Perioperative Mortality and Long-Term Survival in 80 Dogs and 32 Cats Undergoing Excision of Thymic Epithelial Tumors

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Objective: To examine perioperative mortality, long-term survival, causes of death, and prognostic factors for dogs and cats undergoing surgical excision of thymic epithelial tumors (TETs).

Study Design: Multi-institutional case series.

Animals: Eighty dogs and 32 cats.

Methods: Follow-up information was obtained for dogs and cats that underwent surgical excision of a TET between 2001 and 2012.

Results: Perioperative mortality was 20% in dogs and 22% in cats. No independent risk factors for perioperative mortality were identified. The estimated median survival time for all dogs was 1.69 years (95% CI 0.56–4.32) and the 1- and 4-year survival rates were 55% (95% CI 44–67) and 44% (95% CI 32–56). The estimated median survival time for all cats was 3.71 years (95% CI 0.56–unestimatable) and the 1- and 4-year survival rates were 70% (95% CI 53–87) and 47% (95% CI 0–100). Of animals that survived to discharge, 42% of dogs and 20% of cats eventually died of TET-related causes. The presence of paraneoplastic syndromes (hazard ratio [HR] 5.78, 95% CI 1.64–20.45, P = .007) or incomplete histologic margins (HR 6.09, 95% CI 1.50–24.72, P = .01) were independently associated with decreased survival in dogs. No significant predictors of survival were identified in cats. Conclusions regarding the effect of chemotherapy or radiation therapy could not be made.

Conclusions: While there is substantial risk of perioperative death in dogs and cats undergoing surgery for TETs, many animals that survive to discharge have prolonged survival. Survival is significantly decreased in dogs with paraneoplastic syndromes or incomplete histologic margins.
Median survival times were 790 days in 11 dogs and 1,825 days and 21 months in 9 and 12 cats, respectively. In these studies, the only prognostic factors significantly associated with shorter survival were the presence of myasthenia gravis-related megaesophagus in dogs and low lymphocyte percentages within the thymic mass in dogs and cats combined. Radiation therapy and chemotherapy have been used to control residual disease, local recurrence, or metastatic disease, but limited information concerning efficacy is available. The largest report described a multi-institutional study of 17 dogs and 7 cats treated with radiation alone or as adjunctive therapy and reported estimated median survival times of 248 days in dogs and 720 days in cats, with partial or complete responses in 75% of animals. Consistent with these results, 5 of 8 dogs in the recent multi-institutional case series had a partial response to radiation therapy. Reports on the efficacy of chemotherapy for thymoma are available for a small number of cases.

The goal of this study was report on perioperative mortality, long-term survival, causes of death, and prognostic factors for dogs and cats undergoing surgical excision of TETs. A secondary objective was to assess whether survival was improved by the administration of chemotherapy or radiation therapy.

MATERIALS AND METHODS

Case Selection

Electronic medical record searches identified all dogs and cats that underwent surgical excision of a histologically confirmed TET at 6 referral institutions between January 2001 and June 2012. Animals that survived the perioperative period were included only if long-term follow-up information was available.

Data Collection

Information obtained from medical records included species, breed, sex, age, body weight, history, physical examination findings, presenting clinical signs, documented paraneoplastic syndromes, results of pre-operative laboratory tests (complete blood counts and serum biochemistry analysis), results of thoracic imaging (radiographs, ultrasound, and computed tomography [CT]), surgical findings, histologic findings, adjunctive treatment (radiation therapy and chemotherapy), documented distant and local recurrences and their treatment, documented metastatic disease, and date and cause of death.

