treated dogs do not experience significant reduction in tumour burden. Prior therapy is associated with reduced risk of disease progression. Prospective, controlled randomised trials are warranted to assess objective response and confirm the impact of response to treatment on prognosis reported here.

References

1. Liptak JM. Canine thyroid carcinoma. *Clin Tech Small Anim Pract*. 2007;22(2):75-81.

2. Barber LG. Thyroid tumors in dogs and cats. *Vet Clin North Am Small Anim Pract*. 2007;37(4):755-773.

3. Campos M, Kool M, Daminet S, Ducatelle R, Rutteman G, Kooistra H, et al. Upregulation of the pi3k/akt pathway in the tumorigenesis of canine thyroid carcinoma. *J Vet Intern Med*. 2014;28(6):1814-1823.

4. Wucherer KL, Wilke V. Thyroid cancer in dogs: An update based on 638 cases (1995–2005). *J Am Anim Hosp Assoc*. 2010;46(4):249-254.

5. Carver JR, Kapatkin A, Patnaik AK. A comparison of medullary thyroid carcinoma and thyroid adenocarcinoma in dogs: A retrospective study of 38 cases. *Vet Surg*. Jul-Aug 1995;24(4):315-9. doi:10.1111/j.1532-950x.1995.tb01336.

6. Vail DM, Thamm DH, Liptak JM. *Withrow and macewen's small animal clinical oncology*. vol Sixth edition. Saunders; 2020.

7. Broome M, Peterson M, Walker J. Clinical features and treatment outcomes of 41 dogs with sublingual ectopic thyroid neoplasia. *J Vet Intern Med*. 2014;28(5):1560-1568.

8. Campos M, Ducatelle R, Rutteman G, Kooistra HS, Duchateau L, de Rooster H, et al. Clinical, pathologic, and immunohistochemical prognostic factors in dogs with thyroid carcinoma. *J Vet Intern Med*. Nov-Dec 2014;28(6):1805-13. doi:10.1111/jvim.12436

9. Pack L, Roberts RE, Dawson SD, Dookwah HD. Definitive radiation therapy for infiltrative thyroid carcinoma in dogs. *Vet Radiol Ultrasound*. 2001;42(5):471-474.

10. Klein M, Powers B, Withrow S, Curtis C, Straw R, Ogilvie G, et al. Treatment of thyroid carcinoma in dogs by surgical resection alone: 20 cases (1981-1989). *J Am Vet Med Assoc*. 1995;206(7):1007-1009.

11. Frederick AN, Pardo AD, Schmiedt CW, Hinson WD, Youk AO, Urie BK. Outcomes for dogs with functional thyroid tumors treated by surgical excision alone. *J Am Vet Med Assoc*. 2020;256(4):444-448.

12. Brearley M, Hayes A, Murphy S. Hypofractionated radiation therapy for invasive thyroid carcinoma in dogs: A retrospective analysis of survival. *J Small Anim Pract*. 1999;40(5):206-210.

13. Lee BI, LaRue SM, Seguin B, Griffin L, Prebble A, Martin T, et al. Safety and efficacy of stereotactic body radiation therapy (sbrt) for the treatment of canine thyroid carcinoma. *Vet Comp Oncol*. 2020;18(4):843-853.

14. Théon AP, Marks SL, Feldman ES, Griffey S. Prognostic factors and patterns of treatment failure in dogs with unresectable differentiated thyroid carcinomas treated with megavoltage irradiation. *J Am Vet Med Assoc*. 2000;216(11):1775-1779.

15. Nadeau M-E, Kitchell BE. Evaluation of the use of chemotherapy and other prognostic variables for surgically excised canine thyroid carcinoma with and without metastasis. *Can Vet J*. 2011;52(9):994.

16. Fineman L, Hamilton T, De Gortari A, Bonney P. Cisplatin chemotherapy for treatment of thyroid carcinoma in dogs: 13 cases. *J Am Anim Hosp Assoc*. 1998;34(2):109-112.

17. Sheppard-Olivares S, Bello NM, Wood E, Szivek A, Biller B, Hocker S, et al. Toceranib phosphate in the treatment of canine thyroid carcinoma: 42 cases (2009-2018). *Vet Comp Oncol*. 2020;4(18):519-527.

18. London C, Mathie T, Stingle N, Clifford C, Haney S, Klein MK, et al. Preliminary evidence for biologic activity of toceranib phosphate (palladia®) in solid tumours. *Vet Comp Oncol*. 2012;10(3):194-205.

19. Lee SL. Complications of radioactive iodine treatment of thyroid carcinoma. *J Natl Compr Canc Netw*. 2010;8(11):1277-1287.

20. Worth A, Zuber R, Hocking M. Radioiodide (131) i therapy for the treatment of canine thyroid carcinoma. *Aust Vet J*. 2005;83(4):208-214.

