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ORIGINAL ARTICLE

Prognostic factors and outcome in cats with thymic epithelial tumours: 64 cases (1999-2021)

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Objectives: To describe the clinical presentation, treatment and outcomes of cats diagnosed with thymic epithelial tumours and to determine prognostic factors for survival and recurrence.

Materials and Methods: Clinical records of cats diagnosed with a thymic epithelial tumour between 1999 and 2021 at three referral institutions were retrospectively reviewed.

Results: Sixty-four cats were included. Paraneoplastic syndromes were present in nine cats and metastatic disease was seen in two cats, one at diagnosis and one at the time of recurrence. Median tumour diameter was 6 cm (range, 2 to 15) and a cystic appearance was described on imaging in 25 cats. Surgical excision was attempted in 54 cats with a perioperative mortality rate of 11%. Median survival time for cats surviving to hospital discharge was 897 days (range, 21 to 3322). The 1-, 2- and 5-year survival rates for surgically treated thymic epithelial tumour were 86%, 70% and 66%, respectively. Survival was longer for cats with Masaoka-Koga stage I and II tumours compared to stages III and IV (1366 days *versus* 454 days; P=0.002). Masaoka-Koga stage was the only significant prognostic factor detected on multi-variable analysis, with stage III and IV tumours associated with increased risk of death (hazard ratio: 5.67, 95% confidence interval: 1.29 to 24.91, P=.021). Tumour recurrence occurred in 11 cats at a median of 564 days (range, 93 to 1095); no significant prognostic factors for recurrence were identified.

Clinical Significance: Cats with thymic epithelial tumours had a good long-term prognosis following surgery. Tumour recurrence can occur late in the disease course and ongoing monitoring should therefore be considered. Masaoka-Koga stage may influence survival time and could be used to predict outcome.

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INTRODUCTION

Thymic epithelial tumours (TETs) are uncommon neoplasms of thymic epithelial cells that typically arise in the cranial mediastinum and represent the second most frequent tumour in this location in cats after lymphoma (Souza, 2013). Less common neoplastic conditions include ectopic thyroid carcinoma, heart-base tumours and metastatic neoplasia (Rogers & Walker, 1997; Reichle & Wisner, 2000). Non-neoplastic conditions causing a mediastinal mass are rare and include cysts, abscess, granuloma, benign thymic hyperplasia and haemorrhage (Malik *et al.*, 1997; Rogers & Walker, 1997). While TETs have historically been grouped together under the term "thymoma," this nomenclature can be misleading as it often implies a benign

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process despite metastasis occasionally being reported (Patnaik *et al.*, 2003). Because of their variable histologic features, invasiveness, and potential for malignant clinical behaviour, the term TET is now preferred (Garneau *et al.*, 2014).

TETs are most commonly diagnosed in older cats with a median age at presentation of 9 years (Garneau *et al.*, 2014). Clinical signs often include dyspnoea, coughing, regurgitation, vomiting, weight loss and lethargy, which are the result of an intrathoracic space-occupying mass leading to compression or invasion of adjacent organs and tissues (Gores *et al.*, 1994, Zitz *et al.*, 2008, Garneau *et al.*, 2014). Paraneoplastic syndromes have been reported in up to 22% of cats (Garneau *et al.*, 2014) and include myasthenia gravis (Hague *et al.*, 2015), exfoliative dermatitis (Rottenberg *et al.*, 2004), erythema multiforme (Godfrey, 1999), multi-focal non-inflammatory alopecia (Fournier *et al.*, 2019), pemphigus (Hill *et al.*, 2013), myocarditis (Carpenter & Holzworth, 1982), polymyositis (Carpenter & Holzworth, 1982) and granulocytopenia (Fidel *et al.*, 2008). Interestingly, some of these syndromes are immune-mediated in nature and have been suggested to be due to abnormal maturation and selection of T-cells within the neoplastic thymus (Robat *et al.*, 2013; Weksler *et al.*, 2013). A definitive diagnosis may be achieved through ultrasound-guided cytology; however, differentiation between lymphoma and TET can be challenging when a predominance of small to intermediate lymphocytes is identified. Even though flow cytometry can aid in the diagnosis of canine TETs the high prevalence of double positive CD4/CD8 T-cells in mediastinal lymphoma in cats may limit its utility, and ultimately histopathology may be required for a definitive diagnosis (Bernardi *et al.*, 2020). CT of thorax and abdomen is generally the preferred staging method although metastatic disease to hilar lymph nodes, mesothelium and lungs is uncommonly reported (3 to 14% of cases). CT scan may also help assessing the tumour invasiveness and provides valuable information for surgical planning (Patnaik *et al.*, 2003, Robat *et al.*, 2013, Garneau *et al.*, 2014). Surgical excision is the treatment of choice for TET and, although perioperative mortality rate for cats has been reported to be between 11 and 22%, the outcome for those surviving the post-operative period is considered fair to good with a median survival time (MST) of 2 to 5 years (Gores *et al.*, 1994, Zitz *et al.*, 2008, Garneau *et al.*, 2014). For cats that are not considered surgical candidates or when residual disease is present after surgery, the use of neoadjuvant and adjuvant radiotherapy, chemotherapy and electrochemotherapy has been anecdotally reported (Smith *et al.*, 2001, Tong *et al.*, 2015, Spugnini *et al.*, 2017). Tumour recurrence and long-term metastatic disease appear to be uncommon after excision of feline TETs. In a case series of 10 cats with long-term follow-up, none had tumour recurrence or died of thymoma-related causes (Gores *et al.*, 1994) and, in another study, of 25 cats that survived the postoperative period only three cats and one cat developed recurrence and metastasis, respectively (Garneau *et al.*, 2014).

