

# Clinical features, treatment options, and outcome in dogs with thymoma: 116 cases (1999–2010)

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**Objective**—To describe clinical signs, diagnostic findings, treatment, and outcome and determine factors associated with survival time for dogs with thymoma.

**Design**—Multi-institutional retrospective case series.

**Animals**—116 dogs with thymoma.

**Procedures**—Medical records were searched for information regarding signalment, physical examination findings, results of laboratory testing and diagnostic imaging, medical and surgical treatment, and survival data.

**Results**—Of the 116 dogs with thymoma, 44 (38%) were Labrador Retrievers and Golden Retrievers. Twenty of 116 (17%) dogs had signs of myasthenia gravis (diagnosis was confirmed for 13 dogs). At the time of thymoma diagnosis, 40 (34%) dogs had hypercalcemia, 8 (7%) dogs had a concurrent immune-mediated disease, and 31 (27%) dogs had another tumor; 16 (14%) dogs developed a second nonthymic tumor at a later date. Tumor excision was performed for 84 dogs, after which 14 (17%) had tumor recurrence; prognosis was good for dogs undergoing a second surgery. Median survival time with and without surgical treatment was 635 and 76 days, respectively. Presence of another tumor at the time of thymoma diagnosis, lack of surgical excision, and higher pathological stage were significantly associated with shorter survival time. Hypercalcemia and presence of myasthenia gravis or megaesophagus at the time of thymoma diagnosis, histopathologic subtype of thymoma, or tumor development at a later date was not associated with survival time.

**Conclusions and Clinical Relevance**—Dogs with thymoma, even those with a large tumor burden or a paraneoplastic syndrome, had a good prognosis following surgery. Surgical treatment, tumor stage, and the presence of a second tumor at diagnosis influenced survival time. (*J Am Vet Med Assoc* 2013;243:1448–1454)

Thymomas are neoplasms that originate from the thymic epithelium. Their development in many species, including dogs, cats, rabbits, and ferrets, has been described.<sup>1–6</sup> Although rare, thymoma is one of the most common cranial mediastinal tumors in dogs. Differential diagnoses for thymoma include lymphoma, thymic carcinoma, chemodectoma, thymic branchial cyst, ectopic thyroid tumor, and metastatic carcinoma.<sup>7,8</sup> Thymomas typically develop in older medium- to large-breed dogs and might be more common in Lab-

rador Retrievers and German Shepherd Dogs.<sup>8,9</sup> Most studies<sup>9,10</sup> have not revealed a sex predisposition.

Computed tomographic imaging in dogs with thymoma is used for tumor staging and surgical planning and to distinguish invasive tumors from space-occupying masses. It appears to be more reliable than radiography or ultrasonographic imaging for adequately defining the tumor location, size, and invasiveness.<sup>11</sup>

Thymomas are classified as locally invasive (malignant) or noninvasive (benign) on the basis of CT imaging findings and assessment of resectability; however, this classification is mostly subjective. Thymomas rarely metastasize.<sup>7</sup> There are several histopathologic subtypes (epithelial, lymphocyte rich, and clear cell), and dogs with the lymphocyte-rich form may have a better prognosis.<sup>6,8</sup> In humans, thymomas can be staged by use of the Masaoka-Koga staging system<sup>12</sup>; the tumor stage assigned is based on gross operative findings as well as microscopic invasive properties of the tumor. It has been shown that the Masaoka-Koga tumor stage is significantly correlated with survival rate, with decreases in survival rate being associated with more severe stages.<sup>13</sup>

The paraneoplastic syndromes of myasthenia gravis and megaesophagus have been reported for up to 40% dogs with thymoma, and these syndromes may resolve

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after excision of the tumor.<sup>6,7,14–21</sup> Other paraneoplastic syndromes that are rarely reported include hypercalcemia,<sup>7</sup> severe lymphocytosis,<sup>22</sup> erythema multiforme,<sup>23</sup> and myocarditis causing high-degree atrioventricular block.<sup>7,24</sup> Twenty percent to 40% of dogs with thymoma may also have a nonthymic neoplasm or immune-mediated disease.<sup>6–8,22</sup>

