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Clinico-pathological Features and Outcome of Cats With Thyroid Carcinoma

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Abstract

Objectives:

Thyroid carcinoma (TC) is an uncommon tumour in cats. The aims of this study were to describe the clinical presentation, response to treatment and outcome in a cohort of cats with thyroid carcinoma.

Methods:

This single-institute retrospective study reviewed medical records of cats histologically diagnosed with thyroid carcinoma between 2006 and 2023. Signalment, diagnostic tests, histopathological characteristics, treatment, and survival were evaluated.

Results:

Twenty-five cats were included. The most common presenting clinical signs were a palpable cervical mass, and weight loss. Nineteen cats (76%) received medical treatment for hyperthyroidism at the time of thyroid carcinoma diagnosis, with 14 (74%) demonstrating persistently elevated total thyroxine levels. Twenty-three cats (92%) underwent curative-intent treatment including: thyroidectomy (n = 13), thyroidectomy followed by high-dose radioiodine (HD-RAI) (n = 9) and HD-RAI as single modality (n = 1). Hyperthyroidism resolved in 17 out of 22 cats (77%) after treatment. Follicular carcinoma was the most common histopathologic subtype (n = 10) followed by papillary (n = 2). Metastasis was present in 12 cats (48%); confirmed in 10 cats either by cytology or histopathology and suspected in two cats based on scintigraphy. Median tumour-specific survival for cats receiving curative-intent treatment was not reached, and when all-cause mortality was considered, median overall survival time was 795 days (95% CI 503–1086). No variable was associated with survival in cats receiving curative-intent treatment.

Conclusions:

Cats diagnosed with TC can experience prolonged survivals and normalisation of thyroxine levels when receiving curative-intent treatment. Metastatic rate was moderate but did not impact outcome.

INTRODUCTION

Thyroid carcinoma (TC) is an uncommon endocrine tumour in cats, occurring in 1–3% of those diagnosed with hyperthyroidism.[4] It has been hypothesised that the risk of malignant transformation increases progressively over time when a toxic goitre is not definitively treated.[21] Clinical presentation of cats with TC include polyphagia, weight loss, tachycardia, and presence of a cervical mass as most of

these tumours are hypersecretory (HS), with only four cases of non-hypersecretory (NHS) TC described in the literature.[5,7,8]

Diagnosis of feline TC generally relies upon histopathology. Previously defined criteria for malignancy include mitotic activity, infiltrative pattern, or intra-vascular invasion. However, distinction between adenoma and well-differentiated carcinoma remains challenging for pathologists and correlation with clinical and imaging findings is required.[7] Feline TC has been previously classified into follicular, papillary, compact or mixed histopathologic subtypes.[5,7] Microscopically, a clear distinction between HS and NHS tumours in terms of pattern of growth or cellular morphology has not been identified.[7]

Scintigraphy has been proposed as a diagnostic tool to aid in differentiating carcinoma from its benign counterpart.[10] Scintigraphic features that may assist in identifying carcinoma include multiple and extensive areas of increased radionuclide uptake, heterogeneous uptake pattern with irregular and spiculated margins, linear multifocal uptake patterns, and radionuclide uptake within the cranial mediastinum.[7] Nevertheless, a review of scintigraphic characteristics in eight cats with TC found that this could not reliably distinguish malignant tissue from benign thyroid disease.[7]

The metastatic rate for feline TC has been previously reported between 40–71% based on necropsy evaluation, most commonly affecting regional lymph nodes and lungs.[5,6] However in a series of eight cats with TC that had scintigraphic imaging, metastasis was only suspected in one cat that had diffuse pulmonary radionuclide uptake. However, cytological or histological evaluation of regional lymph nodes was not performed in all cases, and metastatic rate may have been underestimated.[7]

The optimal treatment approach for cats with TC is unknown.[4,5,7] Treatment options include thyroidectomy, HD-RAI, a combination of both, or medical treatment (which treats only the endocrine sequalae, not the tumour itself).[3,4,5] High-dose I^{131} (1100 MBq) has shown success in cats with HS tumours, with hyperthyroidism resolving in 75–100% of cases, and median survival times ranging from 7–76 months.[5,7] For NHS tumours, surgery may play a more important role with one cat surviving 831 days post-thyroidectomy and another 428 days post-thyroidectomy and HD-RAI. Follow-up for the other two NHS cats reported in the literature is not available.[7,8,9] Combination therapy with thyroidectomy and HD-RAI may also be beneficial in cats with large thyroid masses or when functional thyroid tissue is identified on scintigraphy as a result of incomplete excision or metastatic disease.[7]

Due to the limited existing literature on feline TC, the primary aim of this study was to describe the clinical presentation, histopathologic characteristics and outcome following treatment in a larger cohort of cats with TC. A secondary aim was to identify risk factors associated with death in this population.

MATERIALS AND METHODS

Inclusion criteria and data collection

The medical database of the Royal Veterinary College (United Kingdom) was retrospectively reviewed for cats with a histological diagnosis of TC between January 2006 and March 2023. Ethical approval was obtained from the institute's Clinical Research Ethical Review Board (URN SR2022- 0143).

