Outcome following simultaneous bilateral thyroid lobectomy for treatment of thyroid gland carcinoma in dogs: 15 cases (1994–2010)

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Objective—To evaluate the outcome of resection of simultaneous discrete bilateral mobile thyroid gland carcinomas (TGCs) in dogs.

Design—Retrospective case series.

Animals—15 dogs with resected simultaneous discrete bilateral mobile TGCs.

Procedures—Medical records (from 1994 to 2010) were searched for dogs with the appropriate diagnosis and treatment. Information collected included signalment, clinical signs, diagnostic test results, tumor mobility (mobile tumor identified by movement ≥ 1 cm in all planes during palpation), complications, adjuvant treatments, and outcome.

Results—Mobile, discrete, bilateral TGCs were removed in all dogs. Among the 15 dogs, complete parathyroidectomies were necessary in 9; parathyroid tissue was reimplanted in 4 and preserved in 2. Complications included hemorrhage and laryngeal nerve trauma, but without serious consequences. Thirteen dogs received calcitriol with or without supplemental calcium after surgery. In the immediate postoperative period, hypocalcemia developed and was corrected in 11 dogs. At the end of the study, 7 dogs continued to receive calcitriol with or without supplemental calcium, and 8 dogs required long-term thyroid hormone treatment. Six dogs received adjuvant chemotherapy. Local tumor recurrence or de novo distant metastasis was not detected at each dog's last follow-up examination. Median survival time was 38.3 months. Three dogs were lost to follow-up, 8 survived (4.3 to 77 months after surgery), and 4 died of unrelated causes.

Conclusions and Clinical Relevance—In dogs with TGCs undergoing bilateral thyroid lobectomies, a successful outcome can be expected, even when parathyroid gland tissue cannot be preserved. The role of adjuvant chemotherapy in treatment outcome was not clearly defined. (*J Am Vet Med Assoc* 2012;241:95–103)

In dogs, tumors of the thyroid gland are the most common endocrine tumors,[1] but they are overall a relatively uncommon neoplasm, making up only 1.1% to 3.7% of all tumors.[2–5] Thyroid gland carcinomas can either be follicular or parafollicular in origin. In general, TGCs are locally invasive and highly vascular; < 25%[6,7] of them are functional. Approximately 25% to 47% of canine TGCs develop bilaterally.[3,5,8,9] In 1 study,[10] bilateral tumors were typically larger than unilateral tumors and were 16 times as likely to metastasize. Thyroid gland tumors in dogs are commonly malignant, with the likelihood for metastasis as high as 88%; 35% to 38% of patients have gross metastatic disease at the time of initial evaluation.[2,11] The most common site for metastasis is the lungs, with other sites being the regional lymph nodes, jugular veins, and heart.[2,3] Tumor size appears to be predictive of metastasis. Leav et al[8] found that dogs with tumor volumes < 21 cm^3 had a significantly lower risk of metastasis. Cervical vascular invasion by neoplastic cells may also facilitate metastasis.[11]

Abbreviation

TGC	Thyroid gland carcinoma

Treatment options for TGCs include resection, radiation therapy, nuclear medicine, and chemotherapy. The choice of treatment for a particular patient with a thyroid gland tumor depends on tumor size, vascularity, and invasiveness; the presence of gross metastatic disease; and, most importantly, whether the tumor is fixed or mobile upon palpation.[9,12,13] External beam radiation and radioiodide treatment are reserved for patients deemed to have nonresectable tumors, such as fixed, deeply invasive, or bilateral tumors.[1,12] Limited data are available elucidating the role of chemotherapy in treating TGCs.[14] To our knowledge, there are no reports of studies in which the use of adjuvant chemotherapy to extend survival time in dogs following appropriate local tumor control has been definitively explored. Liptak[12] proposed that dogs that underwent treatment for local tumor control should undergo chemotherapy when the greatest diameter of the original tumor was ≥ 5 cm, the tumor was vascularly invasive, or the patient had bilateral tumors. For dogs with TGCs, Radlinsky[13] also recommended adjuvant treatment in the form of

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chemotherapeutic agents or radiation because there is a reported recurrence rate of 45% within 2 years. For thyroid gland tumors in dogs, a rate of local recurrence after surgery of 30% has been reported.[7]

In a study[9] of 20 dogs that underwent excision as sole treatment for mobile thyroid gland tumors, the median survival time was > 36 months. For dogs with fixed tumors, treatment with surgery alone yielded a median survival time of 10 months.[6] Harari et al[11] reported a median survival time of 10.5 months after resection of solid carcinomas in 6 dogs and 8 months after resection of mixed solid-follicular carcinomas in 3 dogs. Following excision of TGCs in dogs, a median survival time of 22 months was reported.[7]