21. Turrel JM, McEntee MC, Burke BP, Page R. Sodium iodide i 131 treatment of dogs with nonresectable thyroid tumors: 39 cases (1990–2003). *J Am Vet Med Assoc*. 2006;229(4):542-548.

22. Daniel GB, Neelis DA. Thyroid scintigraphy in veterinary medicine. *Semin Nucl Med*. 2014;44(1):24-34.

23. Owen LN. Tnm classification of tumours in domestic animal. *World Health Organization*. 1980;

24. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the radiation therapy oncology group (rtog) and the european organization for research and treatment of cancer (eortc). *Int J Radiat Oncol Biol Phys*. 1995;31(5):1341-1346.

25. Ladue T, Klein MK. Toxicity criteria of the veterinary radiation therapy oncology group. *Vet Radiol Ultrasound*. 2001;42(5):475-476.

26. Agency ARPaNS. Discharge of patients undergoing treatment with radioactive substances. In: (APARNSA) ARPaNSA, editor. Radiation protection series No 42002.

27. Nguyen S, Thamm D, Vail D, London CA. Response evaluation criteria for solid tumours in dogs (v1. 0): A veterinary cooperative oncology group (vcog) consensus document. *Vet Comp Oncol*. 2015;13(3):176-183.

28. Meira-Machado L, de Uña-Alvarez J, Cadarso-Suárez C, Andersen PK. Multi-state models for the analysis of time-to-event data. *Stat Methods Med Res*. Apr 2009;18(2):195-222. doi:10.1177/0962280208092301

29. de Wreede LC, Fiocco M, Putter H. The mstate package for estimation and prediction in non- and semi-parametric multi-state and competing risks models. *Comput Methods Programs Biomed*. Sep 2010;99(3):261-74. doi:10.1016/j.cmpb.2010.01.001

30. de Wreede LC, Fiocco M, Putter H. Mstate: An r package for the analysis of competing risks and multi-state models. *Journal of statistical software*. 2011;38(7):1-30.

31. Tsimbas K, Turek M, Christensen N, Vail DM, Forrest L. Short survival time following palliative-intent hypofractionated radiotherapy for non-resectable canine thyroid carcinoma: A retrospective analysis of 20 dogs. *Vet Radiol Ultrasound*. 2019;60(1):93-99.

32. Lyssens A, van den Berg M, Peremans K, Vandermeulen E, Daminet S. 131i treatment with hyperthyroidism caused by a non-resectable ectopic thyroid tumour: 5 cases (2008-2019). *J Small Anim Pract*. 2020:1-8.

33. Chow SM, Law SC, Mendenhall WM, Au SK, Yau S, Yuen KT, et al. Follicular thyroid carcinoma: Prognostic factors and the role of radioiodine. *Cancer*. 2002;95(3):488-498.

34. Danilovic DL, Castro Jr G, Roitberg FS, Vanderlei FA, Bonani FA, Freitas R, et al. Potential role of sorafenib as neoadjuvant therapy in unresectable papillary thyroid cancer. *Arch Endocrinol Metab*. 2018;62(3):370-375.

35. Besic N, Auersperg M, Dremelj M, Vidergar-Kralj B, Gazic B. Neoadjuvant chemotherapy in 16 patients with locally advanced papillary thyroid carcinoma. *Thyroid*. 2013;23(2):178-184.

36. Schlumberger M, Brose M, Elisei R, Leboulleux S, Luster M, Pitoia F, et al. Definition and management of radioactive iodine-refractory differentiated thyroid cancer. *Lancet Diabetes and Endocrinology*. 2014;2(5):356-358.

37. Brose MS, Smit J, Capdevila J, Elisei R, Nutting C, Pitoia F, et al. Regional approaches to the management of patients with advanced, radioactive iodine-refractory differentiated thyroid carcinoma. *Expert Rev Anticancer Ther*. 2012;12(9):1137-1147.

38. Qin L-H, He F-Y, Liao J-Y. Multiple ectopic goiter in the retroperitoneum, abdominal wall, liver, and diaphragm: A case report and review of literature. *World J Clin Cases*. 2020;8(23):6172.