Treatment of thymomas involves surgery, when possible, which yields a median overall survival time of 790 days for dogs with thymomas.<sup>6,7</sup> The roles of chemotherapy and radiation therapy in the treatment of thymomas have yet to be fully investigated. Multidrug protocols similar to those used for treatment of high-grade lymphoma have yielded anecdotal reports of partial and complete responses.<sup>7</sup> With radiation therapy, complete responses were obtained in 2 of 17 dogs and partial responses in 9 of 17 dogs, with a median survival time of 248 days.<sup>25</sup> However, some of these patients concurrently received surgery or chemotherapy. These responses were mostly achieved in dogs with tumors that contained a high percentage of lymphocytes.<sup>3,7,25</sup>

The purpose of the study reported here was to retrospectively compile and analyze data obtained over a 12-year period from a large number of dogs with thymoma, with the intent to better describe the clinical signs and pathological changes, treatment, and outcome and to assess prognostic factors for affected dogs.

## Materials and Methods

**Case selection**—Medical records from 5 institutions (University of Wisconsin-Madison, Michigan State University, University of Pennsylvania, Purdue University, and Colorado State University) were searched for canine thymoma cases from 1999 to 2010. Dogs were included in the study if a diagnosis of thymoma had been made on the basis of cytologic or preoperative, postoperative, or postmortem histopathologic findings.

**Medical record review**—Data abstracted from medical records included signalment, physical examination and clinicopathologic findings at the time of diagnosis and at each recheck visit when available, diagnostic imaging results, treatment, and outcome. Follow-up information for each dog was obtained through a telephone conversation with either the owner or referring veterinarian. For each dog, the thymoma was retrospectively staged, if adequate information was available, with the Masaoka-Koga staging system used in human medicine (Appendix).

**Statistical analysis**—Survival data were evaluated with Kaplan-Meier survival curves generated with the aid of a computerized statistical program.<sup>a</sup> For the dogs included in the study, survival time was defined as the interval from diagnosis of thymoma to death. For thymoma-specific survival time, dogs that died as a result of nonthymoma causes or unknown causes and dogs that were alive or lost to follow-up were censored. For overall survival time, dogs that died as a result of any cause were included; dogs alive at the end of the study or those lost to follow-up were censored. Time to recurrence was defined as the interval in days for regrowth of the tumor after initial resection. Possible prognostic factors (presence of hypercalcemia, presence of para-

neoplastic myasthenia gravis or megaesophagus, histopathologic subtype, Masaoka-Koga thymoma stage, other concurrent nonthymic tumor, development of another nonthymic tumor at a later date, and surgical treatment) were evaluated by comparing survival curves with the log-rank test (Mantel-Cox test). A value of  $P < 0.050$  was considered significant.

## Results

**Signalment**—Medical records for 116 dogs from 5 institutions were included in this retrospective study. There were 31 cases from Michigan State University, 29 from Colorado State University, 28 from the University of Wisconsin-Madison, 23 from the University of Pennsylvania, and 5 from Purdue University. Among the 116 dogs, there were 52 females and 64 males. Breeds represented were Labrador Retriever ( $n = 30$ ), Golden Retriever (14), Beagle (6), Akita (6), Shih Tzu (6), Rottweiler (4), German Shepherd Dog (4), and 2 each of Jack Russell Terrier, Dalmatian, Dachshund, and Soft Coated Wheaten Terrier; there were also 15 mixed-breed dogs and 1 each of 23 other breeds. The mean age of the dogs was 9.5 years (median, 9.4 years; range, 1.5 to 14 years).

**Clinical signs**—Among the 116 dogs, the most common signs were weakness or lethargy ( $n = 38$  [33%]), cough (34 [29%]), high respiratory rate (27 [23%]), vomiting or regurgitation (24 [21%]), polyuria-polydipsia (16 [14%]), anorexia or inappetence (14 [12%]), and weight loss (11 [9%]). Two dogs had edema of the face and neck (precaval syndrome). One dog had cutaneous lesions, which were diagnosed as erythema multiforme on the basis of histopathologic findings. Clinical signs noted at the time of diagnosis had been present for 1 to 6 months (49/116 [42%]), 1 to 4 weeks (26/116 [22%]), < 1 week (24/116 [21%]), and > 6 months (11/116 [9%]). Duration of clinical signs was unknown for 7 of the 116 (6%) dogs. In 16 (14%) dogs, the thymoma was an incidental finding.