Documentation of Paraneoplastic Syndromes. Animals were considered to have myasthenia gravis if consistent clinical signs (megaesophagus, regurgitation, and/or generalized weakness) were present in combination with a positive acetylcholine receptor antibody titer and/or tension response test. Hypercalcemia was considered paraneoplastic if the ionized calcium concentration was elevated above the reference interval, the parathyroid hormone concentration was below the reference interval, and no likely cause other than the TET was detected. For animals that did not have a parathyroid hormone assay performed, hypercalcemia was considered to be paraneoplastic only if elevated preoperative ionized calcium concentrations returned to the reference interval following excision of the TET. Cats were considered to have thymoma-associated exfoliative dermatitis if they had characteristic dermatologic lesions (progressive, non-pruritic erythema, scaling and alopecia) combined with histologic evidence of the syndrome (orthokeratotic hyperkeratosis with interface dermatitis).

Definition of a Cystic Thymic Mass. Masses were defined as cystic if a portion of the mass appeared fluid-filled or cavitated on pre-operative imaging (ultrasound or CT).

Determination of Mass Volumes. The volume of each mass was calculated based on its maximal radius on CT (if performed), ultrasonography (if CT was not performed), or radiography (if neither CT nor ultrasonography were performed). Relative tumor volumes were calculated as the ratio of the volume of the mass (cm³) to the body weight of the animal (kg).

Confirmation of Metastatic Disease. Metastatic disease at presentation and during follow-up was documented by detection of pulmonary nodules on CT or radiographs. Lesions identified at other sites were considered metastatic only if confirmed by cytologic or histologic examination. In animals in which pulmonary nodules were excised at the time of thymic mass excision, metastatic disease was considered present only if confirmed by histologic examination.

Definition of Tumor Invasiveness. Masses were considered locally invasive if resection required removal of a section of pericardium, lung, or cranial vena cava.

Definitions of Complete and Incomplete Histologic Margins. Histologic margins were considered free of disease (complete) if the TET was surrounded by an intact capsule of normal tissue in all sections examined. Margins were considered incomplete if there was no capsule present or if the capsule was not intact in any section.

Postoperative Follow-up. Perioperative mortality was defined as failure to survive to discharge. Animals that survived to discharge were followed for evidence of resolution of pleural effusion and paraneoplastic syndromes, evidence of local or distant tumor recurrence, and cause of death. Animals were considered to have had local tumor recurrence if they developed a subsequent mediastinal mass documented by any imaging modality. Follow-up information that could not be obtained through medical record review was obtained by telephone and email communication with referring veterinarians and owners.
Statistical Analysis

Kaplan–Meier estimates of overall survival probability from the day of surgery were generated for dogs and cats and used to estimate the median survival times and proportions of animals alive at 1, 2, 3, and 4 years following surgery. Animals that died perioperatively and animals that received chemotherapy or radiation therapy were included in the analysis. Deaths were considered to be tumor-related if they occurred during surgery or prior to discharge from the hospital, or were the result of a postoperative complication, lack of resolution of pleural effusion or a paraneoplastic syndrome, development of a paraneoplastic syndrome following surgery, or development of locally recurrent or metastatic disease. Animals alive at the time of the last follow-up and animals that died of causes unrelated to the TET or of unknown causes were right-censored. Deaths due to concurrent neoplasia were considered to be unrelated to the TET. Kaplan–Meier survival curves for dogs and cats were compared using a log-rank test with significance determined at \( P < .05 \).

Univariate logistic regression analysis was used to examine the association between relative tumor volume and the intraoperative finding of tumor invasiveness.

An exploratory univariate logistic regression analysis was performed to examine the effects of clinical parameters considered to have potential to influence perioperative mortality. This analysis was performed separately for dogs and cats. Age was converted to a binary variable using 10 years as an arbitrary division between old and young animals. Relative tumor volume was converted to a binary variable using the median volume for either dogs or cats as the cutoff. Variables significant at \( P \leq .25 \) in the univariate analysis were included in multivariable analysis. Backward stepwise regression was used, with variables retained in the multivariable model at \( P \leq .05 \).

Exploratory univariate Cox proportional hazards regressions were performed to examine the effects of clinical parameters considered to have potential to influence long-term survival. This analysis was performed separately for dogs and cats and only included animals that survived past discharge. Variables significant at \( P \leq .25 \) in the univariate analysis were included in multivariable analysis. Backward stepwise regression was used, with variables retained in the multivariable model at \( P \leq .05 \).