Cats were excluded if the diagnosis of TC was based on cytology or scintigraphy alone, if they had incomplete clinical records, or histological diagnosis was obtained during post-mortem examination.

Data retrieved from medical records included: signalment, comorbidities, clinical signs and duration, duration of prior medical management of hyperthyroidism, physical examination abnormalities, laboratory results including haematology, biochemistry, serum total thyroxine (TT4) concentration, urinalysis, and non-invasive blood pressure. When available, tumour size was recorded and for calculation of the median size, the longest axis was used. Treatment and follow-up data collected included type of treatment and whether this had a curative-intent (HD-RAI, thyroidectomy, or combination of both) or palliative-intent (targeted therapy or antithyroid drugs), and date and cause of death if known. If multiple treatments were performed, time between treatments was recorded. When surgery was performed, type of thyroidectomy (unilateral or bilateral) was documented together with any additional procedures concurrently performed (e.g. lymphadenectomy). The occurrence of any post-treatment complications and their management was recorded. Post-treatment hypothyroidism was defined as low TT4 concentration based on the laboratory reference range in conjunction with clinical signs or concurrently elevated thyroid-stimulating hormone (TSH). For each cat, thyroid status following treatment was documented. Follow-up was obtained via clinical records and telephone contact with referring practices.

A single board-certified anatomic pathologist (DY) retrospectively reviewed the formalin-fixed paraffin-embedded blocks, when available, for morphologic features, histologic subtype, mitotic count (MC; defined as number of mitoses per 10 high-power fields [400x magnification] or an equivalent area of 2.37mm^2), lymphovascular invasion, degree of necrosis, presence of mineralization and results of immunohistochemistry (IHC) if performed. In regard to histologic tumour-free margin (HTFM), they were defined as incomplete when neoplastic cells extended to the edge of the surgical resection margins or 'tumour on ink', close if HTFMs was ≤ 2 mm, and complete when HTFMs was > 2 mm.

Statistical analysis

Frequency and proportion were used to report categorical variables. The Shapiro–Wilk test was used to assess normality of continuous data, which were reported as mean and standard deviation (SD) for normally distributed data, and median and range for non-normally distributed data.

Univariable and multivariable backward stepwise Cox regression analysis was used to evaluate histologic and clinical variables against survival times. Variables significant at $p \leq .20$ in univariable analyses were included in multivariable analysis where variables were retained at $p \leq .05$. Results were presented as hazard ratio (HR) and 95% CIs. Overall survival time (OST) was defined as the number of days between histological diagnosis and death from any cause, whereas tumour-specific survival (TSS)

was defined as the number of days between histological diagnosis and death or euthanasia from tumour-related causes. For survival analysis, only cats receiving definitive treatment were considered, which was defined as treatment intended to provide a disease cure. This group was comprised of patients undergoing thyroidectomy, HD-RAI or both. Those lost to follow-up (LTFU) were excluded from survival analysis. Variables analysed to identify possible predictors of OST and TSS included: TT4 at diagnosis, presence of metastasis, treatment type, MC, presence of mineralisation, necrosis, and lymphovascular invasion. Thyroxine concentration was considered increased (HS TC) if the concentration was above the upper reference limit of the analyser; cats with TT4 within the analyser's reference range were classified as non-hypersecretory (NHS TC). Statistical analysis was performed using Microsoft Excel (version 14.0, Microsoft Corp) and SPSS Statistics (version 30.0, IBM Corp).

RESULTS

Signalment and clinical presentation

Twenty-five cats met the inclusion criteria. Demographic data is summarised in Table 1.

Table 1
Demographics and presenting clinical signs in 25 cats with thyroid carcinoma.

Signalment Variable	**Number**	**Percentage**
Sex and neutered status		
Male neutered	13	52%
Female neutered	12	48%
Breed		
Domestic shorthair	21	84%
Domestic longhair	3	12%
Ragdoll	1	4%
	Median	**Range**
Age (years)	12	9–15
Weight (kilograms)	3.21	2.32–7.7
Presenting Complaint	**Number**	**Percentage**
Cervical mass	19	76%
Weight loss	13	52%
Hyporexia	4	16%
Increased vocalization	4	16%
Polyphagia	2	12%
Polyuria/polydipsia	2	8%
Vomiting	2	8%
Dyspnoea	1	4%

Prior to the diagnosis of TC, 19 (76%) cats were treated medically for their hyperthyroidism with a thionamide, for a median of 364 days (range, 14–2195). Five cats were additionally treated with low doses of I^{131} prior to TC diagnosis; one cat received 145 MBq, one cat 148 MBq and three cats 185 MBq. One cat was receiving an iodine-restricted diet.