**Diagnostic imaging**—Thoracic radiography was performed in 113 of 116 (97%) cases; the remaining 3 dogs underwent CT only. In 110 of the 113 (97%) dogs examined radiographically, a cranial mediastinal mass was observed. For the remaining 3 dogs, a large amount of pleural effusion that masked the cranial mediastinum was detected. Twenty-two of those 113 (19%) dogs had pleural effusion, 14 (12%) dogs had megaesophagus, and 2 (2%) dogs had radiographic evidence of aspiration pneumonia.

Sixty of the 116 (52%) dogs underwent thoracic CT. Of those 60 dogs, 9 had regional lymph node enlargement and 3 had pulmonary metastases. Nine of the 60 dogs had evidence of tumor invasion into the cranial portion of the vena cava. These changes had not been detected by radiography. Computed tomographic measurements of the mass were available for 43 of the 60 (72%) dogs; mean longest diameter was 8.6 cm (median, 7 cm; range, 2 to 30 cm). In 7 of the 60 dogs, the mass was reported as unresectable by the radiologists based on CT findings of invasiveness or large size.

Abdominal ultrasonography was performed in 59 of 116 (51%) dogs. Thirteen of the 59 dogs had splen-

ic nodules; fine-needle aspiration of the nodules was performed in 8 dogs, and microscopic examination of the samples revealed benign changes. Eleven of the 59 dogs had hepatic nodules; fine-needle aspiration of the nodules was performed in all 11 dogs, and microscopic examination of the samples revealed benign changes. Other important findings included an adrenal gland mass in 3 dogs, a hepatic mass in 1 dog, an ovarian tumor in 1 dog, a pyloric antrum mass in 1 dog, and diffuse abdominal tumor (later diagnosed as hemangiosarcoma during necropsy) in 1 dog.

**Cytologic and histologic evaluation**—Definitive diagnosis of thymoma was obtained by histologic evaluation of biopsy specimens in 90 of 116 (78%) cases and by cytologic evaluation of fine-needle aspirate samples of the mediastinal mass in 26 of 116 (22%) cases. For 44 of the 116 (38%) dogs, both histologic and cytologic analyses were performed; findings from the 2 methods were in agreement in 40 of 42 (95%) cases. In 2 cases, the cytologic sample was nondiagnostic because of poor cellularity. In 2 other cases, an initial diagnosis of mast cell tumor and sarcoma was obtained on cytologic evaluation; however, both of these were then reclassified as a thymoma following histologic evaluation. All aspirate samples contained variable amounts of small lymphocytes, mast cells, lymphoblasts, macrophages, and plasma cells. The epithelial component was present in 43 of 70 (61%) cytologic samples for which full reports were available. On histologic examination, tissue samples from 59 of 90 (66%) dogs were diagnosed as differentiated epithelial thymoma, 22 (24%) as lymphocyte rich thymoma, 4 (4%) as clear cell thymoma, 3 (3%) as spindle cell thymoma, and 2 (2%) as pigmented thymoma (these 2 had moderate to large numbers of heavily pigmented melanocytes present throughout the tumor).

Retrospective clinical tumor staging following recent guidelines<sup>26</sup> established to clarify and standardize the Masaoka-Koga staging system was possible for 72 dogs (Appendix). Disease was classified as stage I, II.1, II.2, III, and IV (a and b) in 25 (35%), 9 (13%), 11 (15%), 22 (31%), and 5 (7%) dogs, respectively.

**Clinicopathologic findings**—For 106 of the 116 (91%) dogs, a CBC was performed as part of tumor staging. Of the 106 dogs, 29 (27%) had mild to moderate neutrophilia (2 to 4 times the upper reference limit), 15 (14%) had mild thrombocytopenia, and 9 (8%) had thrombocytosis (up to 2 times the upper reference limit). Twenty of 106 (19%) dogs had lymphocytosis (2 to 4 times upper reference limit in 16 dogs, and > 6 times the upper reference limit in 4 dogs). No recheck CBC data were available for these dogs, so it is unknown whether these values normalized after surgery.