The effect of chemotherapy and radiation therapy were analyzed using time-varying survival regression, which allows evaluation of variables that change after the follow-up period begins. Only animals that received complete radiation therapy protocols were considered.

All statistical analyses were performed using statistical software (SAS 9.3, SAS Institute, Inc., Cary, NC).

RESULTS

Clinical Features

Eighty dogs and 32 cats were included (Table 1). Thirty dogs had been included in a previous study examining histologic subtypes of TETs. Six of these 30 dogs had thymic carcinomas, 7 had atypical thymomas, and 17 had thymomas. All remaining thymic masses included in the present study were diagnosed as either thymic carcinoma (n = 4) or thymoma (78) by the pathology services used by the participating institutions. Reclassification of these tumors into TET subtypes was not performed.

The most frequent dog breeds were Labrador Retrievers (22/80, 28%), mixed breeds (14/80, 18%), and Golden Retrievers (9/80, 11%). The mean age of dogs was 9.8 years (median 10.1 years, range 2.1–15.4 years). The mean body weight of dogs was 28.2 kg (median 30.0 kg, range 3.8–55.5 kg). The most frequent cat breed was domestic shorthairs (17/32, 53%). The mean age for cats was 9.9 years (median 9.8 years, range 4.1–15.5 years). The mean body weight for cats was 5.2 kg (median 4.6 kg, range 3.0–9.0 kg). The most frequent clinical signs reported in dogs were dyspnea (23/80, 29%), cough (19/80, 24%), weakness (18/80, 22%), lethargy (16/80, 20%), inappetence (11/80, 14%), weight loss (11/80, 14%), and regurgitation (8/80, 10%). Three dogs presented with edema in the head and cervical region consistent with cranial venous cava syndrome. The most frequent clinical signs in cats were dyspnea (18/32, 56%), lethargy (8/32, 25%), coughing/wheezing (7/32, 22%), weight loss (6/32, 19%), inappetence (5/32, 16%), and exfoliative dermatitis (4/32, 12%).

A complete blood count and serum biochemistry analysis were performed for each animal. The most frequent abnormalities in dogs were mild neutrophilic leukocytosis (24/80, 30%), anemia (18/80, 22%), hypercalcemia (17/80, 21%), and lymphocytosis (10/80, 12%). The most frequent abnormalities in cats were elevated aspartate aminotransferase activity (9/32, 28%), elevated alanine aminotransferase activity (7/32, 22%), neutrophilic leukocytosis (7/32, 22%), lymphocytosis (6/32, 19%), and anemia (5/32, 16%).

Six dogs and 1 cat had concurrent neoplasia at the time of TET excision. Concurrent tumors in dogs were bronchoalveolar carcinoma, pulmonary papillary adenocarcinoma, splenic