There is limited data on prognostic factors in cats. A microscopic cystic tumour appearance has been historically associated with a favourable outcome (Patnaik *et al.*, 2003) and Zitz *et al.* (2008) identified that a low lymphocyte percentage within the thymic mass was significantly associated with shorter survival when data from dogs and cats were pooled. In dogs, other reported prognostic factors include lack of surgical treatment, development of a second non-thymic neoplasia, incomplete excision and presence of paraneoplastic syndromes (Garneau *et al.*, 2014, Yale *et al.*, 2021), although some studies have not found the latter to be associated with a poor outcome (Robat *et al.*, 2013). In people with TET the strongest prognostic factor after surgical excision is the Masaoka-Koga stage (Table 1). This staging system is based on the presence of local microscopic and/or macroscopic invasion and lymphatic or hematogenous metastasis (Masaoka *et al.*, 1981, Robat *et al.*, 2013). Robat *et al.* (2013) also reported a prognostic role of this staging system in canine TET, with significantly longer survival times reported for stage I, IIA and IIB disease compared to stage III, IVa and IVb (1045 *versus* 224 days). The prognostic role of this system in cats is yet to be evaluated.

Table 1. Masaoka-Koga staging system (Masaoka *et al.*, 1981)

Stage	Description
I	Complete encapsulation of tumour
IIa	Microscopic tumour invasion through capsule
IIb	Macroscopic tumour invasion into surrounding fat
III	Invasion of pericardium, great vessels or lung
IVa	Pleural or pericardial dissemination
IVb	Lymphatic/haematogenous metastasis

The aims of this retrospective case series are firstly to describe the clinical presentation of a large cohort of cats diagnosed with TET and secondly to evaluate prognostic factors for recurrence and survival.

MATERIAL AND METHODS

Case identification

This retrospective study used anonymised clinical data and was approved by the social science research ethical review board of the Royal Veterinary College (URN SR2020-0228). Computerised clinical records database of three small animal referral hospitals were searched for cats that had a cytological or histopathological diagnosis of thymoma or thymic carcinoma between January 1999 and December 2021. Cats in which a TET had been diagnosed during the study period and had comprehensive clinical records were included in the study. Cats without a subsequent definitive diagnosis, with incomplete medical records or that presented for tumour recurrence were excluded.

Data collection

Information regarding signalment, presenting clinical signs and duration, physical examination findings, comorbidities, laboratory tests (complete blood cell counts [CBC], serum biochemistry and urinalysis), diagnostic findings, tumour size, staging results, cytological and histopathological reports, treatment

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(surgery, chemotherapy or radiotherapy), documented tumour recurrences, regional or distant metastasis and date and cause of death were obtained from the medical records. Comorbidities collected from medical records were defined as any chronic health condition diagnosed prior to detection of the TET.

Clinical signs that occurred at sites distant from the tumour or clinical-pathological abnormalities that resolved after excision of the TET for which no other identifiable causes were documented were considered to be paraneoplastic syndromes. Cats with paraneoplastic myasthenia gravis had to have compatible clinical signs and a positive nicotinic acetylcholine receptors (AChRs) antibody testing. If this was not performed, then myasthenia gravis was classified as "suspected." Cats with serum ionised calcium of >1.4 mmol/L were considered to be affected by paraneoplastic hypercalcaemia and those with a lymphocyte count of >10×109/L on peripheral blood were considered to be affected by paraneoplastic lymphocytosis.

Determination of tumour size was performed by assessing the maximum tumour diameter on CT scan, thoracic ultrasound and/or thoracic radiographs. A cystic appearance was determined based on imaging if the tumour had fluid-filled cavitations. The presence or absence of a pleural effusion was also recorded.

Diagnostic techniques were performed at the clinician's discretion and included ultrasound-guided fine needle aspiration, tru-cut biopsy, surgical biopsy or a combination of those. Cytology and histopathology reports for each case were retrospectively reviewed and information regarding mitotic count (MC), presence or absence of capsular invasion, histological subtype and margin assessment were collected. Tumours were classified as thymoma or thymic carcinoma based on the final diagnosis described in the histopathology report. Reports were considered inconclusive or non-diagnostic when a diagnosis other than TET could not be excluded or when cellularity was insufficient to confirm the diagnosis.

Histological samples were examined in all cases by a board-certified pathologist or a pathology resident under supervision. Mitotic count was only recorded if calculated as the total number of mitotic figures in 10 microscopic ×400 high-power fields (HPF). Tumour margin assessment was described as complete if cancer cells were not present at the surgical margin or incomplete if cancer cells were present at the cut margin or the surgical report described a marginal tumour resection with visible macroscopic disease being left at the surgical site. Capsule invasion was recorded as present or absent as described in the histopathology report.

For cats where information about microscopic capsular invasion based on the histopathology description, macroscopic invasion based on imaging or intraoperative surgical reports, and complete staging with thoracic and abdominal imaging was available, a Masaoka-Koga stage was assigned (Table 1). For the purpose of this study, the substage classification a/b was not used.