For 114 of the 116 (98%) dogs, serum biochemical analysis was performed at the time of diagnosis. Thirty-two (28%) dogs had high total calcium concentration (11.5 to 13.5 mg/dL [ $n = 17$ ], 13.5 to 15.5 mg/dL [8], and > 15.5 mg/dL [7]). Nineteen (17%) dogs had high alanine aminotransferase activity (up to 1.5 times the upper reference limit [ $n = 9$ ], 1.5 to 4 times the upper reference limit [9], and 4 to 10 times the upper refer-

ence limit [1]). Twenty-four (21%) dogs had high alkaline phosphatase activity (up to 2.5 times the upper reference limit [ $n = 17$ ], 2.5 to 5 times the upper reference limit [6], and 5 to 20 times the upper reference limit [1]). Ionized calcium concentrations were available for 81 of the 114 (71%) dogs, and values were high in 37 of those 81 (46%) dogs (1.32 to 1.6 mmol/L [ $n = 24$ ], 1.6 to 2.0 mmol/L [9], and > 2.0 mmol/L [4]; reference range, 1.15 to 1.32 mmol/L). Twenty-nine of those 37 dogs also had high total calcium concentration, whereas total calcium concentration was within reference range for 8 dogs. Forty of the 114 (35%) dogs had total or ionized hypercalcemia at the time of thymoma diagnosis. Ionized calcium concentration normalized after surgery in 25 of 27 dogs for which recheck values were available. The 2 dogs for which ionized calcium concentrations did not normalize underwent partial resection because of the volume and invasiveness of the tumor. Assessment of serum parathyroid hormone concentration was performed in 9 dogs with hypercalcemia; 8 dogs had results consistent with hypercalcemia of malignancy, and 1 had results consistent with primary hyperparathyroidism. In that 1 dog, an adenoma was confirmed by means of cervical ultrasonography and was subsequently excised. For another dog, a diagnosis of primary hyperparathyroidism was made following detection of a parathyroid gland adenoma by use of cervical ultrasonography during a workup for hypercalcemia. The adenoma was not excised. Results of a parathyroid hormone assessment obtained for this dog were consistent with hypercalcemia of malignancy. Urinalysis was performed in 73 of 116 (63%) dogs. Eight of the 73 (11%) dogs had a urinary tract infection (numerous bacterial rods present in the urine); bacterial culture of urine samples were not performed for any of the 8 dogs.

**Neurologic evaluation**—Thirteen of 116 (11%) dogs were determined to have myasthenia gravis on the basis of detection of serum anti-acetylcholine receptor antibody (8 dogs) or positive results of an edrophonium chloride test (5 dogs). Of these 13 dogs, 9 had megaesophagus and 4 had no other signs except lethargy. Seven of 16 dogs with megaesophagus did not undergo diagnostic testing for myasthenia gravis.

**Other diseases**—Thirty-one of the 116 (27%) dogs had a second nonthymic tumor at the time of thymoma diagnosis. These tumors included 6 soft tissue sarcomas; 5 pulmonary carcinomas; 3 mast cell tumors; 3 adrenal gland masses; 2 each of heart base tumor, chondrosarcoma, and melanoma; and 1 each of hepatocellular carcinoma, testicular tumor, parathyroid gland adenoma, ovarian tumor, pyloric antrum mass, lymphoma, hemangiosarcoma, and thyroid gland carcinoma. Eight dogs had other immune-mediated diseases; 2 dogs had keratoconjunctivitis sicca, and 1 dog each had polyarthritis, masticatory muscle myositis, perianal fistula, hypothyroidism, immune-mediated thrombocytopenia, and diabetes mellitus. Four dogs had concurrent laryngeal paralysis at the time of thymoma diagnosis. Sixteen of the 116 (14%) dogs developed other tumors at a later date (mean, 472 days from the time of diagnosis; median, 368 days; range, 30 to 1,433 days from the time of diagnosis). These included 3 pulmonary

carcinomas, 2 abdominal hemangiosarcomas, 2 soft tissue sarcomas, and 1 of each osteosarcoma, mast cell tumors, lymphoma, mammary tumor, digital tumor, oral squamous cell carcinoma, oral undifferentiated sarcoma, brain tumor, and hepatic neuroendocrine tumor.