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dogs</th>
<th>%</th>
<th>Cats</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory signs</td>
<td>39/80</td>
<td>49</td>
<td>24/31</td>
<td>77</td>
</tr>
<tr>
<td>Anemia</td>
<td>18/80</td>
<td>22</td>
<td>5/31</td>
<td>16</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>17/80</td>
<td>21</td>
<td>0/31</td>
<td>0</td>
</tr>
<tr>
<td>Paraneoplastic hypercalcemia</td>
<td>4/80</td>
<td>5</td>
<td>0/32</td>
<td>0</td>
</tr>
<tr>
<td>Lymphocytosis</td>
<td>10/80</td>
<td>12</td>
<td>6/31</td>
<td>19</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>23/79</td>
<td>29</td>
<td>11/31</td>
<td>36</td>
</tr>
<tr>
<td>Incidental thymic mass</td>
<td>15/80</td>
<td>19</td>
<td>2/31</td>
<td>6</td>
</tr>
<tr>
<td>Cystic thymic mass</td>
<td>16/80</td>
<td>20</td>
<td>15/31</td>
<td>48</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>18/80</td>
<td>22</td>
<td>2/32</td>
<td>6</td>
</tr>
<tr>
<td>Megaesophagus</td>
<td>10/80</td>
<td>12</td>
<td>0/32</td>
<td>0</td>
</tr>
<tr>
<td>Paraneoplastic disease</td>
<td>22/80</td>
<td>28</td>
<td>7/32</td>
<td>22</td>
</tr>
<tr>
<td>Concurrent neoplasia</td>
<td>6/80</td>
<td>8</td>
<td>1/32</td>
<td>3</td>
</tr>
<tr>
<td>Metastasis</td>
<td>7/79</td>
<td>9</td>
<td>1/32</td>
<td>3</td>
</tr>
<tr>
<td>Invasive thymic mass</td>
<td>27/79</td>
<td>34</td>
<td>9/31</td>
<td>29</td>
</tr>
<tr>
<td>Complete histologic margins</td>
<td>19/47</td>
<td>40</td>
<td>13/15</td>
<td>87</td>
</tr>
</tbody>
</table>
hemangiosarcoma, anal sac adenocarcinoma, pelvic limb fibrosarcoma, and pelvic limb mast cell tumor (1 each). These tumors were excised at the time of TET excision. One cat that presented initially with inappetence that did not resolve after thymic tumor excision was diagnosed with oral squamous cell carcinoma at 2 weeks after surgery and was euthanatized 57 days after surgery.

Eight dogs and 2 cats were initially suspected to have pulmonary metastases based on preoperative imaging. Pulmonary metastases were confirmed by histology in 2/8 dogs. In the remaining 8 animals, the suspected pulmonary metastases were either not biopsied at surgery but presumed to be TET-related (n = 3), or were determined by histologic examination to be concurrent primary pulmonary neoplasms noted above (n = 2), or to be benign (n = 3). Two other dogs and 1 cat had TET-related metastases involving the mesothelium and 1 of these dogs also had TET metastasis to a sternal lymph node. All of these metastases were confirmed by histologic examination. A total of 7 dogs and 1 cat were considered to have TET-related metastases on presentation.

Surgery

The tumor was approached via a median sternotomy in 72/80 dogs and 28/32 cats and via a lateral intercostal approach in 4/80 dogs and 4/32 cats. A thoracoscopic approach was used in 4/80 dogs. Relative tumor volumes greater than the median volume were associated with intraoperative finding of tumor invasion into the lungs, pericardium, or vena cava in dogs (OR 1.01, 95% CI 1.00–1.02, P = .02) but not in cats (OR 0.99, 95% CI 0.97–1.01, P = .32). Complete or partial lung lobectomies were performed in 21 dogs and 4 cats. Partial pericardectomies were performed in 6 dogs and 6 cats. One of 3 dogs with cranial vena cava syndrome had a tumor thrombus in the caval lumen and 2 had compression of the cranial vena cava by the TET. Sections of the wall of the cranial vena cava were removed in 4 dogs, including the dog with a tumor thrombus in the caval lumen. The remaining 3/4 dogs, one of which had cranial vena caval syndrome, had tumor invasion into the caval wall but the tumor did not penetrate into the lumen. In the third dog that presented with cranial vena caval syndrome, the TET compressed the cranial vena cava but was removed without caval venotomy.

Overall Survival

Kaplan–Meier analysis of overall survival probability for dogs and cats, including those that died perioperatively and those that received chemotherapy or radiation therapy, resulted in estimates of median survival time of 1.69 years (95% CI 0.56–4.32) for dogs and 3.71 years (95% CI 0.56-unestimatable) for cats (Fig 1). The estimated 1-, 2-, 3-, and 4-year survival proportions were 55% (95% CI 44–67), 44% (95% CI 32–56), 44% (95% CI 32–56), and 44% (95% CI 32–56), respectively for dogs and 70% (95% CI 53–87), 63% (95% CI 43–83), 63% (95% CI 43–83), and 47% (95% CI 0–100), respectively for cats. There was no significant difference in the survival functions for dogs and cats (P = .25).