Intra- and post-operative complications were obtained from the medical records. Intraoperative complications were defined as adverse effects or complications occurring from skin incision to skin closure. Postoperative complications were defined as an adverse effects or complications occurring after skin closure.

TETs were considered unresectable based on the results of the diagnostic imaging or intraoperatively based on the appearance of the TET and the experience of the surgeon.

For cats that received chemotherapy, the drug type, protocol, doses, number of treatments and whether administration was in the macroscopic or microscopic setting were recorded. Antineoplastic drugs included carboplatin (124 to 178 mg/m2 IV q3 weeks), metronomic cyclophosphamide (15 mg/m^2 PO sid rounded to the nearest tablet size) and L-asparaginase (400 IU/kg SC). Chemotherapy toxicity was retrospectively graded according to the VCOG-Common Terminology Criteria for Adverse Events (VCOG-CTAE version 2, LeBlanc *et al.*, 2021). Dose reductions were performed at the clinician's discretion when toxicity occurred.

For cats treated with radiotherapy, the type of protocol (conventionally fractionated *versus* hypofractionated), the intent (palliative *versus* curative), the total dose delivered and whether this was used as sole treatment or in the neoadjuvant/adjuvant or relapse setting was recorded. For cats whose total radiotherapy dose was recorded, this ranged from 42 to 48Gy delivered in 10 to 16 fractions.

Prednisolone or NSAIDs (meloxicam) were used at standard dosages alone or in association with surgery, chemotherapy, radiotherapy or in the palliative setting.

Response to treatment was assessed using the Veterinary Cooperative Oncology Group Response Criteria in Solid Tumours (VCOG RECIST, version 1.0). This was classified as complete response (CR) if there was a 100% resolution of the tumour, partial response (PR) if there was >30% reduction in the overall tumour size, stable disease (SD) if there was <30% reduction but <20% increase in tumour size, and progressive disease (PD) if there was an increase in the tumour size of >20%. (Nguyen *et al.*, 2015). Restaging procedures were performed either using thoracic radiographs or CT in some cats at variable time intervals (3 to 6 months) or when clinical concerns arose, and imaging modality was based on the clinicians' preference.

To obtain follow-up information, referring veterinarians and/or owners were contacted via telephone. Tumour progression was defined as recurrence of a mediastinal mass documented on imaging investigations or development of distant metastasis confirmed to be thymoma/thymic carcinoma-related by cytology or histopathology.

Statistical analysis

Descriptive statistics were computed for all variables. Categorical variables were described as frequency and percentages. Continuous variables were tested for normality using Shapiro–Wilk test. If normally distributed, data was summarised as mean and standard deviation. If non-normally distributed, data were summarised using median and range.

Overall survival time (OST) was calculated from the day of surgery to the date of death or censorship and time to progression (TTP) was defined as the days between surgery to detection of tumour recurrence or metastasis. Cats were censored from survival analysis if they were alive at the time of analysis, died for reason unrelated to the TET or were lost to follow-up. Cats that

were not operated on, were euthanased intraoperatively or died before discharge were excluded from the survival analysis.

The Kaplan–Meier method and Cox proportional hazards analysis were performed to determine the possible effects of factors influencing survival time and recurrences. The explanatory variables were those previously listed. All variables were initially tested separately via univariate Cox proportional hazards analysis, and variables identified as P<0.2 were used to build a multi-variate Cox proportional hazards model. Cox proportional hazards analysis results are reported as odds ratios, 95% confidence intervals, and the associated P-value. For all tests, a P value <0.05 was considered statistically significant. Analyses were performed using Microsoft Excel 2020 and SPSS 26.0 (IBM SPSS statistics, version 26.0; IBM Corp, Armonk, New York).

RESULTS

Demographics and clinical presentation

Sixty-four cats met the study eligibility criteria. The population included 40 neutered male cats and 24 female cats (22 neutered and two entire). The most represented breed was domestic short hair (n=38, 59.4%) followed by British short hair (n=7, 10.9%), British blue (n=4, 6.3%), Burmese (n=3, 4.7%), Maine Coon (n=3, 4.7%), Abyssinian (n=3, 4.7%), Russian blue (n=2, 3.1%), domestic long hair (n=2, 3.1%), Persian (n=1, 1.6%) and Bengal (n=1, 1.6%). At the time of surgery, median bodyweight was 4 kg (range, 3 to 7 kg) and median age was 10 years (range, 3 to 17 years). The most common presenting clinical signs were dyspnoea/tachypnoea (n=38, 59.4%), cough (n=11, 17%), lethargy (n=8, 12.5%), anorexia (n=5, 7.5%), weight loss (n=4, 6.3%) and vomiting (n=4, 6.3%). In most cats, a combination of clinical signs was reported. Median duration of clinical signs before presentation was 10 days (range, 1 to 90 days). Seven cats (11%) without TET-associated clinical signs were incidentally diagnosed during investigations into unrelated problems.

Nine cats (14.1%) presented with a paraneoplastic syndrome at diagnosis but this was the main presenting clinical sign in only four cats. The paraneoplastic syndromes included lymphocytosis (n=4, ranging from 10.9×10^9 to 19.2×10^9), myasthenia gravis (n=3, confirmed with AchRs antibodies in two and suspected in one), exfoliative dermatitis (n=1) and ionised hypercalcaemia (n=1). Twenty-five cats (39.1%) had co-morbidities at the time of diagnosis, the most common being: hypertrophic cardiomyopathy (n=7, 10.9%), hyperthyroidism (n=4, 6.3%) and chronic kidney disease (n=4, 6.3%).