**Treatment and survival time**—Eighty-four of the 116 (72%) dogs underwent excision of the thymoma. Of those 84 excisions, 79 were performed through a median sternal approach, 2 were performed by thoracoscopy, and 3 were performed with lateral thoracotomy. Six of the 84 dogs had tumor thrombi removed from the vena cava; 1 dog died 1 day after surgery, and the remaining 5 dogs lived 8, 224, 330, 1,062, and > 263 days after surgery. Nine surgeries were aborted because of the extensive invasiveness of the tumor; 5 of those 9 dogs did not undergo preoperative CT, and 4 had CT evidence that the mass was likely unresectable because of its invasiveness or size. In 3 dogs, surgery was successful despite the tumor being reported as unresectable on the basis of CT findings. Unilateral phrenic nerve section occurred in 15 of 84 (18%) dogs. Cardiac arrest occurred in 6 of 84 dogs during surgery; all but 1 patient were successfully resuscitated. Among the 84 dogs, postoperative complications included aspiration pneumonia ( $n = 7$ ), hemorrhage (6), infection (5), hypocalcemia requiring treatment (3), and seroma formation at the surgical site (3). In 1 dog, clinical signs of myasthenia gravis resolved completely after surgery, and in 2 dogs, the signs resolved partially. Clinical signs of myasthenia gravis were persistent after surgery in 2 dogs.

Chemotherapy was administered to 17 of the 116 (15%) dogs. Preoperative standard-dose chemotherapy with carboplatin was administered to 2 dogs; 1 dog each was treated with doxorubicin and cyclophosphamide, doxorubicin alone, L-asparaginase alone, or vincristine and cyclophosphamide. Metronomic administration of cyclophosphamide was used in 1 dog. Preoperative chemotherapy was given to these 7 dogs in an attempt to diminish the tumor and facilitate excision. Two dogs received chemotherapy (carboplatin and vincristine) as the sole treatment. Progressive disease was evident in those 9 dogs. After surgery, 7 dogs in which tumor excision was incomplete received carboplatin ( $n = 5$ ), cisplatin (1), or vinorelbine alone (1).

Thirteen of the 116 (11%) dogs received radiation therapy (7 hyperfractionated protocols [2 applied prior to surgery, 3 applied after surgery, and 2 applied as the only treatment] and 6 coarse fractionated protocols [1 applied prior to surgery, 2 applied after surgery, and 3 applied as the only treatment]). Information regarding response to radiation was available for 8 dogs. Five dogs had a partial response, 3 of which received a palliative protocol; 1 dog had stable disease, and 2 dogs had progressive disease. One of the dogs with a partial response underwent surgery 1 month after treatment. Duration of partial response was 1 month for one dog and at least 4 months for another dog. One dog that received both chemotherapy (vincristine) and radiation therapy (2 fractions [4 Gy each]) as the only treatment was euthanized 13 days after the time of diagnosis because of acute paraplegia secondary to a spinal cord sarcoma (diagnosed after necropsy).

Seventeen of the 116 (15%) dogs received prednisone or prednisolone. Prednisone or prednisolone was administered for the treatment of hypercalcemia in 6 dogs and for the treatment of immune-mediated diseases in 3 dogs. Prednisone was the sole treatment in 8 of the 116 (7%) dogs. Four of those dogs were hypercalcemic, and hypercalcemia resolved in 1 dog and improved in 2 dogs for which follow-up serum calcium concentrations were available. Four of the 8 dogs receiving prednisone alone had survival times of 330, 355, > 439, and 485 days; 2 dogs were lost to follow-up, and the remaining 2 dogs had survival times of 23 and 72 days. The survival times of 3 additional dogs that received no treatment were > 95, > 112, and 760 days.

Thymoma recurrence was noted in the medical records of 14 (17%) dogs; the mean interval after surgery to tumor recurrence was 518 days (median, 362 days; range, 32 to 2,170 days). A second resection was performed in 5 dogs. One dog died during surgery as a result of laceration of the cranial portion of the vena cava. One dog died of an unknown cause 15 months after the second surgery, and another dog was euthanized 11.5 months after the second resection because of progressive pulmonary metastases from a thyroid adenocarcinoma. A fourth dog had a pulmonary carcinoma resected at the time of second thymoma surgery and was subsequently treated with 6 doses of carboplatin. This dog was still alive at the last follow-up 6 months after the second surgery. The remaining dog died 20 months after the second surgery because of a second thymoma recurrence and uncontrollable hypercalcemia. Two dogs for which a second surgery was declined lived 21.5 and 24 months after diagnosis of tumor recurrence. The other 5 dogs for which a second surgery was declined survived 7, 21, 29, 46, and 87 days after recurrence was detected.