Perioperative Mortality

Sixteen dogs (20%) and 7 cats (22%) died perioperatively (Table 2). Four dogs died or were euthanatized during surgery including 2 due to unresectable disease, 1 due to severe hemorrhage from a cranial vena cavotomy and 1 due to cardiopulmonary arrest. Three dogs died of postoperative complications including hemorrhage (n = 2) and pyothorax (n = 1). The remaining dogs died from other TET-related and/or anesthesia-related complications. All 7 cats died or were euthanatized during the immediate postoperative period. These included 2 cats that did not regain consciousness due to presumed cerebrovascular infarction. In one of these cats, both common carotid arteries were known to have been ligated during surgery. Postmortem examinations were not performed in these 2 cats.

Univariate analysis of the effects of potential risk factors for perioperative mortality of dogs identified preoperative anemia (OR 2.60, 95% CI 0.79–8.5, P = .12), preoperative pleural effusion (OR 2.29, 95% CI 0.73–7.14, P = .16) and whether the TET was an incidental finding (OR 0.24, 95% CI 0.03–1.96, P = .18) for inclusion in multivariable analysis; however, no independent risk factors for perioperative mortality were identified. In cats, no clinical variables were

| Table 2 Causes of Perioperative Mortality Among 80 Dogs and 32 Cats Undergoing Excision of Thymic Epithelial Tumors |
|-----------------------------------------------|----------------|----------------|
| Cause of Death                             | Dogs | Cats |
| Cardiopulmonary arrest (intra- or postoperative) | 5    | 2    |
| Hemorrhage (intra- or postoperative)        | 3    | 0    |
| Unresectable tumor                         | 2    | 0    |
| Pneumonia                                  | 2    | 1    |
| Myasthenia gravis                          | 1    | 0    |
| Pyothorax                                  | 1    | 1    |
| Respiratory failure                        | 1    | 0    |
| Unknown                                    | 1    | 1    |
| Suspected cerebrovascular infarction        | 0    | 2    |
| Total                                      | 16   | 7    |
associated with perioperative mortality in univariate analysis ($P > .25$).

Survival After Discharge

Of the 64 dogs and 25 cats that survived the perioperative period, 27 dogs (42%) and 5 cats (20%) eventually died or were euthanatized because of TET-related causes (Table 3). One dog and 1 cat died at home shortly after discharge of presumed complications of the surgery. Resolution of pleural effusion and paraneoplastic syndromes after TET excision was variable (Table 4). One dog and 3 cats developed myasthenia gravis following surgery. All 3 dogs that presented with cranial vena cava syndrome had resolution of head and neck edema following surgery.

Univariate analysis of the effects of potential prognostic factors on long-term survival of dogs identified preoperative anemia (HR 2.04, 95% CI 0.84–4.99, $P = .12$), preoperative paraneoplastic syndromes (HR 1.67, 95% CI 0.74–3.77, $P = .21$), incomplete histologic margins (HR 2.38, 95% CI 0.93–5.99, $P = .09$), perioperative death (HR 3.14, 95% CI 1.35–7.29, $P = .01$), failure of pleural effusion to resolve (HR 2.93, 95% CI 1.43–6.00, $P = .01$), failure of myasthenia gravis to resolve (HR 4.10, 95% CI 1.76–9.53, $P = .03$), and age >10 years (HR 0.57, 95% CI 0.26–1.27, $P = .17$) for inclusion in multivariable analysis. The analysis showed that preoperative paraneoplastic syndromes (HR 5.78, 95% CI 1.64–20.45, $P = .007$) and incomplete histologic margins (HR 6.09, 95% CI 1.50–24.72, $P = .01$) were independently associated with increased survival.