The most common clinical sign at presentation was the presence of a cervical mass (n = 19 [76%], Table 1) with fourteen cats (74%) demonstrating persistently elevated total thyroxine levels despite medical or low dose of I^{131} (LD-RAI) treatment. The median tumour size was 4.4 cm in the longest axis (range, 0.9–6.8). Comorbidities were recorded in 16 cats (64%) including: hypertrophic cardiomyopathy (n = 3 [12%]), chronic enteropathy (n = 3 [12%]), feline lower airway disease (n = 3 [12%]), azotemic

chronic kidney disease (n = 3 [12%]) and one each (4%) of external otitis and skin allergies. One cat was previously diagnosed with a meningioma and salivary carcinoma.

Diagnostic investigations

Haematological and biochemical results were available for review in 16 and 13 cats respectively and abnormalities are summarised in Table 2.

Table 2
Main haematological and biochemical abnormalities.

Signalment Variable	Number	Percentage
Complete blood cell count (CBC)		
Neutrophilia	2	12.5%
Lymphopenia	3	18.8%
Biochemistry		
Alanine aminotransferase	9	69.2%
Alkaline phosphatase	6	46.2%
Gamma glutamyl transferase	1	7.7%
Hypercholesterolemia	4	30.8%
Hyperbilirrubinemia	1	7.7%
Urea	7	53.9%
Creatinine	7	53.9%
Hypercalcemia	2	15.4%

TT4 concentrations at time of TC diagnosis were available in 17 cats (68%) with a median TT4 of 146 nmol/l (range, 26.8–615; reference interval [RI] 19–65). Twenty-two (88%) cats had HS and 3 (12%) cats had NHS TCs.

Computed tomography (CT) was performed in 10 (40%) cats; in six (60%) this included neck, thorax and abdomen and in four (40%) neck and thorax only. Two cats underwent focal neck ultrasound alongside thoracic radiographs. Of the 15 (60%) cats that underwent scintigraphy this was the sole imaging modality in six (40%) and was used alongside other imaging modalities in nine (60%).

Five cats had scintigraphy with technetium-99m prior to treatment and in four (80%) scintigraphy was highly suspicious of TC. Scintigraphy revealed varying radioisotope uptake patterns: increased uptake in the left cervical region with linear multifocal patterns (n = 1); extensive uptake in the cervical region extending from the larynx to thoracic inlet on the right and into the cranial thorax (n = 1); four areas of

positive uptake on the ventral aspect of the thoracic inlet and uptake in the right cervical lymph node (n = 1); area of intense uptake in the left cervical area extending to the thoracic inlet, and uptake in the ipsilateral retropharyngeal lymph node (n = 1). In one cat, there was marked increase of radioisotope uptake in the right thyroid gland, but features raising concern for neoplasia were not seen. The remaining 10 cats that underwent scintigraphy had this performed following surgery to assess the extent of the disease.

Cytology from the thyroid mass was performed in nine (36%) cats and in six (67%) it was diagnostic for a thyroid epithelial tumour. In the other 3 cats it was consistent with a basal cell tumour, carcinoma of unknown origin, and neutrophilic inflammation (one each [11.1%]).

Based on both imaging and pathological findings, 21 (84%) cats had unilateral and four (16%) had bilateral TC. Twelve cats (48%) were reported to have metastasis; six (50%) confirmed on histopathology, four (33%) based on cytology, and in two (17%) cats it was suspected based on scintigraphy alone. The most common locations for metastasis were the regional lymph nodes (n = 10 [40%]), primarily the ipsilateral retropharyngeal lymph nodes (n = 9 [36%]) and in one (4%) cat to the ipsilateral superficial cervical lymph node. Four (16%) cats had distant metastasis to the lungs (n = 3 [12%]) and skeletal muscle (n = 1 [4%]). Two (8%) cats had both lymph node and distant metastasis. In 6 (26%) cats, ectopic thyroid tissue was suspected, on scintigraphy although this tissue was not available for histopathological examination.

Histopathology

Formalin-fixed paraffin-embedded tissue samples were available for review in 15 cats. Follicular TC was the most common histopathologic subtype identified (n = 11 [73.3%]), followed by papillary (n = 2 [13.3%]). Immunohistochemistry with antibodies against thyroglobulin was available in three cases. In the first one, based on haematoxylin and eosin, a diagnosis of TC was favoured given the acinar/alternating papillary arrangements. However, a glandular origin (salivary), could not be completely excluded based on intracytoplasmic mucoid inclusions. There was a weak to moderate positive cytoplasmatic labelling of approximately 50% of neoplastic cells with anti-thyroglobulin antibodies, confirming follicular TC (Fig. 1E). In the two remaining cases, it was not possible to differentiate between follicular compact and C-cell subtype, and immunohistochemistry with thyroglobulin was performed. In both cases, there was weak to moderate cytoplasmic labelling of approximately 75% of neoplastic cells making them both compact (solid) tumours.