Seven dogs died within a week after surgery as a result of surgery- or disease-related complications (ie, acute respiratory distress, megaesophagus and aspiration pneumonia, or disseminated intravascular coagulation). Twelve dogs receiving no treatment were euthanized within a week after diagnosis because of aspiration pneumonia or hemorrhage following ultrasound-guided tumor sample collection, and 1 dog was euthanized because of diffuse abdominal metastatic ovarian carcinoma.

Forty-two dogs died because of thymoma or thymoma-related postsurgical complications. Cause of death was unknown for 25 dogs. Ten dogs died of another type of neoplasm, and 14 dogs died of another disease. Fourteen dogs were alive at the time of study completion. Eleven dogs were lost to follow-up. Necropsy was performed in 16 dogs, and cardiac myositis was detected in 1 dog.

**Prognostic factors**—Median survival time as determined by Kaplan-Meier survival analysis for all dogs was 425 days. Thymoma-specific survival time was 220 days. For dogs treated surgically, median survival time was 635 days, which was significantly ( $P < 0.001$ ) higher than the finding for dogs not treated surgically (median survival time, 76 days). Dogs with a second nonthymic tumor at the time of thymoma diagnosis had a significantly ( $P = 0.03$ ) shorter survival time (282

vs 568 days), compared with the survival time among dogs without a second tumor at the time of thymoma diagnosis. Dogs with tumors classified as lower Masaoka-Koga stage I, II.1, or II.2 had a significantly ( $P < 0.001$ ) longer survival time than did dogs with tumors classified as stage III or IVa or IVb (1,045 vs 224 days). Histopathologic subtype did not influence survival time. There was no difference in survival time between dogs with or without hypercalcemia at the initial evaluation, regardless of whether all dogs (224 vs 460 days;  $P = 0.28$ ) or only those that underwent surgery (635 vs 770 days;  $P = 0.51$ ) were considered. No difference in survival time was found between dogs with and without myasthenia gravis or megaesophagus, dogs that did or did not develop a second nonthymic tumor at a later date, or dogs in which phrenic nerve section did or did not occur during surgery.

## Discussion

Compared with other cancers in dogs, thymoma is an uncommon disease, as evidenced by the scarce number of available reports of large studies and the relatively small number of cases in the present study, despite evaluation of a 12-year period at 5 academic institutions. As in prior investigations, dogs of the present study were older, with a median age of 9.4 years. No sex predisposition was noted. Labrador Retrievers and Golden Retrievers were the most commonly represented breeds, accounting for 26% and 12%, respectively, of all dogs in the study. In previous studies,<sup>8</sup> Labrador Retrievers and German Shepherd Dogs have been most frequently represented; however, only 4 German Shepherd Dogs were included in our study.

Clinical signs among the 116 dogs were generally nonspecific, and most were associated with the respiratory tract or attributable to the presence of paraneoplastic myasthenia gravis. One dog had erythema multiforme, and another had high-grade atrioventricular block and myocarditis (the latter diagnosed at necropsy). These conditions have only rarely previously been described as paraneoplastic syndromes in dogs with thymoma. Unfortunately, these dogs were euthanized shortly following surgery, so it was unknown whether these abnormalities would have resolved following thymoma excision. Duration of clinical signs was most commonly 1 to 6 months, which is consistent with the slowly progressive nature of the disease.

Results of diagnostic imaging for the dogs of the present study were similar to those reported previously, with the presence of a mediastinal mass being the most important element. Presence of pleural effusion or large size of the mass can obscure other important abnormalities, and 3 dogs in our study had pulmonary metastasis at the time of thymoma diagnosis, which was detected with CT only. For people, CT is the recommended imaging method for mediastinal masses and should be performed when possible in dogs with mediastinal masses. It appears that MRI might be an equally sensitive imaging technique to reliably diagnose and predict resectability of thymomas, but this has yet to be investigated in dogs.<sup>26</sup>

Previously published data suggest that the epithelial component of thymomas does not always exfoliate well.<sup>7</sup> In 1 study,<sup>7</sup> epithelial cells were only present in only 3 of 17 cytologic samples (1 sample/dog). In the present study, 43 of 70 (61%) samples (1 sample/dog) evaluated had neoplastic epithelial clusters. Cytologic and histopathologic findings correlated in most cases in our study population, suggesting that the combined findings of a mediastinal mass and cytologic evidence of a mixed population of small lymphocytes and mast cells with or without epithelial cells would suffice to recommend excision. Flow cytometry of tumor aspirate samples has recently been described as a useful tool for discriminating mediastinal lymphoma from thymoma, with thymomas containing  $> 10\%$  CD4<sup>+</sup>CD8<sup>+</sup> cells.<sup>27</sup> This can aid further in the diagnosis of thymomas, reducing the need for biopsy procedures, which are invasive and associated with greater morbidity rate. Although histopathologic subtypes of thymoma have been described and lymphocyte-rich forms are possibly associated with a better prognosis,<sup>6</sup> subtypes had little influence on the degree of tumor invasiveness or survival time in the present study.