39. Güngör B, Kebat T, Ozaslan C, Akilli S. Intra-abdominal ectopic thyroid presenting with hyperthyroidism: Report of a case. *Surg Today*. 2002;32(2):148-50. doi:10.1007/s005950200008

40. He X, Soleimanpour SA, Clines GA. Adrenal metastasis as the initial diagnosis of synchronous papillary and follicular thyroid cancer. *Clin Diabetes Endocrinol*. Nov 4 2020;6(1):19. doi:10.1186/s40842-020-00109-0

41. Davidson M, Olsen RJ, Ewton AA, Robbins RJ. Pancreas metastases from papillary thyroid carcinoma: A review of the literature. *Endocr Pract*. Dec 2017;23(12):1425-1429. doi:10.4158/ep-2017-0001

42. Malhotra G, Upadhye TS, Sridhar E, Asopa RV, Garde PS, Gawde S, et al. Unusual case of adrenal and renal metastases from papillary carcinoma of thyroid. *Clin Nucl Med*. 2010;35(9)

43. Gomez Hernandez K, Hafezi-Bakhtiari S, Pierre A, Szentgyorgyi E, Brown DH, Krzyzanowska MK, et al. Metastatic thyroid carcinoma to the gastric body. *The Journal of Clinical Endocrinology & Metabolism*. 2014;99(11):3958-3959. doi:10.1210/jc.2014-2521

44. Liu M, Chai L, Luo Q, Ruan M, Cheng L, Lv Z, et al. 99mtc-pertechnetate-avid metastases from differentiated thyroid cancer are prone to benefit from 131i therapy: A prospective observational study. *Medicine (Baltimore)*. Aug 2017;96(33):e7631. doi:10.1097/md.0000000000007631

45. Marks SL, Koblik PD, Hornof WJ, Feldman EC. 99mtc-pertechnetate imaging of thyroid tumors in dogs: 29 cases (1980-1992). *Journal of American Veterinary Medical Association*. Mar 1 1994;204(5):756-60.

46. Taeymans O, Peremans K, Saunders J. Thyroid imaging in the dog: Current status and future directions. *J Vet Intern Med*. 2007;21(4):673-684.

47. Avram AM. Radioiodine scintigraphy with spect/ct: An important diagnostic tool for thyroid cancer staging and risk stratification. *J Nucl Med Technol*. 2014;42(3):170-180.

48. Gilliland FD, Hunt WC, Morris DM, Key CR. Prognostic factors for thyroid carcinoma: A population-based study of 15,698 cases from the surveillance, epidemiology and end results (seer) program 1973–1991. *Cancer*. 1997;79(3):564-573.

49. Ito Y, Hirokawa M, Higashiyama T, Takamura Y, Miya A, Kobayashi K, et al. Prognosis and prognostic factors of follicular carcinoma in japan: Importance of postoperative pathological examination. *World J Surg*. 2007/07/01 2007;31(7):1417-1424. doi:10.1007/s00268-007-9095-2

50. Mitchell M, Hurov L, Troy G. Canine thyroid carcinomas: Clinical occurrence, staging by means of scintiscans, and therapy of 15 cases. *Vet Surg*. 1979;8(4):112-118.

51. Sgouros G, Song H, Ladenson PW, Wahl RL. Lung toxicity in radioiodine therapy of thyroid carcinoma: Development of a dose-rate method and dosimetric implications of the 80-mci rule. *J Nucl Med*. 2006;47(12):1977-1984.

52. Sürücü E, Bekiş R, Şengöz T, Demir Y, Çelik AO, Orbay Ö, et al. The effect of radioiodine on the intima media thickness of the carotid artery. *Mol Imaging*. 2013;22(3):85.

53. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: Potential and pitfalls. *Br Med J*. 2009;338

54. Who handbook for reporting results of cancer treatment (World Health Organization) 26 (1979).

[†]Philips Argus Epic (prior to March 2018); Equine Scanner H.R. MiE Scintron (from April 2018); General Electric Maxi 400AV

## Tables and figures

Table 1. Patient and tumour characteristics of 66 dogs with thyroid neoplasia. Abbreviations: T4 total thyroxine; WHO, World Health Organization

Table 2. Detection of distant metastasis or multicentric disease by computed tomography, thoracic radiographs and scintigraphy in 65 dogs with thyroid neoplasia.

Table 3A. RECIST response in 34 dogs with thyroid neoplasia treated with radioactive iodine. Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumours; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 3B. Subjective clinical response in 58 dogs with thyroid neoplasia treated with radioactive iodine. Abbreviations: CR, complete response; Non-CR CB, non-complete response clinical benefit; PD, progressive disease.

Table 4. Prognostic factors in dogs with thyroid neoplasia treated with radioactive iodine. Abbreviations: PFI, progression-free interval; HR, hazard ratio.

Table 5. Summary of adverse events. Abbreviations: VRTOG, Veterinary Radiation Therapy Oncology Group; RTOG, Radiation Therapy Oncology Group.

Supplementary Table 1. Response to $^{131}$I in dogs treated with a second dose at progression. Patient 63 received toceranib following progression after the second treatment. All other dogs received no additional treatments for their thyroid carcinoma. Abbreviations: RECIST, response evaluation criteria in solid tumours; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; WHO, World Health Organization; PFI, progression free interval; OST, overall survival time.