Although the thyroid gland is anatomically described as a single gland in humans, the same distinction is not clear in veterinary species.[15,16] In humans, the connecting isthmus between the left and right thyroid gland lobes is commonly present,[15] whereas in dogs, the isthmus is commonly absent.[16] Moreover, the anatomic description of the gland in adult dogs is paired structures, with each being synonymously referred to as a gland or a lobe.[16] Thus, the thyroid gland in dogs is a singular structure with left and right lobes.[17]

To our knowledge, published guidelines are lacking regarding excision of bilateral thyroid gland tumors. It has been our experience that intraoperative complications and overall survival rate for dogs with simultaneous discrete mobile bilateral thyroid gland tumors are similar to those for dogs with unilateral thyroid gland tumors and that any resulting hypoparathyroidism can be readily managed. The purpose of the study reported here was to evaluate the outcome of resection of simultaneous discrete bilateral mobile TGCs in dogs. It was our hypothesis that dogs with simultaneous bilateral mobile discrete TGCs would be amenable to single-session bilateral thyroid lobectomies, even when parathyroid glandular tissue was not preserved. We also proposed that bilateral tumor development does not always necessitate a need for adjuvant chemotherapy.

Materials and Methods

Case selection—The medical record database at the Colorado State University Veterinary Teaching Hospital was searched for dogs undergoing bilateral thyroid gland lobectomies from January 1, 1994, to March 31, 2010. For inclusion in the study, dogs had to have mobile (tumor movement ≥ 1 cm in all planes during palpation), discrete, bilateral TGCs and had to have undergone bilateral thyroid gland lobectomies in a single surgery.

Medical records review—The medical records of the dogs that met the inclusion criteria were reviewed, and follow-up information was obtained from both the referring veterinarians and clients. The information gathered included signalment, clinical signs, diagnostic test results and postoperative clinicopathologic findings, tumor mobility (determined via palpation in awake and anesthetized dogs), intraoperative and postoperative complications and subsequent management, histopathologic classification, tumor stage, adjuvant treatments, and outcome.

Variables used to assess outcome included presence or absence of distant metastasis, local tumor recurrence, and survival time. The immediate postoperative period was defined as the 2-week interval from time of surgery to time of suture removal; longer-term follow-up commenced after suture removal. For dogs that died, death was classified as being attributable to TGC if it was a result of metastasis or local tumor recurrence or as not being attributable to TGC if it was secondary to complications arising from surgery or adjuvant treatments. The latest follow-up date was June 30, 2010, and statistical analyses performed included data collected on that date. For dogs that had documented follow-up examinations, the minimum duration of follow-up was 4 months. All TGCs were staged according to the World Health Organization TNM staging system (**Appendices 1 and 2**).

Statistical analysis—Kaplan-Meier product limit curve analyses were performed to determine overall censored survival time and to assess variables such as supplemental thyroid hormone administration and chemotherapy. A value of $P < 0.05$ was considered significant for all analyses.

Results

Fifteen dogs met the inclusion criteria and underwent bilateral thyroid gland lobectomies between January 1, 1994, and March 31, 2010. All 15 dogs had bilateral TGCs confirmed via histologic examination of the lobes following removal. The age range of the dogs was 7.6 to 11.9 years (mean ± SD, 9.8 ± 1.4 years). There were 4 Beagles, 3 mixed-breed dogs, 2 Golden Retrievers, 1 Maltese, 1 Malamute, 1 Husky, 1 Old English Sheepdog, 1 Australian Heeler, and 1 English Pointer. Seven of the dogs were spayed females, 1 was a sexually intact male, and 7 were castrated males.

All dogs had palpable discrete masses in the ventral aspect of the cervical region. The masses were detected either by the owner (4 cases) or by a referring veterinarian during routine examination of the dog (6 cases). It was unclear whether the remaining 5 masses were detected by the owner or veterinarian. At the initial examination, 8 of the 15 dogs did not have clinical signs related to the tumor; 5 dogs had respiratory tract signs (ie, coughing, dyspnea, or both), and 2 dogs had nonspecific signs (ie, lethargy, inappetence, vomiting, or a combination of these signs).

Tumor mobility was a critical criterion for determining resectability. Each dog in the study had bilateral mobile discrete TGCs as determined via thorough manual palpation of the cervical mass. Palpation was performed in awake dogs or, if necessary to better determine tumor mobility, in sedated or anesthetized dogs. Movement of ≥ 1 cm in all planes during palpation was indicative of mobile tumors.