In the present study, at least 35% of dogs had hypercalcemia. This was presumed to be a paraneoplastic condition because all dogs for which recheck assessment of calcium concentration was performed after complete tumor resection had normalization of this variable. Hypercalcemia was consistent with parathyroid hormone–related protein–mediated hypercalcemia of malignancy, which supports findings in previously published reports.<sup>7,28</sup> Presence of hypercalcemia at the time of thymoma diagnosis was not a negative prognostic factor in the present study. Paraneoplastic peripheral lymphocytosis has previously been described,<sup>22</sup> and in our study, 4 dogs had severe lymphocytosis. Unfortunately, no data from postsurgical recheck CBCs were available for these dogs.

A definitive diagnosis of myasthenia gravis was obtained in 13 (11%) dogs of the present study. Seven other dogs with clinical signs of megaesophagus were not evaluated for myasthenia gravis. In 1 study,<sup>7</sup> dogs with thymoma and megaesophagus had a poor prognosis, with a median survival time of 4 days following surgery. In the present study, no difference in survival time was observed between dogs with and without myasthenia gravis or megaesophagus, possibly because perioperative and postoperative care for high-risk anesthetic and surgical patients has improved in the past 20 years. Although the pathophysiology of myasthenia gravis development still remains unclear in animals with thymoma, it is suggested that those patients may have an abnormal production of antibodies against myeloid cells of the thymus, which are antigenically similar to the receptor-bearing muscle cells at the neuromuscular junction.<sup>29</sup>

In humans, several other immune-mediated diseases are often associated with the presence of a thymoma.<sup>30</sup> Similar observations were made in a previous study<sup>6</sup> and in the present study; in the latter, 8 dogs had concurrent immune-mediated diseases such as immune-mediated thrombocytopenia, keratoconjunctivitis sicca, perianal fistula, hypothyroidism, masticatory

tory muscle myositis, hypothyroidism, polyarthritis, or diabetes mellitus, all of which support a deficiency in immune response.

Up to 40% of humans with thymomas may also have concurrent neoplasms.<sup>30</sup> In the present study, 27% of dogs had a second nonthymic tumor at the time of thymoma diagnosis and another 14% later developed another neoplasm. Regular and thorough follow-up examinations, including thoracic and abdominal imaging, should therefore be recommended for dogs with thymoma. The presence of a second nonthymic tumor at the time of thymoma diagnosis was associated with a significant decrease in survival time. When another tumor developed at a later date, no negative influence on survival time was noted.

Seventy-two percent of dogs underwent excision of the thymoma in the present study. Dogs treated surgically had a significantly longer survival time than did dogs for which surgical treatment was not performed, a finding that is consistent with previous reports.<sup>6</sup> Six dogs had tumor thrombi removed from the vena cava, and 5 of the 6 had long survival times. Phrenic nerve section occurred in 18% of cases but did not appear to impact survival time. Postoperative complications were rare and mostly manageable. Nine surgeries were aborted because of the extent of disease. Five of those dogs had no CT examination prior to surgery, and 4 dogs had CT findings that suggested that the mass was unresectable. This supports the recommendation that a preoperative CT examination should be performed when possible to determine the degree of invasiveness of the mass. However, resectability cannot be determined on the basis of CT results alone; this decision should be based on the surgeon's judgment during surgery and will most likely depend on the surgeon's experience. Indeed, in 3 dogs of the present study, CT findings were indicative of an unresectable mass but excision was subsequently performed successfully. Thymoma recurrence was identified in 12 of 84 (14%) dogs, and dogs that underwent a second surgery had long survival times after the second surgery, supporting the recommendation of a second thymoma resection when recurrence of the tumor is diagnosed.