Figure 1. Transverse computed tomography (CT) images of the neck of the same dog (A) prior to $^{131}$I treatment and; (B) 99 days following $^{131}$I treatment. The contrast-enhancing tumour in (A) is extensive and the causes the trachea to deviate leftwards. The asterisk highlights the thyroid tumour that reduced by 35% following treatment.

Figure 2. Estimated Kaplan-Meier function showing the progression-free interval (PFI) for 56 dogs. Median PFI [95% CI] was 301 [217-578] days.

Figure 3. Estimated Kaplan-Meier function showing the overall survival (OST) for 55 dogs. Median OST [95% CI] was 564 [421-867] days.

Figure 4. Cox proportional hazard model showing the predicted time-until-progression for treatment naïve or previously treated dogs with thyroid carcinoma treated with $^{131}$I. Shaded region indicates the 95% confidence interval. Dashed lines indicate the median for each group.

# Response of canine thyroid carcinomas to radioiodine: Table 4

Table 4. Prognostic factors in dogs with thyroid neoplasia treated with radioactive iodine. Abbreviations: PFI, progression-free interval; HR, hazard ratio.

| Prognostic factor | Tumour progression HR (95% CI) | P-value | Death following progression HR (95% CI) | P-value |
|---|---|---|---|---|
| Prior treatment (n = 18)<br>Treatment naïve (n = 48) | 0.260 (0.123-0.548) | **0.0004** | 0.934 (0.445-1.96) | 0.857 |
| Progressive disease (n = 8)<br>Other response (n = 51) | - | - | 1.393 (0.5806-3.342) | 0.458 |
| Palladia at progression (n = 16)<br>No Palladia at progression (n = 50) | - | - | 0.6088 (0.3026-1.225) | 0.164 |
| Stage III (n = 24)<br>Stage II (n = 10) | 3.143 (1.1788-8.380)<br>Reference | **0.0221** | 1.339 (0.4405-4.073)<br>Reference | 0.607 |
| Stage IV (n = 32)<br>Stage II (n = 10) | 2.203 (0.8375-5.795)<br>Reference | 0.1095 | 1.468 (0.4942 – 4.358)<br>Reference | 0.490 |
| Age (n=66) | 1.016 (1.006-1.027) | **0.00251** | 1.006 (0.9958-1.016) | 0.25 |
| Dose $^{131}$I (MBq/kg) (n=66) | 1.002 (0.9972-1.006) | 0.44 | 1.001 (0.9972-1.006) | 0.52 |
| Clinical signs at diagnosis (n = 44)<br>No clinical signs at diagnosis (n = 22) | 1.789 (0.9611-3.33) | 0.0665 | 1.271 (0.6532-2.471) | 0.481 |
| Elevated T4 (n = 11)<br>Normal/low T4 (n = 59) | 0.4056 (0.1607-1.024) | 0.0561 | 0.623 (0.1912-2.03) | 0.432 |
| Hypercalcemia (n = 9)<br>Normal calcium (n = 57) | 0.7876 (0.338-1.858) | 0.586 | 0.8061 (0.3242-2.004) | 0.643 |
| Ectopic location (n = 8)<br>Eutopic location (n = 58) | 0.8694 (0.3432-2.203) | 0.768 | 1.975 (0.7617-5.120) | 0.162 |