Follicular carcinomas were characterised by the presence of cuboid cells arranged in variably sized follicles with variable content (colloid, empty lumens), or more dense nests and packets, all supported within a thin fibrovascular stroma. For papillary carcinomas, the polygonal cells were arranged in irregular papilliform projections, supported by a thick fibrous stroma. (Fig. 1 [A, B, C, D]). Seven metastatic lymph node samples were available for review. In Fig. 1E, an example of nodal metastasis of a follicular TC can be appreciated, where well-differentiated thyroid follicles are multifocally present

within the subcapsular, paracortical and medullary sinuses. The microscopic appearance of the tumour cells in all samples reviewed, was heterogenous. There was variable degree of atypia, necrosis, mineralisation and mitoses. The median mitotic count was three (range, 0–37). Complete excision was achieved in five cases, although narrow histologic margins were seen in four tumours. The remaining 10 tumours were incompletely excised with neoplastic cells extending to the histological margins.

Treatment and outcome

Twenty-two (88%) cats underwent surgery. Three (13%) and 10 (43.5%) cats had bilateral and unilateral thyroidectomy performed, respectively. Concurrent lymphadenectomy was performed in nine (40.9%) cats. Two (8%) cats required a second surgery due to local tumour recurrence at 18 and 28 months, respectively. Nine (36%) cats had adjuvant HD-RAI due to incomplete excision (n = 2), metastasis (n = 4), and ongoing hyperthyroidism (n = 3). One (4%) cat had HD-RAI as the sole treatment modality. All cats treated with HD-RAI received the same dose of 1100 MBq. One (4%) cat diagnosed with NHS TC was treated with toceranib phosphate and treatment was palliative in one (4%) cat.

Post-surgical complications were seen in four (17.4%) cats. One cat had laryngeal paralysis, two developed hypocalcaemia, and one developed both hypocalcaemia and laryngeal paralysis; all complications occurred in cats that underwent bilateral thyroidectomy. Of the three cats that developed hypocalcaemia, two recovered with calcium supplementation, and one was euthanised. Complications following HD-RAI were seen in two (20%) cats; both developed acute kidney injury which led to death in one.

Hyperthyroidism resolved in 17 (77.3%) cats after curative-intent treatment. Two (9%) cats remained persistently hyperthyroid; one had thyroidectomy alone, and one had thyroidectomy followed by HD-RAI. In both cats, there was an improvement in clinical signs, and both were restarted on anti-thyroid medication. One of these cats was euthyroid for 624 days following thyroidectomy, at which point an increased TT4 concentration was noticed, and TC recurrence was confirmed by cervical imaging. In three (13.6%) cats, there was no available follow up TT4 values available.

Eight (36%) cats became hypothyroid following treatment; three (14%) after thyroidectomy, four (18%) after combined surgery and HD-RAI, and one (4%) cat following HD-RAI alone; five (23%) required thyroid supplementation.

Follow-up information was available for 18 (72%) cats. Median follow-up time was 266 days (range, 14–1911). Thirteen (72%) cats died or were euthanised, and five (28%) cats were alive at the time of writing. Of those cats that died or were euthanised, five (38%) were due to tumour-related causes: two (15%) due to complications from treatment, and three due to disease progression (n = 2 [15%]) or persistent clinical signs (n = 1 [8%]). Median OST was 795 days (95% CI 503–1086). Median TSS was not reached (range 54–1991).

Risk factors associated with survival

Results of univariable analysis exploring prognostic factors in cats receiving curative-intent treatment are presented in Table 3.

Table 3
Results of univariable analysis exploring prognostic factors for overall survival time (OST) in 23 cats receiving curative-intent treatment for thyroid carcinoma. *CI = confidence interval, HR = hazard ratio, NR = not reached, HD-RAI: high-dose radioactive iodine*

Variable		Median OST (days)	*P*-value	HR (95% CI)
Clinical				
TT4 at diagnosis	-	-	.159	0.99 (0.97–1.00)
Treatment	Thyroidectomy (n = 12)	590	.468	-
	HD-RAI (n = 1)	NR		
	Both (n = 9)	946		
Metastasis at diagnosis	No (n = 13)	588	.154	0.22 (0.03–1.77)
	Yes (n = 10)	NR		
Histopathological				
Mitotic count	-	-	.178	0.63 (0.33–1.23)
Necrosis	Absent (n = 4)	795	.476	1.88 (0.33–10.54)
	Present (n = 8)	590		
Mineralisation	Absent (n = 7)	266	.275	0.29 (0.03–2.66)
	Present (n = 5)	795		
Lymphovascular invasion	Absent (n = 9)	588	.391	0.49 (0.09–2.52)
	Present (n = 8)	1911		

Although not significant, cats treated with both surgery and HD-RAI had numerically longer OST (946 days vs 590 days, p = 0.468) compared to those treated with surgery alone (Fig. 2). Variables with a *p*-value ≤ .20 on univariable analysis were included in the multivariable model, but none retained significance ($p < .05$). Only five cats had a TSS time, so exploration of prognostic factors for TSS was not performed.