Incomplete margins appeared subjectively to be associated with failure of pleural effusion to resolve and development of pleural effusion following surgery. All 4 dogs with pleural effusion and complete margins had resolution of effusion following surgery, while only 2/6 dogs with pleural effusion but incomplete margins had resolution of the effusion. Survival times of dogs with persistent pleural effusion ranged from 30 to 111 days (mean 61 days, median 52 days). There were 3 dogs with incomplete margins that did not have pleural effusion before surgery but that developed pleural effusion within 83–241 days after surgery. Survival times of these dogs ranged from 116 to 242 days (mean 176 days, median 171 days). No dogs with complete margins developed pleural effusion following surgery.

Too few cats experienced TET-related deaths after discharge to permit univariate analysis.

Chemotherapy, Radiation Therapy, and Re-Excision Surgery

Chemotherapy was administered to 13 dogs and 1 cat. Chemotherapy was administered in the early postoperative period in 5 dogs and 1 cat because of metastatic disease (n = 2), incomplete histologic margins (n = 3), and persistent pleural effusion (n = 1). Six dogs received chemotherapy for treatment of a locally recurrent TET. Two of these 6 dogs had undergone 2 re-excisions each for local recurrence prior to receiving chemotherapy. Two dogs received chemotherapy for treatment of concurrent non-thymic neoplasia (mast cell tumor and multicentric lymphoma). Chemotherapy agents and dosing regimens were variable. There were no documented responses of measurable disease to chemotherapy, but monitoring intervals and protocols were inconsistent.

Five dogs received radiation therapy adjunct to the initial surgery (n = 2) or after development of local recurrence (n = 3). Each of the dogs receiving radiation therapy for local recurrence had undergone a single (n = 1) or 2 (n = 2) re-excisions for local recurrent disease and received radiation therapy to treat subsequent recurrences. Radiation therapy was most often given in 16 3GY fractions on a Monday through Friday schedule. One dog had a documented partial response of a locally recurrent TET to radiation therapy, with tumor reduction from 3.5 cm × 4.0 cm × 2.5 cm to 2.5 cm × 2.5 cm × 2.0 cm. The recurrent tumor was then excised but the dog was euthanatized because of a subsequent local recurrence 2 years later.

For the 3 dogs that underwent 2 re-excisions of locally recurrent tumor prior to receiving chemotherapy or radiation therapy, the intervals between the first and second re-excisions ranged from 243 to 602 days.

Time-varying regression analysis showed that dogs that received chemotherapy had significantly shorter survival times than dogs that did not (HR 4.35, 95% CI 1.83–10.38, $P < .001$). Dogs that received radiation therapy also had significantly shorter survival times than dogs that did not (HR 4.91, 95% CI 2.52–9.59, $P < .001$).

Table 3 Causes of Late Tumor-Related Death Among 80 Dogs and 32 Cats Undergoing Excision of Thymic Epithelial Tumors

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Dogs</th>
<th>Cats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local recurrence</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Failure of myasthenia gravis to resolve</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Failure of pleural effusion to resolve</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Metastases</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Local and metastatic recurrence</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Postoperative development of pleural effusion</td>
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<td>0</td>
</tr>
<tr>
<td>Postoperative complication</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 4 Postoperative Resolution of Pleural Effusion and Paraneoplastic Syndromes Among 80 Dogs and 32 Cats Undergoing Excision of Thymic Epithelial Tumors

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Dogs</th>
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<tbody>
<tr>
<td></td>
<td>Outcome</td>
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<tr>
<td>Pleural effusion</td>
<td>Resolution</td>
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<tr>
<td></td>
<td>Perioperative death</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>No resolution</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>No resolution</td>
<td>6</td>
</tr>
<tr>
<td>Myasthenia gravis*</td>
<td>Perioperative death</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Resolution</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Required medication</td>
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<tr>
<td>Exfoliative dermatitis</td>
<td>Perioperative death</td>
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</tr>
<tr>
<td></td>
<td>No resolution</td>
<td>1</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>Resolution</td>
<td>2</td>
</tr>
</tbody>
</table>

*Myasthenia gravis developed following surgery in 1 dog and 3 cats.
1.53–15.77, \(P = .008\)). The number of cats receiving adjuvant therapy was too small to permit statistical analysis.