# Response of canine thyroid carcinomas to radioiodine

Running title: Radioiodine for canine thyroid carcinoma

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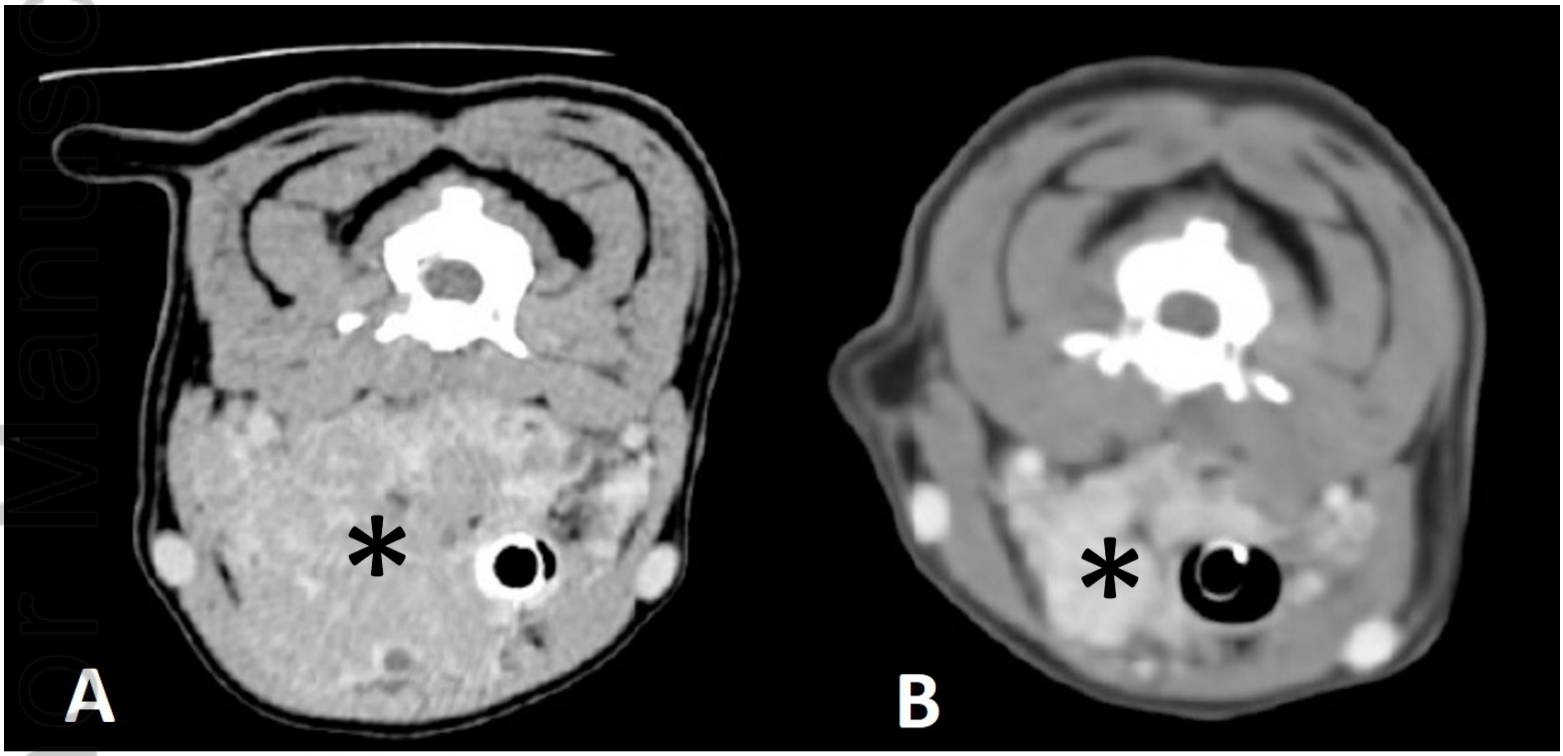


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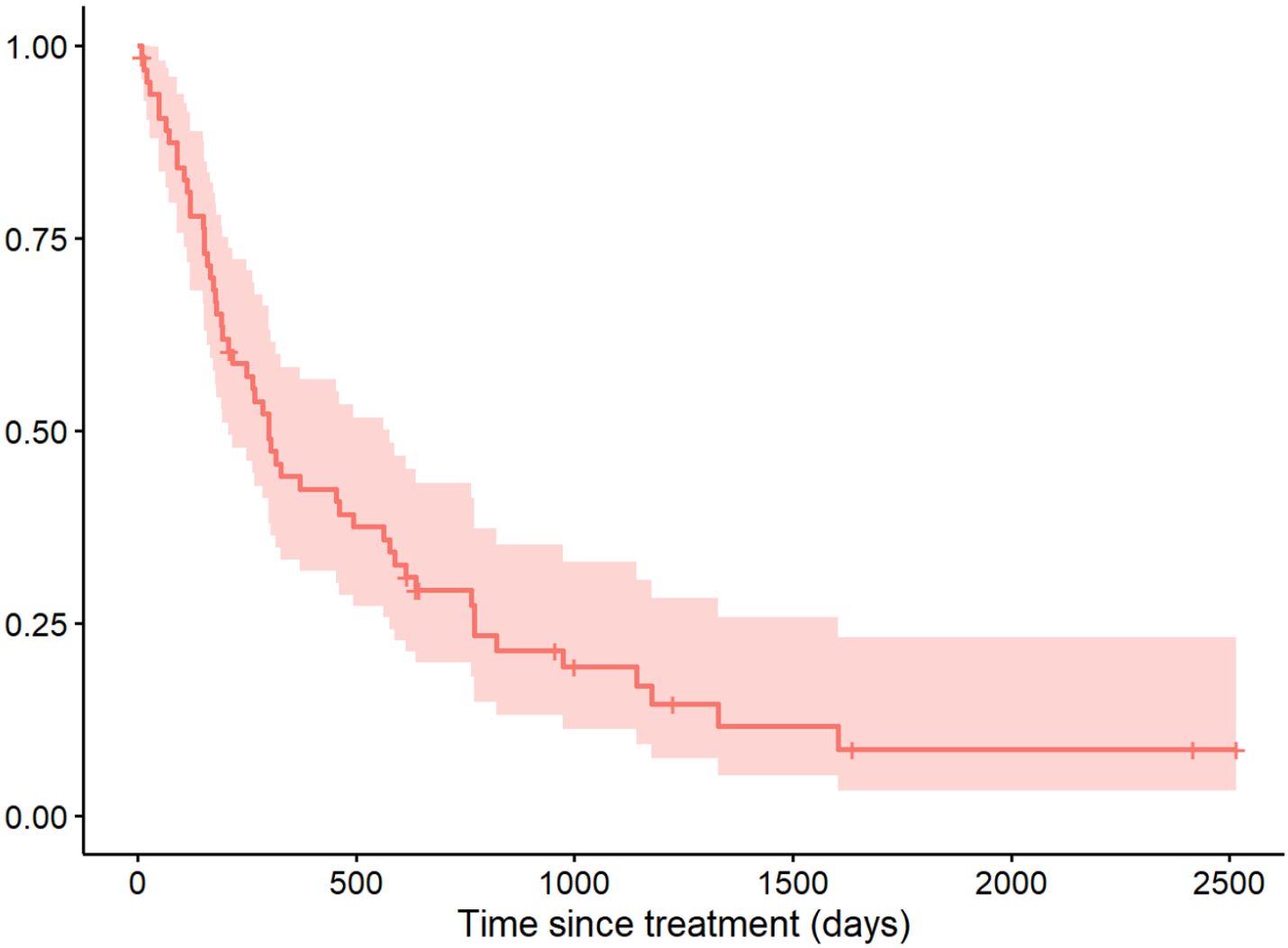