Diagnostic investigations and Masaoka-Koga staging system

Complete blood count was available in 55 cats; the most common abnormalities included lymphocytosis (n=9, 16%), anaemia (n=6, 11%) and neutrophilia (n=6, 11%). In 26 cats (47%), at least one abnormality was seen in the CBC. The remainder were within the reference limits. Serum biochemistry was available in 54 cats; the most common abnormalities included elevated creatinine kinase (n=10, 18.5%) and elevated creatinine (n=6, 11%). In 25 cats (46%), serum biochemistry was within the reference limits. Feline leukaemia virus (FeLV) and feline immunodeficiency virus (FIV) in-house ELISA tests (Idexx laboratories) were performed in 24 cats: one cat tested positive for FeLV and all cats were negative for FIV.

Thoracic imaging reports were available for review in 62 cats (96.9%) including thoracic and abdominal CT in 25 cats, thoracic CT only in seven cats, thoracic ultrasonography in 35 cats, thoracic radiographs in 20 cats, echocardiography in six cats and magnetic resonance imaging in three cats. Abdominal imaging reports were available for review in 39 cats (60.9%) including CT in 25 cats and abdominal ultrasonography in 14 cats. A combination of these imaging modalities was used in 31 cats. A cranial mediastinal mass was detected in all cases with a median tumour diameter of 6 cm (measurements performed in 38 cats; range, 2 to 15 cm). Measurements of the tumour diameter were reported in all cats undergoing thoracic CT and 5 cats with thoracic ultrasound but were not recorded in the remaining cats.

A cystic appearance was reported on imaging in 25 masses, and pleural effusion was present in 21 cats. Sixteen of the 21 effusions (76%) were analysed: seven were modified transudates (43.8%), four were chylous effusions (25%), three were transudates (18.8%) and two were haemorrhagic (12.5%).

Only one cat was suspected to have pulmonary metastases at diagnosis: multiple, nodular lung lesions were observed on CT, however, cytological or histopathological samples were not obtained (Table 2). This cat did not undergo surgical resection but received palliative radiotherapy instead.

Forty-four masses were sampled pre-operatively via fine needle aspiration, 10 masses via tru-cut biopsy and 8 masses via both methods. From the 52 cytological samples, 32 samples were consistent with thymoma (61.5%), one sample was consistent with

Table 2. Clinical characteristics, laboratory and radiological findings in 64 cats with thymic epithelial tumours

	No. of cats affected /No. cats evaluated (%)
Clinical characteristics	
Dyspnoea/tachypnoea	38/64 (59.4)
Cough	11/64 (17.1)
Lethargy	8/64 (12.5)
Anorexia/inappetence	5/64 (7.5)
Vomiting	4/64 (6.3)
Weight loss	4/64 (6.3)
Paraneoplastic disease	9/64 (14.1)
Laboratory findings	
Ionised hypercalcaemia	1/54 (1.9)
Anaemia	6/55 (10.9)
Lymphocytosis	9/55 (16)
Neutrophilia	6/55 (10.9)
Azotaemia	6/54 (11.1)
Elevated creatine kinase	10/55 (18.5)
Imaging findings	
Pleural effusion	21/61 (34.4)
Cystic thymic mass	25/60 (41.7)
Metastasis	1/62 (1.6) at diagnosis and 2/62 (3%) when considering follow-up period

thymic carcinoma (1.9%), 16 samples were inconclusive (30.8%) and three samples were non-diagnostic (5.8%).

From the 18 masses that were sampled via tru-cut biopsy, 15 samples were consistent with thymoma (83.3%), one sample was consistent with thymic carcinoma (5.6%) and two samples were non-diagnostic (11.1%). In those cases where both cytology and histopathology were performed, results were both compatible with the diagnosis of TET.

Thirty-two cats were staged using the Masaoka-Koga staging system. Sixteen had stage I (50%), four had stage II (12.5%), 10 had stage III (31.3%) and two had stage IV (6.3%) disease (Table 3).

Treatment and perioperative mortality

Fifty-four (84.4%) cats underwent surgery. In 10 cats, surgical intervention was not performed. Of these, three were euthanased upon diagnosis. In two cats, surgery was not performed due to a comorbidity: one cat died at 32 days due to concomitant maxillary neoplasia and the other died at 30 days due to congestive heart failure. Two cats received palliative prednisolone with survival of 7 and 365 days. One cat received palliative radiotherapy (dose unknown) and achieved a PR before being euthanased 150 days after diagnosis. The other two cats were lost to follow-up.

All surgeries were performed by, or under the direct supervision of a European College of Veterinary Surgeons (ECVS) board-certified surgeon. A median sternotomy was used as surgical approach in all cats. Concomitant surgical procedures performed included a subtotal pericardiectomy (n=4), thoracic duct ligation (n=2), right cranial lung lobectomy due to severe adhesions (n=2) and sternal lymphadenectomy due to enlargement of the sternal lymph nodes observed on CT scan (n=1).

Surgery was uncomplicated in 49 of 54 cats (85%). Intraoperative complications were recorded in five cats (9%) and included hypotension (n=3) and haemorrhage (n=2, one requiring blood-derived products). In three cats (5%) the TET was considered invasive and unresectable by the surgeon, and the cats were euthanased intraoperatively.