DISCUSSION

This study aimed to describe the clinical presentation, histopathologic characteristics and outcome following definitive-intent treatment in a larger cohort of cats with TC. Similar to previous case series and reports, we confirmed that the prognosis for feline TC is generally fair to good with median TSS not reached when surgery, HD-RAI or combination treatment was performed.[4,7,8] Median OST was 795 days; there was a numerical, but not statistically significant, difference in median OST between cats treated with surgery alone (590 days) or cats treated with surgery followed by HD-RAI (946 days) and further exploration of the optimal therapeutic approach may be worthwhile in a larger cohort of cats with TC. No other prognostic factors were identified.

As previously observed in other studies, mixed breed cats appeared overrepresented in our study, but a sex predisposition was not identified.[5,7,8] The median age of the cats in this study was 12 years, in line with previous literature.[5] The clinical presentation for cats with TC was typical of hyperthyroidism, except for cats with NHS, where the main complaint was the presence of a cervical mass without any additional clinical signs. This highlights the importance of maintaining thyroid neoplasia as a differential in cats with a ventral neck mass, even when euthyroid.

In our study, 76% of cats were receiving medical treatment for hyperthyroidism before being diagnosed with TC, for a median of 364 days. Most of these cats were treated with an antithyroid medication (thionamide), one cat also had an iodine-restricted diet, and five cats were also treated with low doses of I^{131} (145–185 MBq). These cats were not included in the group of cats receiving I^{131} in addition to surgery as, according to previous studies, these are not considered ablative doses for thyroid carcinoma.[5] It has been hypothesized that the risk of malignancy developing seems to increase progressively over time when a toxic goitre is not definitively treated but biopsy to confirm progression from adenoma to carcinoma was not available in any of the cats to confirm this. [21]

A goitre may be detected on physical examination of hyperthyroid cats. Description of physical examination characteristics of TC is largely variable however, and not predictive of TC, even for larger cystic masses.[7] In the present study, 76% of cats with TC had a palpable ventral cervical mass. In a retrospective study looking at thyroid cysts in cats, thyroid carcinoma was identified in 4/40 cats.[16] Thus, there is a clear overlap in clinical features between hyperthyroidism and TC and in cases with unusual palpable masses, those refractory to medical management or LD-RAI, TC should be suspected.

In cats, nuclear scintigraphy is generally considered to be the imaging technique of choice for the thyroid gland as it provides valuable information regarding both thyroid tissue localisation and physiology.[21] Advantages include its ability to differentiate bilateral vs unilateral thyroid disease, assess thyroid size and activity, and identify ectopic or metastatic, functional thyroid tissue.[7] Scintigraphy is an important diagnostic technique in hyperthyroid cats when there is a suspicion of malignancy, as it can help assess the extent of the tumour as well as the presence of metastasis or ectopic tissue.[7] In our study, ectopic thyroid tissue was suspected in six cats, however, whether this was metastasis from the main tumour or adenomatous hyperplasia could not be confirmed without histological evaluation. As there are no

definitive scintigraphic features to reliably identify neoplasia, and some “cold” tumours may not show definitive radionucleotide uptake, combination imaging with a CT scan is needed in some cats, although specific characteristics to differentiate TC from adenomatous or hyperplastic changes have not been described.[22] When a CT scan is performed ideally this occurs after scintigraphy if contrast is given since iodinated contrast agents may alter subsequent iodine uptake by the thyroid.

In people with TC, determination of malignancy is based on ultrasound characteristics, with biopsies needed for definitive confirmation.[15] Characteristics such as nodule size, echogenicity, borders, vascularity, and presence of calcifications have been reported to have a 64–77% sensitivity and 82–90% specificity for detecting malignancy. [17] Similar studies are lacking in veterinary medicine.

Metastatic disease was confirmed in 48% of the cats, which is in line with previous literature.[5] However, Hibbert *et al*. 2009 reported metastasis in only one cat out of eight. Nonetheless, sampling with either cytology or histology was not performed in all cases, so metastatic rate could have been underestimated.[4] Based on this finding, complete staging is recommended as the results can impact treatment options required to achieve an effective tumour control, although the presence of metastasis does not seem to influence prognosis.

Previously defined histopathologic criteria for malignant thyroid tumours include mitotic activity, infiltrative pattern, or intra-vascular invasion. Feline TC has been previously classified as follicular, papillary, or mixed.[5,7] In this study, follicular subtype was the most common. This contrasts with a previous study where the most common morphological diagnosis was mixed compact and follicular carcinoma, with follicular or papillary being less common.[5] In the present study there were too few cases in each histopathologic subtype to assess its value as a prognostic factor, but this should be explored in future studies.