**DISCUSSION**

The estimated median survival times for dogs and cats undergoing excision of thymic epithelial tumors in this study (1.69 and 3.71 years, respectively) are similar to those reported previously.\(^{11,14,43}\) However, median survival time fails to capture the extreme variability in outcome for animals with TETs, and may be misleading to owners considering surgery. Our results show that the perioperative mortality rate associated with surgery for TETs in dogs and cats is approximately 20%. During the subsequent 2 years, approximately 42% of dogs and 20% of cats that survive to discharge die of a variety of tumor-related causes. TET-related deaths beyond 2 years are unusual and surgical excision may be curative in a large proportion of animals that survive to that point.

Although overall survival prospects for dogs and cats with thymic epithelial tumors are similar, the spectrum of clinical findings on initial presentation differs between species. Dogs were more likely than cats to present with hypercalcemia, myasthenia gravis or megaesophagus. Hypercalcemia was infrequently confirmed to be paraneoplastic; however, stringent criteria were used, and the true frequency was likely underestimated. Cats frequently presented with respiratory signs. Cranial vena cava syndrome was infrequently observed in dogs and not observed in cats. Consistent with previous reports, relatively few dogs or cats presented with metastatic disease.

In dogs, large relative tumor volumes were associated with tumor invasion of the lungs, pericardium or cranial vena cava. Preoperative CT or magnetic resonance imaging should be considered for animals with tumors that are considered large (for example, those that displace the heart or extend beyond its cranial border) or for animals with edema of the head or neck consistent with cranial vena cava syndrome. Although non-angiographic contrast-enhanced CT has poor sensitivity for cranial vena cava invasion,\(^{12}\) CT angiography and current 3-dimensional reconstruction techniques may improve sensitivity.

While small TETs discovered as incidental findings often can be removed through a lateral intercostal thoracotomy or with thoracoscopic surgery,\(^{35}\) median sternotomy is essential for removal of large tumors. This approach provides visualization of important anatomic structures on both sides of the chest and is not associated with noticeably greater postoperative morbidity than lateral thoracotomy.\(^{36}\) The surgeons’ decisions to use median sternotomy for most dogs and cats in this study were likely based on these considerations.

At surgery, approximately one third of dogs and cats were found to have invasive tumors that required some combination of complete or partial lung lobectomy, partial pericardiectomy, and or resection of a portion of the wall of the cranial vena cava. Cranial vena cava syndrome in the dogs in our study was caused by either a tumor thrombus within the cranial vena cava or by cranial vena caval compression. The presence or absence of preoperative cranial vena cava syndrome was not consistently correlated with the presence or absence of invasion of the cranial vena cava wall.

The substantial perioperative mortality rates observed in the study reflect the physical compromise of the animals by the disease and the challenges inherent to the surgical procedure and perioperative management. No clinical variable was significantly associated with perioperative mortality, although the power of the analysis was limited by the relatively small number of animals that died perioperatively. Tumor and animal-related factors such as the size, invasiveness and vascularity of the mass, paraneoplastic syndromes, severity of clinical signs, and the animal’s and comorbidities are likely risk factors.

Two cats were euthanatized because they failed to regain consciousness following surgery and were presumed to have suffered cerebrovascular infarction. In 1 cat, both common carotid arteries were ligated during tumor removal. Cerebral blood supply in cats is largely dependent on carotid blood flow,\(^{37}\) and bilateral ligation is contraindicated. Intraoperative discovery of extensive involvement of the brachycephalic or common carotid arteries in cats should prompt careful cytoreduction and/or consideration of radiation therapy or chemotherapy.

The most frequent cause of long-term tumor-related death in dogs and cats was local tumor recurrence, consistent with the finding that the tumors were frequently found to be invasive in both species. The limited experience with re-excision reported here suggests that excision of locally-recurrent tumor with or without adjunctive therapy can substantially prolong survival. Intermittent followup with thoracic radiography or CT should be offered to owners who would consider re-excision. In dogs, most deaths not caused by local tumor recurrence were caused by metastasis or failure to resolve pleural effusion or myasthenia gravis. Although 1 cat presented with confirmed metastatic disease, deaths due to metastatic disease were not observed in cats.