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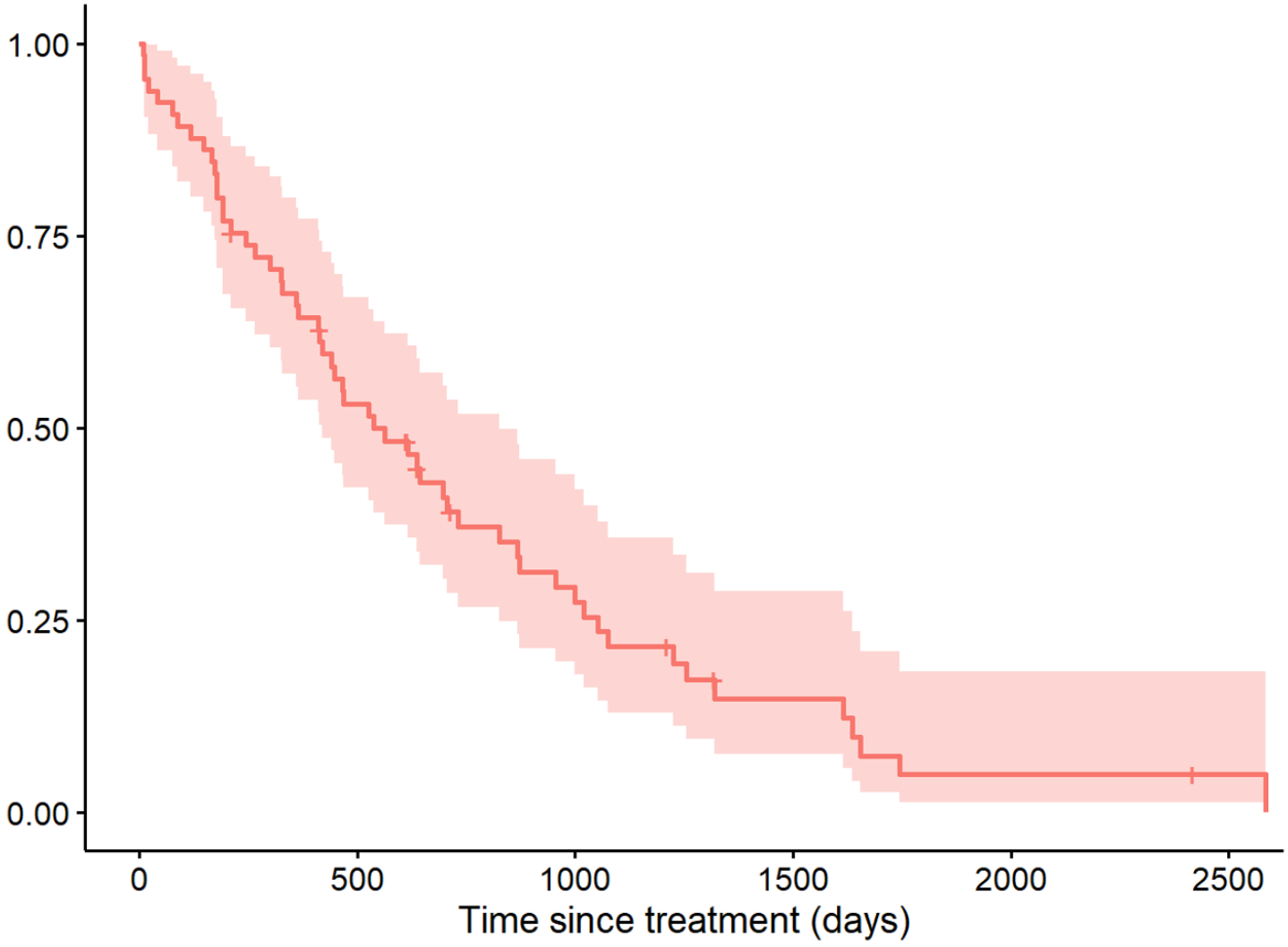