In the postoperative period, 10 cats suffered a complication (20%), including: haemorrhage (n=2; one requiring transfusion of blood-derived products and one requiring a surgical reintervention), anaemia (n=2), hypotension (n=2), surgical site infection at the level of the thoracostomy tube (n=1), transient megaoesophagus (n=1), Horner's syndrome (n=1) and aspiration pneumonia (n=1). As a result of these complications, cardiopulmonary arrest occurred in three cats leading to death. Fifty-one cats survived the surgical procedure. Three cats died in the immediate postoperative period resulting in an overall perioperative mortality rate of 11% (6/54). These three cats along with three other cats that died in the immediate postoperative period were excluded from survival analysis.

Forty-eight (89%) cats survived to be discharged from the hospital. Masaoka-Koga stage was available for five out of six cats that did not survive the perioperative period: four cats had stage III and one stage IV.

Three cats received antineoplastic drugs, with two receiving adjunctive chemotherapy postoperatively. One cat with an incompletely excised, non-metastatic thymic carcinoma received carboplatin; 178 mg/m^2 IV was administered initially for one dose then reduced to 124 mg/m^2 due to grade II neutropenia detected 2 weeks after treatment that persisted for 32 days. The lower dose was administered every 3 weeks for four doses, before changing to metronomic cyclophosphamide (14.5 mg/m^2 PO sid) and meloxicam (0.05 mg/kg PO sid) following recurrence of the pleural effusion. One cat with a completely excised thymoma received palliative metronomic cyclophosphamide (14.23 mg/m^2 PO sid) and meloxicam (0.05 mg/kg PO sid) at the time of recurrence for 60 days before being euthanased.

One cat received a single dose of L-asparaginase (400 IU/kg SC) before tru-cut biopsy results confirmed a TET. This was administered empirically due to marked clinical deterioration and a suspicion of mediastinal lymphoma. Surgery was performed and no adjunctive chemotherapy was administered postoperatively.

Three cats received radiotherapy postoperatively; two in the adjuvant setting and one at the time of recurrence. One cat with incomplete TET resection received 48 Gy over 16 fractions immediately postoperatively, achieved a PR but experienced recurrence at 300 days. A second surgery was performed, and disease recurred 60 days after the second surgery. This cat was subsequently lost to follow-up. The second cat received 42 Gy over 10 fractions following incomplete excision. A PR was reported on first restaging with thoracic radiographs 30 days after radiotherapy and the cat remained in PR on restaging at 90, 180, 360, 540 and 720 days after radiotherapy. This cat was subsequently lost to follow-up. The third cat received 42 Gy over 15 fractions following recurrence at 417 days and experienced a CR. This cat remains alive at last follow-up, 597 days after surgical excision.

Table 3. Masaoka-Koga stage and histological findings for cats with thymic epithelial tumours

	No. of cats affected/No. of cats evaluated (%)
Masaoka-Koga stage	
Stage I	16/32 (50)
Stage II	4/32 (12.5)
Stage III	10/32 (31.3)
Stage IV	2/32 (6.3)
Histological findings	
Thymoma	44/50 (88)
Thymic carcinoma	6/50 (12)
Capsular invasion	
Present	8/50 (16)
Absent	42/50 (84)
Lymphovascular invasion	
Present	1/23 (4.3)
Absent	22/23 (95.7)
Margin assessment	
Complete	24/40 (60)
Incomplete	16/40 (40)
Follow up	
Recurrence	11/48 (22.9)

Histopathological findings

A histopathological diagnosis of TET was made in all cats undergoing surgery but reports were available for review in 50 (93%)

cats. Thymoma was diagnosed on histopathology in 44 cats (88%) and thymic carcinoma in six cats (12%).

The median mitotic count per 10 HPF was one (range, 0 to 20) and capsular invasion was described in eight cats (16%). Evaluation of surgical margins was available in 40 cats (74%) with complete excision reported in 24 cats (60%) and incomplete excision in 16 cats (40%). Histopathology of the sternal lymph nodes excised in one cat revealed no evidence of regional metastasis.

Outcome and prognostic factors

Follow-up time was available in 36 of 48 cats (75%) surviving to discharge and ranged from 31 to 3322 days (median, 897 days).

Among those 48 cats, 10 cats remained alive at the time of study completion. Eight cats died or were euthanased during the follow-up period for causes directly or suspectedly related to TET between 21 and 960 days, including recurrence (n=5), pleural effusion (n=1), dyspnoea (n=1) and cranial vena cava thrombus (n=1).

MST for cats surviving to hospital discharge was 897 days (range, 21 to 3322 days). Based on Kaplan–Meier estimates, the 1-, 2- and 5- year survival were 86%, 70% and 66%, respectively.

Tumour recurrence was identified in 11 cats at a median TTP of 564 days (range, 93 to 1095 days): six had incomplete margins and five recurred despite histological complete excision. Local recurrence developed in all cats with concurrent regional (axillary lymph node) metastasis found in one cat. Two cats with recurrence underwent a second surgery at 300 and 1095 days, respectively, from the initial surgery. The first cat experienced a second recurrence 60 days after and was subsequently lost to follow-up and the second cat was lost to follow-up immediately after the second surgery.

Masaoka-Koga stage could be evaluated in seven cats with recurrence: one cat had stage I, two cats had stage II and four cats had stage III tumours. During the follow-up period, four cats were diagnosed with second tumours during restaging: one nasal adenocarcinoma, one mediastinal ectopic thyroid adenoma, one ocular tumour and one humeral osteosarcoma.