In dogs, the presence of a paraneoplastic syndrome (myasthenia gravis or hypercalcemia) or incomplete histologic margins were independently associated with decreased long-term survival. Of the paraneoplastic syndromes that may be present in dogs with TETs, myasthenia gravis in particular appears to influence survival prospects. The syndrome either failed to resolve or required ongoing postoperative medical management in 9 of 19 affected dogs. Myasthenia gravis may result in megaesophagus, aspiration pneumonia and exertional weakness, all of which may be refractory to medical therapy and challenging for owners to manage. Interestingly, 1 dog and 3 cats developed myasthenia gravis following surgery. This phenomenon previously has been reported in cats,\(^{14}\) and is also occasionally seen in people.\(^{38–40}\) Although the mechanism remains unclear, some people can present without signs of myasthenia gravis despite having elevated acetylcholine receptor antibody titers.\(^{38}\) It has also been proposed that large numbers of auto-antigenic specific T-cells are exported from thymic epithelial tumors into the peripheral bloodstream, and that these cells may persist for many years, eventually producing acetylcholine receptor antibodies.\(^{38,41}\)
Thymic epithelial tumors often cannot be resected with complete margins of normal tissue that appear adequate to the surgeon, because much of their surface area does not contact adjacent anatomic structures. However, they often have a thin capsule of compressed normal tissue at their periphery that the surgeon cannot appreciate grossly but that can be visualized microscopically.24 A finding of complete histologic margins generally implies that this capsule is intact, not that the surgeon has achieved wide resection margins. A finding of incomplete margins implies that tumor is not completely encapsulated or has ruptured through its capsule, or that the capsule was compromised during surgical excision. We noted that pleural effusions that were present prior to surgery tended to persist in dogs with incomplete margins but not in dogs with complete margins. In addition, we noted that dogs with incomplete margins occasionally developed pleural effusion following surgery, whereas dogs with complete margins did not. As is the case when myasthenia gravis fails to resolve, persistent pleural effusion or development of pleural effusion following surgery may prompt owners to consider euthanasia early in the postoperative period.

We could not draw reliable conclusions regarding the efficacy of chemotherapy or radiation therapy for TETs from our study. The apparent negative impact of these modalities on survival was likely observed because they were typically administered when surgical margins were incomplete or when local recurrence or metastatic disease were identified. In animals in which local recurrence was treated with surgery and adjunctive chemotherapy or radiation therapy, the contributions of each modality to outcome could not be evaluated. Although 1 dog with local recurrence of a TET had a documented response to radiation therapy, stronger evidence for the efficacy of radiation can be found in prior studies.11,34 These studies suggest that radiation therapy can be beneficial in the management of unresectable, incompletely resected, or recurrent TETs. Neoadjuvant chemotherapy and radiation therapy are known to improve tumor resectability in people with locally advanced thymic tumors.43,44

Our study was limited by factors common to multi-institutional retrospective studies. Information obtained by review of medical records can be inaccurate or incomplete. Treatment modalities and followup protocols across institutions are not standardized. Causes of death were rarely confirmed by postmortem examination. Some animals that were lost to followup or considered to have died of unknown causes may have died of tumor-related causes, resulting in underestimation of TET-related deaths. Finally, the power of all statistical analyses performed was limited by relatively small sample sizes, particularly for the series of cats.

In summary, the prognosis for dogs and cats undergoing surgical excision of thymic epithelial tumors is variable, but similar in both species. Although perioperative and long-term tumor-related deaths are frequent, a substantial proportion of animals can be expected to have prolonged survival. The presence of paraneoplastic syndromes and incomplete histologic margins are associated with decreased survival times in dogs.

DISCLOSURE

The authors report no financial or other conflicts related to this report.

REFERENCES