Immunohistochemistry with thyroglobulin was performed in three cases, to confirm thyroid origin. A recent case series looking at pathological and immunohistochemical characterisation of thyroid neoplasia in cats identified TC in only 1/31 cats.[20] The tumour was positive to thyroglobulin, pancytokeratin, chromogranin A and negative for calcitonin, TTF-1, PAX8, S100 and vimentin.[20] In humans, most of the neoplastic lesions originating from the thyroid gland are diagnosed based on well-characterized histologic features. Nonetheless, a subset of tumours with follicular architecture lack features of malignancy, making the distinction between benign and malignant conditions difficult. For example, in tumours not derived from follicular thyroid epithelium, the use of ancillary techniques such as immunohistochemistry and molecular analysis can significantly improve diagnosis and aid TC subclassification.[25] Immunohistochemistry could therefore aid in identification of TC in cats. In humans, papillary TC accounts for approximately 84% of all thyroid cancers, followed by poorly differentiated carcinoma (~ 5%), medullary (~ 4%) and anaplastic TC (~ 1%).[14] Prognosis is determined by stage and histological subtype, with anaplastic or poorly differentiated carcinomas having a poorer prognosis.[14]

Both surgery and HD-RAI have been proposed as effective treatments for TC. Naan *et al.* 2006 reported TC in three cats treated with surgery and, whilst one cat died after 12 days, two remained alive six and 22 months after surgery.[4] Complications associated with thyroidectomy include haemorrhage, nerve injury (vagosympathetic trunk and the recurrent laryngeal nerve) and hypocalcaemia (in bilateral thyroidectomy).[4] Only one cat died from post-operative complications (hypocalcaemia) after bilateral thyroidectomy. Cats with large goitres may have thyroid tissue that extends into the thoracic inlet; in these cats with substernal disease, surgical removal may be difficult. Some cats may also present with tissue in ectopic sites, or metastatic disease at diagnosis. Although many of the cats in the present case series required adjunctive treatment due to disease persistence or recurrence following surgery it was difficult to tell retrospectively from the medical records whether or not this was expected prior to surgery. Thyroidectomy may be offered to owners in terms of an 'excisional biopsy' – with resolution of hyperthyroidism and no need for additional treatment as a possible and welcome treatment outcome, but not wishing to risk possible serious surgical complications such as laryngeal paralysis if the mass was infiltrative.

In our cohort of cats, nine cats were treated with HD-RAI due to recurrence or persistent hyperthyroidism. Although surgery may still have a role to play in cats with HS tumours where extensive local disease or metastasis is present, combination with HD-RAI needs to be considered.[7,8]. Radioactive iodine is the treatment most likely to result in complete destruction of a functioning TC. Its advantage is based on its capacity to treat all functional thyroid tissue regardless of the site, including any residual disease following surgery. In previous studies reporting TC treated with RAI, hyperthyroidism successfully resolved in 7/7 cats in one study and in 6/8 cat in another.[7,8] In our cohort, hyperthyroidism resolved in 10/13 cats. In the population of cats included in the present study, only one cat received HD-RAI as monotherapy. This cat was alive at the time of collecting the data, 385 days from diagnosis, despite the presence of metastasis. Nine cats were treated with adjuvant HD-RAI due to persistent clinical signs of hyperthyroidism following surgery. The combination of both treatments resulted in resolution of hyperthyroidism in eight cats, of which four became hypothyroid. Clinical signs of hypothyroidism were not observed in any cat, however, similarly to that reported by Hibbert *et al* 2009.[7] The main complication seen in our study after treatment with HD-RAI was acute development of azotaemia in 2 cats due to reduction in GFR, making HD-RAI a safe and efficient treatment modality. All cats in our study undergoing I^{131} received a dose of 1100 MBq subcutaneously based on previously reported data.[7,8] Higher doses are required given the increased tumour size and the fact malignant cells retain I^{131} less efficiently. [7] HD-RAI monotherapy is actually the most common treatment used in the authors' institution when TC is suspected, it is just that this treatment is usually administered without histopathology being obtained first, so most cats treated in this manner were not included in the present study.

The median OST in our cohort of cats that received definitive treatment was 795 days and median TSS was not reached. Previous literature reports OSTs ranging from 7–76 months.[5,7,8] Six cats were alive at

the time of data collection and 12 cats died or were euthanised. Only five cats died of tumour-related causes, including post-treatment complications in two cats.

The main limitation of this study is inherent to its retrospective, single-centre nature. Staging, treatment and follow-up in this group of cats were not standardised and relied mainly on the responsible clinicians' decisions at the time. Surgery was performed in both first opinion and referral settings, by clinicians with different levels of surgical experience, which could have impacted the outcome post-thyroidectomy. Due to the small number of patients in each group, statistical power was low.

CONCLUSIONS

Cats diagnosed with TC can experience prolonged survival despite the presence of metastasis, when treated with thyroidectomy with or without HD-RAI. Resolution of hyperthyroidism is seen in most cases. Treatment is generally well tolerated with low risk of complications. Further studies are needed to corroborate our findings and further explore prognostic factors in a larger cohort, to optimise treatment strategies.

Abbreviations

TC: thyroid carcinoma

HD-RAI: high-dose radioactive iodine

HS: hypersecretory

NHS: non-hypersecretory

TT4: total thyroxine

TSH: thyroid stimulating hormone

IHC: immunohistochemistry

MC: mitotic count

HTFM: histologically tumour free margin

SD: standard deviation

HR: hazard ratio

OST: overall survival time

TS: tumour specific survival

LFTU: lost to follow up

RI: reference interval

CT: computed tomography

LD-RAI: low dose radioactive iodine

Declarations

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

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ETHICAL APPROVAL

The work described in this manuscript involved the use of non-experimental (owned or unowned) animals. Established internationally recognised high standards (‘best practice’) of veterinary clinical care for the individual patient were always followed and/or this work involved the use of cadavers. Ethical approval from a committee was therefore not specifically required for publication in JFMS. Although not required, where ethical approval was still obtained, it is stated in the manuscript.