Of the three cats with myasthenia gravis, two experienced resolution after surgery. Of these, one was treated with pyridostigmine and prednisolone and experienced resolution at 120 days and the second showed reducing anti-AChR antibody titres at 90 days and experienced resolution at 150 days. The third cat's myasthenia gravis did not improve; this cat had tumour recurrence at 180 days.

Cats with TET classified as Masaoka-Koga stage I and II had significantly longer MST compared with TET classified as Masaoka-Koga stage III and IV (1366 days *versus* 454 days; P=0.002, Fig 1). There was no difference in MST between cats with complete and incomplete excision (980 days *versus* 730; P=0.278) and between cats with a histological diagnosis of thymoma and thymic carcinoma (962 days *versus* 564; P=0.153).

Logistic regression analysis was used to determine factors associated with survival and recurrence with possible confounding factors taken into account. After the initial model was refined by backward-stepwise elimination the best fit model for survival included cystic appearance, tumour diameter, Masaoka-Koga stage, pleural effusion, histological diagnosis (thymoma *versus* thymic carcinoma) and tumour recurrence (Table 4). In the final multiple-regression model, the only factor associated with an increased risk of death included Masaoka-Koga stage III to IV (Table 5). No prognostic factors were found to be significantly associated with TTP (Table 6).

DISCUSSION

The results of this retrospective study suggest that cats undergoing TET excision have a good long-term survival and cats with a lower Masaoka-Koga stage may live longer after surgery than those with a more advanced disease stage.

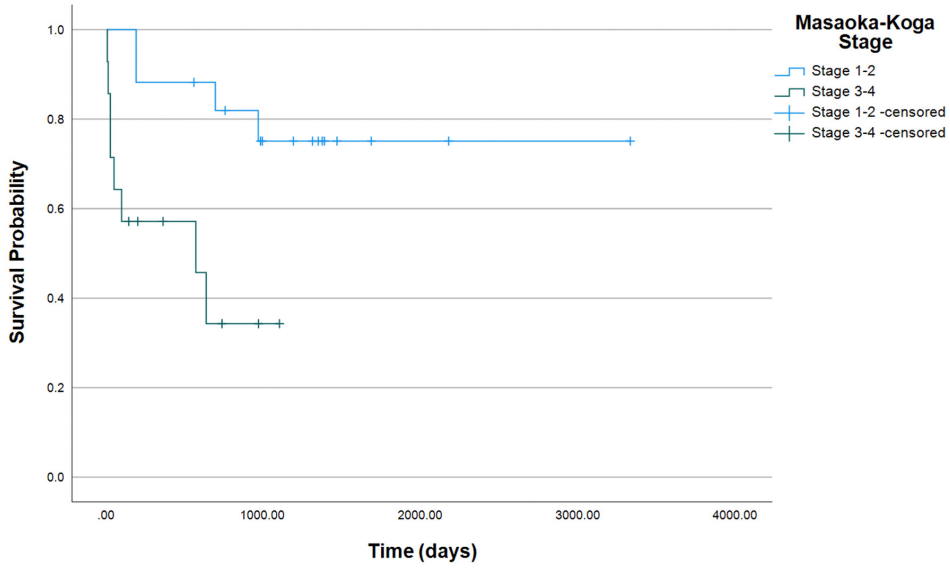

FIG 1. Kaplan-Meier survival curve for cats with Masaoka-Koga stage I and II *versus* stage III and IV thymic epithelial tumours

Table 4. Simple logistic regression results determining factors associated with survival time after surgical intervention of thymic epithelial tumours in cats

Logistic regression	Survival		
	OR	95% CI	P value
Age	0.96	0.78 to 1.18	0.743
Purebred	0.58	0.15 to 2.17	0.425
Gender	1.27	0.38 to 4.23	0.693
Bodyweight	1.40	0.77 to 2.55	0.269
Duration of clinical signs	0.90	0.77 to 1.05	0.212
Respiratory signs	1.68	0.45 to 6.25	0.432
Paraneoplastic syndrome	0.25	0.03 to 1.98	0.290
Cystic appearance	**6.49**	**1.38 to 30.50**	**0.018**
Tumour diameter	**1.16**	**0.98 to 1.39**	**0.080**
Pleural effusion	**2.85**	**0.89 to 9.08**	**0.076**
Masaoka-Koga stage	**4.66**	**0.13 to 16.02**	**0.015**
Histological diagnosis (thymoma *versus* carcinoma)	**0.40**	**0.10 to 1.48**	**0.170**
Capsular invasion	0.88	0.22 to 3.53	0.860
Mitotic count	0.80	0.33 to 1.91	0.626
Complete excision	0.47	0.11 to 1.89	0.292
Recurrence	**2.65**	**0.80 to 8.72**	**0.109**

OR Odds ratio, CI Confidence interval
Reference category used in logistic regression. Variables highlighted in bold qualified for inclusion in the multiple regression analysis at P<0.20

Table 5. Multiple logistic regression results determining factors associated with survival time after surgical intervention of thymic epithelial tumours in cats

Logistic regression	Survival		
	OR	95% CI	P value
Cystic appearance	3.02	0.58 to 15.63	0.187
Tumour diameter	1.10	0.91 to 1.35	0.305
Pleural effusion	0.52	0.74 to 3.67	0.512
Masaoka-Koga stage	**5.67**	**1.29 to 24.91**	**0.021**
Histological diagnosis (thymoma *versus* carcinoma)	0.50	0.76 to 22.98	0.485
Recurrence	3.43	0.74 to 15.83	0.113