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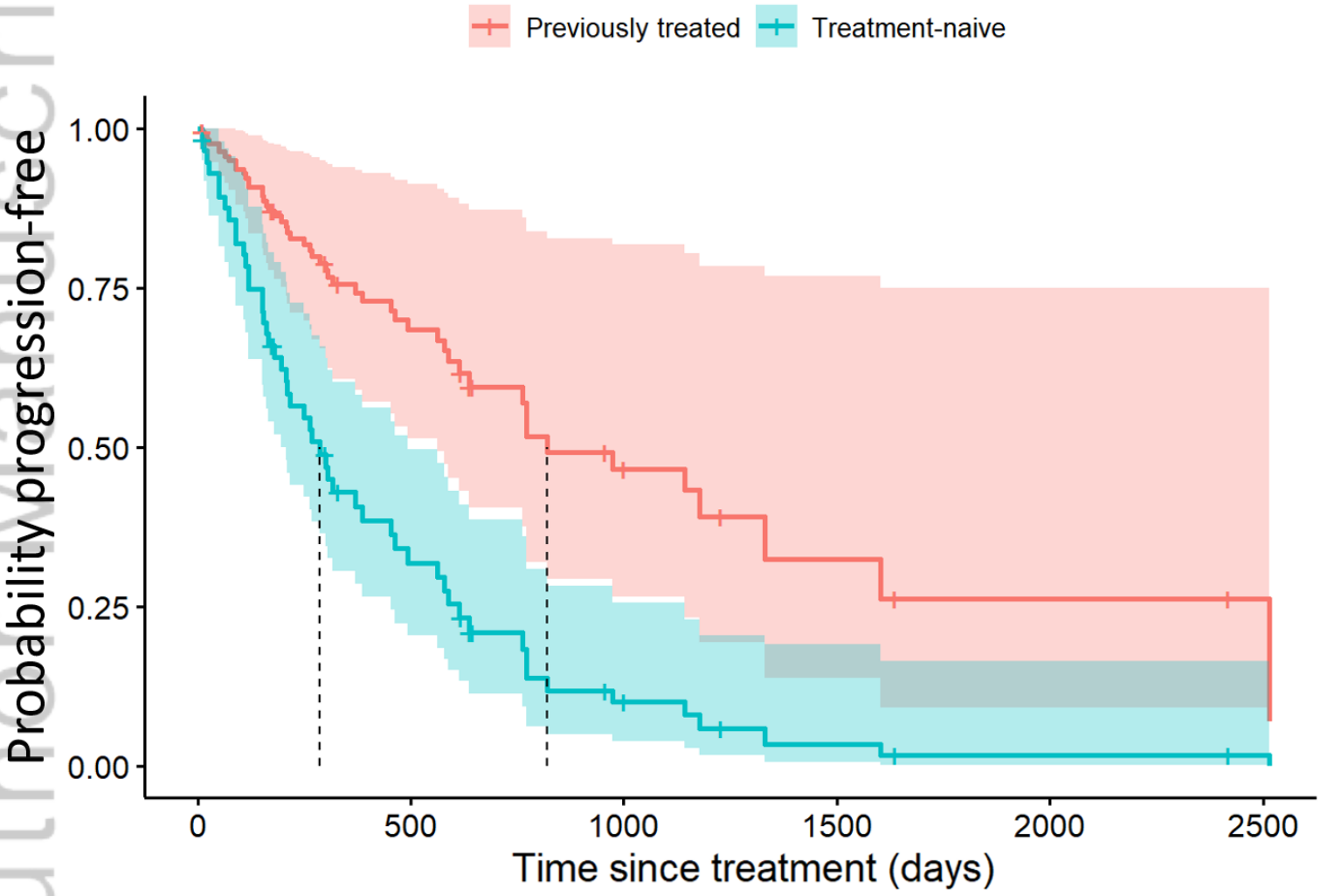