Staging with the human Masaoka-Koga system was associated with outcome for the dogs of the present study: there was a significantly longer survival time for dogs with the less severe stages of disease. It appears that this system could therefore be applied to all dogs undergoing surgical treatment of a thymoma and used as an additional tool to predict survival time.

In a previous report,<sup>7</sup> it was suggested that a subgroup of dogs with thymoma will have very slowly progressive disease. In the present study, long survival times were noted for 7 dogs that received prednisone alone or no treatment. Additionally, although most dogs for which a second surgery was declined at the time of diagnosis had a grave prognosis, 2 dogs had long survival times without additional treatment.

In the present study, dogs with thymoma were treated with various chemotherapy agents prior to or after surgery; however, no response was evident. Radiation therapy resulted in a partial response in 5 of 8 dogs; however, response was short-lived. This was simi-

lar to findings in previous reports.<sup>7,25</sup> Further studies are necessary to evaluate optimal use of chemotherapy and radiation therapy in dogs with thymoma, especially dogs with unresectable tumors.

Limitations of the present study are those inherent to its retrospective nature. Specifically, the number of dogs with hypercalcemia and myasthenia gravis was likely underestimated because of incomplete diagnostic testing. Additionally, CT scanning was not performed on all dogs, and only 16 dogs underwent necropsy; therefore, some dogs with metastases or a second nonthymic tumor were likely not identified.

Thymoma in dogs undergoing tumor excision and in a subset of dogs with a slowly progressive subtype appears to be associated with a good prognosis. Paraneoplastic syndromes are common but do not appear to influence survival time. A high Masaoka-Koga stage, presence of a second nonthymic tumor at the time of thymoma diagnosis, and lack of surgical treatment are negative prognostic factors in dogs with thymoma.

a. Prism, version 6.0, GraphPad Software Inc, La Jolla, Calif.

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## Appendix

Masaoka-Koga staging system for thymomas in people used to classify thymoma stage in 72 dogs.

Stage	Definition
I	Grossly and microscopically completely encapsulated tumor
II	1. Microscopic transscapular invasion 2. Macroscopic invasion into thymic or surrounding fatty tissue, or grossly adherent to but not breaking through mediastinal pleura or pericardium
III	Macroscopic invasion into neighboring organ (ie, pericardium, great vessel, or lung)
IVa	Pleural or pericardial dissemination
IVb	Lymphogenous or hematogenous metastasis

(From Koga K, Matsuno Y, Noguchi M, et al. A review of 79 thymomas: modification of staging system and reappraisal of conventional division into invasive and non-invasive thymoma. *Pathol Int* 1994;44:359–367. Reprinted with permission. Copyright © 2008, John Wiley and Sons.)



## From this month's AJVR

### Association between subcutaneous fat thickness measured on thoracic radiographs and body condition score in dogs

Deborah E. Linder et al

**Objective**—To determine whether subcutaneous fat thickness measured on thoracic radiographs was associated with body condition score (BCS) in dogs.

**Animals**—87 client-owned dogs (41 males and 46 females) with a median age of 10.0 years (range, 1 to 16 years) and median weight of 20.3 kg (range, 3.1 to 58.0 kg).

**Procedures**—Age, sex, body weight, and breed were recorded. Body condition scores (scale from 1 to 9) and muscle condition scores were assigned by a single investigator. Subcutaneous fat thickness was measured at the level of the eighth rib head on a dorsoventral or ventrodorsal radiographic view of the thorax by a single investigator. Ratios of subcutaneous fat thickness to the width of the midbody of T8 on the ventrodorsal or dorsoventral radiographic view (T8 ratio) and to the length of the midbody of T4 on a right lateral radiographic view (T4 ratio) were calculated and compared with BCS by means of the Spearman correlation method.

**Results**—Median BCS was 6 (range, 1 to 9), and all muscle condition scores were represented. There were significant correlations between BCS and T4 ratio ( $r = 0.86$ ) and between BCS and T8 ratio ( $r = 0.84$ ).

**Conclusions and Clinical Relevance**—Results indicated that in this population, there was a significant association between BCS and subcutaneous fat thickness measured on thoracic radiographs. Findings suggested that measuring subcutaneous fat thickness could aid in the retrospective assignment of BCS in studies involving dogs in which BCS was not recorded in the medical record. (*Am J Vet Res* 2013;74:1400–1403)



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