OR Odds ratio, CI Confidence interval.
Variable highlighted in bold is statistically significant (significance set at P<0.05)

Table 6. Simple logistic regression results determining factors associated with recurrence after surgical intervention of thymic epithelial tumours in cats

Logistic regression	Tumour recurrence		
	OR	95% CI	P value
Age	0.83	0.61 to 1.14	0.261
Purebred	0.02	0.00 to 23.81	0.302
Gender	0.77	0.23 to 2.55	0.674
Bodyweight	0.92	0.46 to 1.82	0.818
Duration of clinical signs	1.00	0.93 to 1.08	0.885
Respiratory signs	1.21	0.31 to 4.75	0.778
Paraneoplastic syndrome	0.73	0.15 to 3.58	0.701
Cystic appearance	1.34	0.35 to 5.17	0.667
Tumour diameter	1.12	0.89 to 1.40	0.307
Pleural effusion	1.71	0.48 to 6.08	0.402
Masaoka-Koga stage	0.92	0.21 to 3.94	0.915
Histological diagnosis (thymoma *versus* carcinoma)	1.15	0.24 to 5.48	0.861
Capsular invasion	0.62	0.14 to 2.66	0.525
Mitotic count	0.98	0.83 to 1.16	0.870
Complete excision	1.27	0.33 to 4.82	0.716

OR Odds ratio, CI Confidence interval
Reference category used in logistic regression. No variables had a P<0.20, therefore multivariable analysis was not performed

TET is an uncommon disease and cats typically present with respiratory signs attributable to the presence of an intrathoracic mass or due to associated paraneoplastic syndromes (Robat *et al.*, 2013). It is worth noting that 11% of cats in this population had an incidentally identified cranial mediastinal mass.

In this study nine cats were diagnosed with a paraneoplastic syndrome including lymphocytosis, myasthenia gravis, exfoliative dermatitis and ionised hypercalcaemia. Studies in dogs have suggested that these could negatively affect outcome (Garneau *et al.*, 2014) however, due to the low number of affected cats, this could not be evaluated in the present study.

Up to 40% of human patients with TET have a concurrent neoplasia and 27% of dogs with TET had a second non-thymic tumour at the time of the TET diagnosis with another 14% developing another neoplasm during the follow-up period (Robat *et al.*, 2013, Thongprayoon *et al.*, 2013). Robat *et al.* (2013) reported the presence of a second non-thymic tumour at the time of TET diagnosis was associated with a significant decrease in survival time, whereas no negative influence on survival time was noted if another tumour developed later. In the present study population only one cat had a concomitant maxillary neoplasia; however, complete staging was not performed in all cats and concurrent neoplasms could have been missed. During the follow-up period only four cats developed a non-thymic neoplasia but it remains uncertain if TET could increase this risk.

In this study cats that underwent surgery via median sternotomy had a perioperative mortality of 11%, which is the same as Zitz *et al.* (2008) but lower than the 22% reported by Garneau *et al.* (2014). In those cats not surviving to discharge where Masaoka-Koga stage system could be applied, an advanced disease stage (III to IV) was found in all of them. This likely reflects a more invasive tumour behaviour and difficult excision in those cases and may prompt the clinician to inform clients of a possible increased risk of perioperative complications or to consider alternative treatments (*e.g.* radiotherapy) instead. It is worth noting that cats that died in the perioperative period were excluded from the survival analysis and this should be taken into consideration when interpreting the survivals reported as it could have induced survival bias.

For incompletely resected or non-resectable tumours, a multimodal treatment approach may need to be considered (Zitz *et al.*, 2008, Rohrer-Bley *et al.*, 2018). In this study, radiation therapy resulted in a PR in two cats and CR in another. Our findings are consistent with the limited available studies (Kaser-Hotz *et al.*, 2001, Smith *et al.*, 2001, Rohrer-Bley *et al.*, 2018); one previous paper described the successful reduction in tumour size in three cases of suspected feline TET with a radiation protocol using 18 Gy over three fractions (Kaser-Hotz *et al.*, 2001). Of those, one cat was well controlled for 4 years before recurrence happened (Kaser-Hotz *et al.*, 2001). A second retrospective study assessed the use of radiation therapy for seven cats with TET, using a variety of protocols (ranging from daily to weekly treatments) and total doses of 15 to 54 Gy administered. The response

to radiotherapy could be evaluated in four of seven cats, two cats experienced a PR and two experienced a CR (Smith *et al.*, 2001). The MST for all seven cats was 720 days (range, 485 to >1825; Smith *et al.*, 2001). Similarly, Rohrer-Bley *et al.* (2018) described rapid tumour reductions in three cats with TET treated with neoadjuvant radiotherapy (36 Gy delivered over 12 fractions) with survivals of 261, 362 and 680 days. These findings are encouraging and suggest further exploration would be worthwhile.

While three cats with TET were treated with various chemotherapy agents before or after surgery, the objective response to treatment and adverse events were not assessed in any of them. This, together with the small number of cases receiving chemotherapy and the variable clinical circumstances under which it was given, precluded assessment of its efficacy. Further studies are needed to assess the role of chemotherapy when incomplete excision occurs in the absence of radiotherapy or in the neoadjuvant setting.