INFORMED CONSENT

Informed consent (verbal or written) was obtained from the owner or legal custodian of all animals described in this work (experimental or non-experimental animals, including cadavers) for all procedure(s) undertaken (prospective or retrospective studies). For any animals or people individually identifiable within this publication, informed consent (verbal or written) for their use in the publication was obtained from the people involved.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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AUTHORS' CONTRIBUTIONS

CF managed at least one of the patients included in the study, retrospectively collected the data, conducted the statistical analysis and wrote the article. GH contributed with data collection. HS managed the scintigraphy and performed treatment with radioactive iodine in most cases. AY and AG supervised the medical oncological management of most of the patients. AY conducted the statistical analysis. DY reviewed all the available histological samples. AG, AY, DY and HS supervised the writing of the article. All authors read and approved the final manuscript.

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Figures

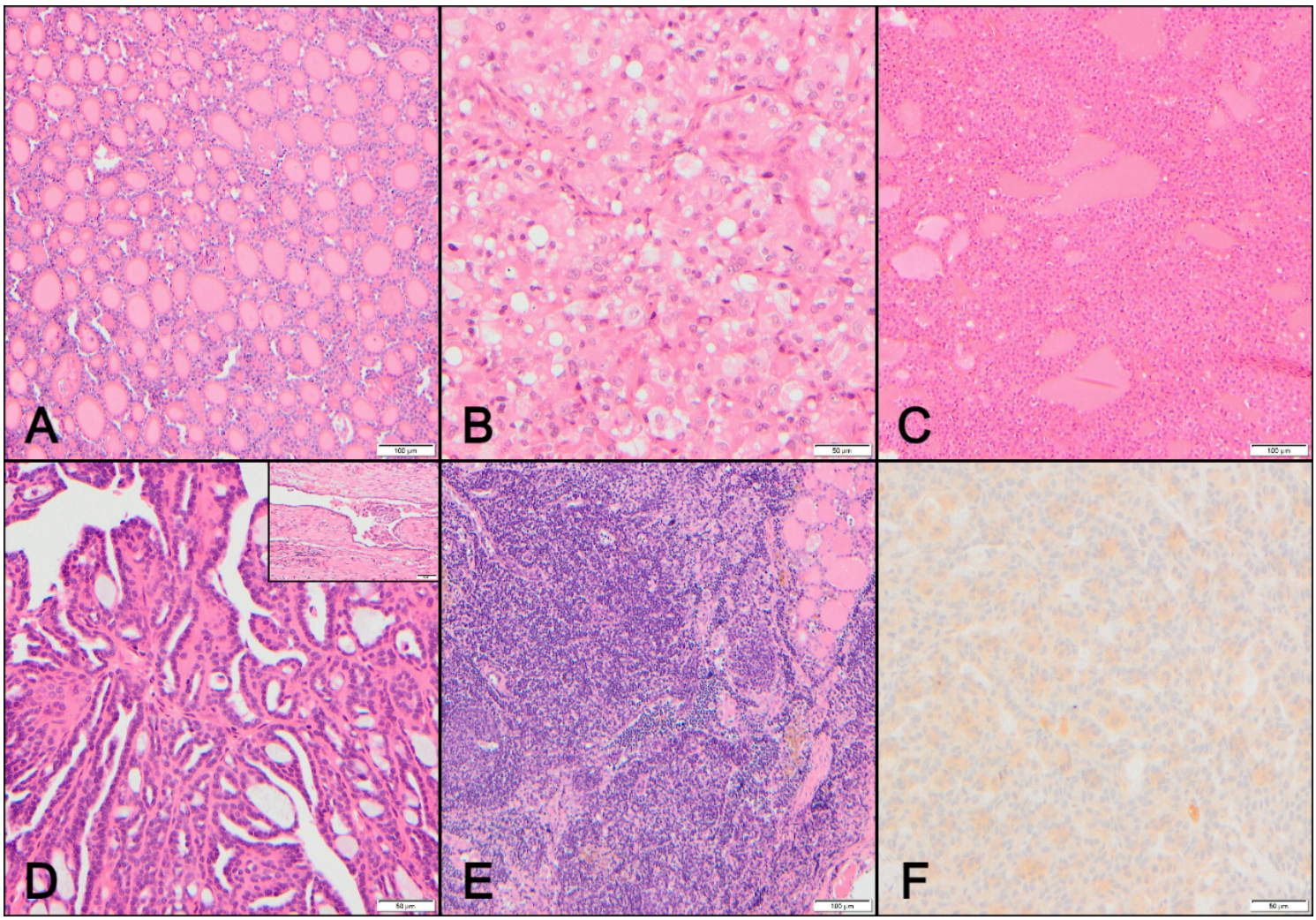


Figure 1

Histopathology characterization feline thyroid carcinoma. (A) H&E. 10x. Follicular TC. Neoplastic cells are arranged in follicles containing colloid. (B) H&E. 20x. Compact TC. Neoplastic cells are arranged in dense sheets with no follicle formation. (C) H&E. 10x. Follicular Compact TC. Neoplastic cells are variably arranged in dense sheets and follicles containing colloid. (D) H&E. 20x. Papillary Carcinoma. Neoplastic cells are arranged in arborising papillary projections supported by a thick fibrovascular stroma. Inset: Evidence of lymphovascular invasion. (E) H&E. 10x. Lymph node metastasis of a follicular

carcinoma. (F) Immunohistochemistry with antibodies against thyroglobulin. There is weak to moderate positive cytoplasmic (specific) labelling of approximately 50% of neoplastic cells.

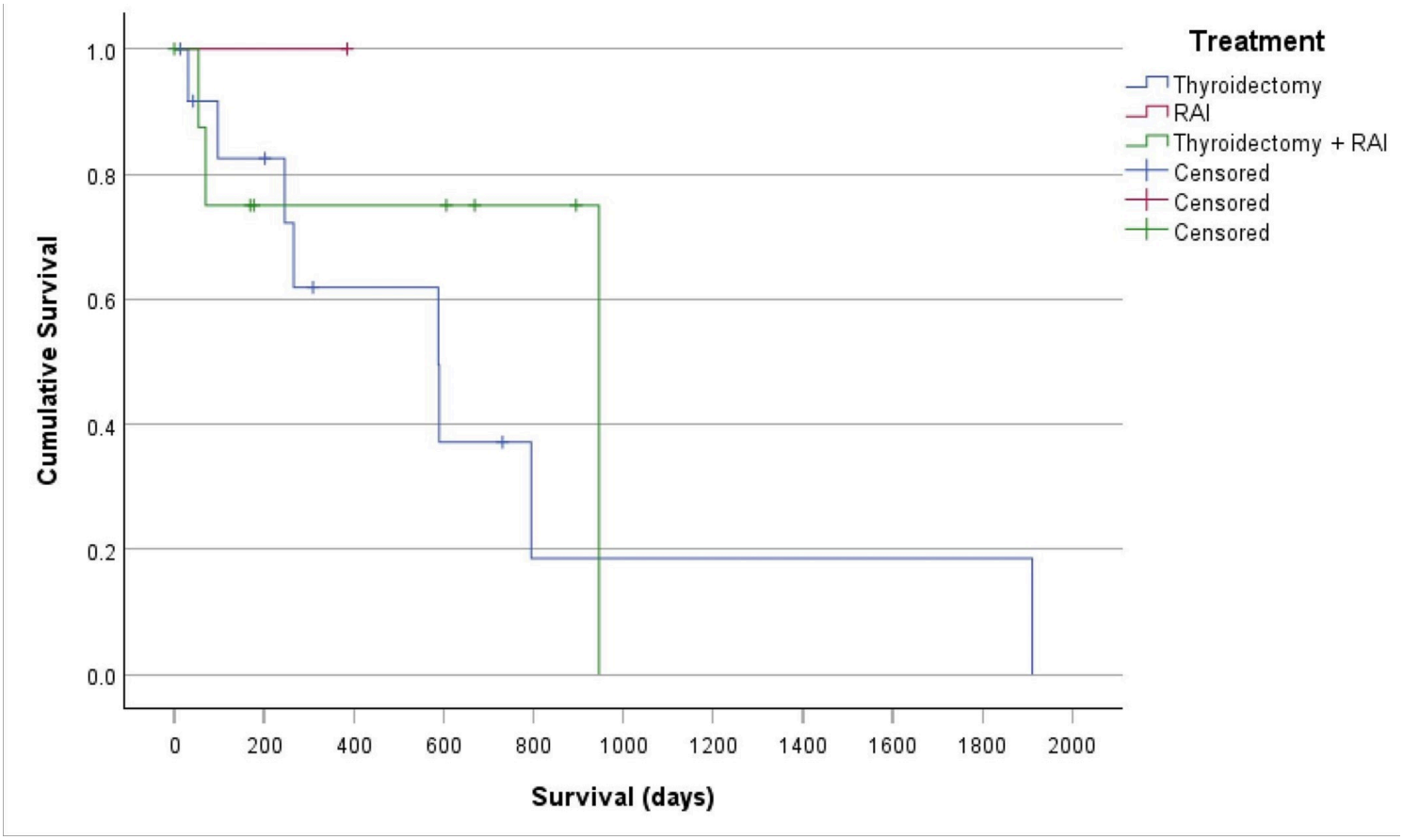


Figure 2

Kaplan-Meier curve showing survival times for 23 cats treated with thyroidectomy, high-dose radioactive iodine (HD-RAI), or both for thyroid carcinoma. *P* = .468.