VCO_12770_Figure 4.png

# Response of canine thyroid carcinomas to radioiodine: Table 1

Table 1. Patient and tumour characteristics of 66 dogs with thyroid neoplasia. Abbreviations: T4 total thyroxine; WHO, World Health Organization

| | **N (%)** |
|---|---|
| **Sex** | 66 |
| Male | 38 (57.6) |
| Female | 28 (42.4) |
| **Age (years)** | 66 |
| Median | 9.9 |
| Range | 5-14.8 |
| **Weight (kg)** | 65 |
| Median | 20.4 |
| Range | 2-52.2 |
| **Breed** | 66 |
| Beagle | 18 (27.3) |
| Labrador | 12 (18.2) |
| Other | 36 (54.5) |
| **Clinical signs at diagnosis** | 66 |
| Yes | 44 (66.7) |
| No | 22 (33.3) |
| **Tumour location** | 66 |
| Bilateral cervical | 22 (33.3) |
| Unilateral cervical | 36 (54.5) |
| Ectopic basihyoid | 7 (10.6) |
| Ectopic heart base | 1 (1.5) |
| **T4 elevated at diagnosis** | 59 |
| Yes | 11 (18.6) |
| No | 48 (81.4) |
| **Total calcium elevated at diagnosis** | 60 |
| Yes | 9 (15.0) |
| No | 51 (85) |
| **WHO Stage** | 66 |
| II | 10 (15.2) |
| III | 24 (36.4) |
| IV | 32 (48.5) |
| **Diagnosis** | 66 |
| Cytology | 25 (37.9) |
| Histology | 22 (33.3) |
| Presumptive | 19 (28.8) |
| **Treatment naïve** | 48 (72.7) |
| **Residual measurable disease** | 18 (27.3) |
| Prior surgery | 10 (15.2) |
| Prior toceranib | 4 (6.1) |
| Prior cytotoxic chemotherapy | 4 (6.1) |
| Prior external beam radiation | 1 (1.5) |

# Response of canine thyroid carcinomas to radioiodine: Table 2

Table 2. Detection of distant metastasis or multicentric disease by computed tomography, thoracic radiographs and scintigraphy in 65 dogs with thyroid neoplasia.

| Staging | Number | No metastasis detected | Metastasis | Metastasis also on scintigraphy | Metastasis detected on scintigraphy not identified on other modality |
|---|---|---|---|---|---|
| Computed tomography | 22 | 13 | 9 | 4 | 4 |
| *Pulmonary* | | | 4 | 2 | 2 |
| *Mediastinal* | | | 3 | 2 | 2 |
| *Abdominal* | | | 1 | 0 | 0 |
| *Lymph node* | | | 1 | 0 | 0 |
| | | | | | |
| Thoracic radiographs | 29 | 18 | 11 | 10 | 10 |
| *Pulmonary* | | | 9 | 9 | 8 |
| *Mediastinal* | | | 2 | 1 | 2 |
| Scintigraphy | 65 | 35 | 30 | - | - |
| *Pulmonary* | | | 24 | - | - |
| *Mediastinal* | | | 6 | - | - |
| *Abdominal* | | | 0 | - | - |
| *Lymph node* | | | 1 | - | - |

# Response of canine thyroid carcinomas to radioiodine: Table 3

Table 3A. RECIST response in 34 dogs with thyroid neoplasia treated with radioactive iodine. Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumours; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

| | **n** | **% total** |
|---|---|---|
| **RECIST response** | **34** | |
| **CR** | 4 | 11.7 |
| **PR** | 8 | 23.5 |
| **SD** | 14 | 41.2 |
| **PD** | 8 | 23.5 |

Table 3B. Subjective clinical response in 58 dogs with thyroid neoplasia treated with radioactive iodine. Abbreviations: CR, complete response; Non-CR CB, non-complete response clinical benefit; PD, progressive disease.

| | **n** | **% total** |
|---|---|---|
| **Subjective response** | **58** | |
| **CR** | 4 | 6.9 |
| **Non-CR CB** | 46 | 79.3 |
| **PD** | 8 | 13.8 |

# Response of canine thyroid carcinomas to radioiodine: Table 5

Table 5. Summary of adverse events. Abbreviations: VRTOG, Veterinary Radiation Therapy Oncology Group; RTOG, Radiation Therapy Oncology Group.

| **Adverse events (VRTOG/RTOG)** | **N (%)** |
|---|---|
| Grade 2 low T4/non-thyroidal illness | 18/18 (100) |
| Grade 1 bruising/erythema | 2/66 (3.0) |
| Grade 1 anemia | 1/39 (2.6) |
| Grade 4 neutropenia | 1/39 (2.6) |
| Grade 1 neutropenia | 1/39 (2.6) |
| Grade 5 pneumonitis | 1/55 (1.5) |