In this study, the human Masaoka-Koga staging system was used, and it was associated with outcome for the cats undergoing TET excision: there was a significantly longer MST (1084 days) for cats with the lower disease stages (I to II). This staging system could therefore be applied to all cats undergoing surgical treatment of a TET and used as additional information to predict survival time. Moreover, cats with more advanced stages may benefit from closer monitoring or adjunctive therapy.

No differences were observed when comparing cats with completely or incompletely excised TET or when comparing the histological diagnosis between thymoma and thymic carcinoma. The importance of TET histological subtypes (thymoma *versus* thymic carcinoma) still needs to be clarified. Firstly, different subtype schemes have been used in both human and veterinary medicine, although more recently the World Health Organisation scheme (Marx *et al.*, 2015) has been adopted. Secondly, there is marked interobserver variation when assigning the histological subtypes in human TET (Dawson *et al.*, 1994, Detterbeck, 2006, Verghese *et al.*, 2008). Nevertheless, most human studies show that thymic carcinoma has the worst survival, but whether this has independent prognostic significance is unclear (Kondo *et al.*, 2004, Rea *et al.*, 2004, Rieker *et al.*, 2008, Weissferdt & Moran, 2015, Knetki-Wróblewska *et al.*, 2021). These histologic subtypes have not demonstrated prognostic significance in dogs (Burgess *et al.*, 2016; Yale *et al.*, 2021).

As suggested in previous studies, the metastatic rate of TETs was low (3%) despite including six cats with thymic carcinomas (Patnaik *et al.*, 2003; Garneau *et al.*, 2014). Local recurrence was higher than previously reported and was identified in 11 cats (23%) and occurred late in the disease course, at a median TTP of 564 days (Table 7). Five cats experienced recurrence despite histologically confirmed complete excision but no factors were found to be helpful for predicting recurrence. Assessment of margin status in TETs may prove difficult due to tumour adherences to other structures and lack of tissue orientation; unless those relevant areas are inked, there is a risk that margins in some TETs could have been underestimated. The largest previous study on feline TET reported a 9% recurrence rate (Garneau *et al.*, 2014). Based on these results, regular, active monitoring should be offered to owners of cats even if diagnosed with suspected completely excised TETs. Further studies are warranted to identify factors influencing recurrence and to analyse the effect of adjuvant therapies on the rate of recurrence, especially in cats with microscopic or macroscopically incompletely excised tumours.

This retrospective study has some limitations. This is the largest study of TETs in a purely feline population, but case numbers prevent us from being definitive about certain statistical findings. The multi-centre nature of the study and the long-time frame were associated with heterogeneous diagnostic and treatment approaches, and a significant number of patients that were lost to follow-up. Additionally, some cats were not fully staged or advanced imaging was not performed and the Masaoka-Koga staging system could not be applied. This staging system has also inherent limitations, as it relies on the presence of invasion on CT or intraoperatively, and those observations can sometimes be inaccurate. Restaging procedures were not standardised; this could have been due to variable owner compliance, the costs associated with imaging investigations or inconsistent recommendations made by different clinicians and could lead to tumour recurrence or metastasis being underestimated. A referral hospital bias may also be present: this includes case management by specialised surgeons, closer case monitoring and higher owner motivation to treat.

Table 7. Summary of the available literature† describing treatment and outcomes of feline thymic epithelial tumours

	No. of cats	Treatment	Recurrence (no. of cats)	Metastasis (no. of cats)	Median survival time (days)	Survival rates
Gores *et al.* (1994)	12	Surgery	0	0	Survivals ranged from >180 to 1860	–
Smith *et al.* (2001)	7	Radiotherapy ±surgery ±chemotherapy	3	–	720	–
Patnaik *et al.* (2003)	14	Surgery ±chemotherapy ±radiotherapy	1	3	–	–
Zitz *et al.* (2008)	9	Surgery	1	0	1825	89% at 1-year and 74% at 3-years
Garneau *et al.* (2014)	32	Surgery ±chemotherapy	3	1	>1350	70%, 63%, 63% and 47% at 1-, 2-, 3- and 4-years
Present study	64	Surgery ±chemotherapy ±radiotherapy and palliative treatment	11	2	897	86%, 70%, and 66% at 1-, 2- and 5-years

†Studies included had a minimum of five cats

This study suggests that surgical excision of TET in cats is associated with a favourable long-term prognosis; however, late local recurrence is a risk. Cats with advanced Masaoka-Koga stage may benefit from closer active monitoring after surgery or adjuvant therapy. The role of radiotherapy and chemotherapy in cats warrants further study. A better understanding of tumour biology and trials of adjunctive therapy is also needed and may allow a more individualised treatment approach.

Conflict of interest

None of the authors of this article has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

Author contributions

Thomas A. Marks: Conceptualization (equal); data curation (equal); validation (equal); writing – original draft (equal). **Matteo Rossanese:** Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); supervision (equal); validation (equal); writing – original draft (equal). **Andrew D. Yale:** Conceptualization (equal); data curation (equal); methodology (equal). **Sarah Stewart:** Conceptualization (equal); supervision (equal); writing – review and editing (equal). **Katherine Smallwood:** Conceptualization (equal); data curation (equal); writing – review and editing (equal). **Konstantinos Rigas:** Conceptualization (equal); data curation (equal); writing – review and editing (equal). **Alexandra Guillén:** Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); supervision (equal); validation (equal); writing – original draft (equal).

Data availability statement

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

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