Prior to surgery, fine-needle aspiration of the mass was performed in 9 dogs, and the results of cytologic evaluation of the aspirate specimens were suggestive of thyroid gland neoplasia. Seven dogs underwent ultrasonographic examination of the cervical region to examine size and vascularity of the mass. The absence of a connecting isthmus between the right and left thyroid gland lobes was noted for 2 dogs, but there were no

reports to indicate whether an isthmus was observed ultrasonographically in the rest of the dogs. The thyroid gland masses of 2 dogs were assessed via nuclear scintigraphy. Three-view thoracic radiography for tumor-staging purposes was performed for all dogs. Possible pulmonary metastasis was detected in only 1 dog. For 10 dogs, tumors were classified as stage T_2a, N_0, and M_0; for 4 dogs, tumors were classified as stage T_3a, N_0, and M_0. For 1 dog, the TGC was presumed to be stage T_1a, N_0, and M_1 because the dog had a mammary gland tumor.

Prior to surgery, a CBC and serum biochemical analyses were performed for each dog. One dog had a mildly high serum ionized calcium concentration (1.53 mm/L; reference range, 1.19 to 1.48 mm/L), and 2 dogs had mildly high serum total calcium concentration (11.8 and 12.0 mg/dL; reference range, 9.2 to 11.7 mg/dL) without concurrent ionized calcium concentration verification. Serum total thyroxine concentration was assessed in 10 of the 15 dogs. Four dogs had low serum total thyroxine concentrations (0.8, 0.7, 0.7, and 0.5 µg/dL; reference range, 1.2 to 3.1 µg/dL), and 2 dogs had high serum total thyroxine concentrations (7.4 and 4.5 µg/dL); these dogs had no associated clinical signs. Four dogs were euthyroid (2.0 and 1.6 µg of thyroxine/dL of serum). None of the dogs were treated with supplemental levothyroxine sodium prior to thyroidectomy.

Computed tomographic scans were performed on 3 dogs prior to surgery, which enabled further characterization of any potential local tissue and vascular invasion by the TGCs. A connecting isthmus between the thyroid lobes was evident in 1 dog. For all dogs, a standard ventral cervical surgical approach was used, and care was taken to minimize handling of the tumors to avoid disruption of tumor vasculature. Marginal excision of the TGC with dissection adjacent to the tumor capsule was performed in all dogs. Hemostasis was achieved by use of a combination of monopolar and bipolar electrocautery, hemoclips, and a bipolar electrocautery vessel sealing system.[a] Gross vascular tumor thrombi were detected in 6 dogs; 1 of these dogs had a markedly distended caudal thyroid vein, which contained a tumor thrombus that extended all the way to the thoracic inlet. Nine dogs did not have salvageable parathyroid glands because of gland incorporation within the tumor. Four dogs had a single parathyroid gland (which was not incorporated with the TGC) reimplanted into the sternohyoideus or sternothyroideus muscle. In 2 dogs, 1 or both parathyroid glands were preserved (ie, glands were not incorporated into the tumor or disrupted during tumor excision).

On the basis of information derived via manual palpation, cervical ultrasonography, cervical CT imaging, and intraoperative measurements, 3 dogs had tumor diameters > 7 cm in 1 of the 2 lobes. Tumor volumes were calculated for 8 dogs (including the aforementioned 3 dogs) for which measurements were recorded in the medical records, 5 of which had tumor volumes > 21 cm^3.

The only important intraoperative complication was hemorrhage, which occurred in 4 dogs. Two of those dogs required a blood transfusion for hypovolemic support. For both dogs, intraoperative mean arterial blood pressure was 50 mm Hg (lower reference limit, ≥ 60 mm Hg); 1 dog had a low PCV (23%; reference range, 40% to 55%) and total protein concentration (3.2 g/dL; reference range, 6.0 to 7.5 g/dL) immediately prior to initiation of the blood transfusion.

Although it was standard institutional practice to perform laryngeal examinations to assess baseline recurrent laryngeal nerve competence because of that nerve's anatomic proximity to the thyroid gland lobes, performance of such examinations and the findings were not reported in each dog's medical record. Records indicated that preoperative and postoperative laryngeal examinations were performed in 5 dogs, and a single postoperative laryngeal examination was performed in 1 dog. All 5 dogs had apparently normal laryngeal function before surgery. Immediately after surgery, 2 dogs had normal laryngeal function, and 4 dogs had evidence of postoperative laryngeal dysfunction. These 4 dogs had unilateral recurrent laryngeal nerve damage or transection because the nerve incorporated in the TGC. Three of the 4 owners reported that their dogs had no subsequent problems with laryngeal dysfunction or paralysis; 1 dog was lost to follow-up.

For all 15 dogs, surgical margins of the resected tumors were examined histologically. However, clean surgical margins (ie, margins devoid of tumor cells) were achieved in only 1 dog because excisions were performed in the fragile tissue plane immediately adjacent to the tumor capsule.

Two dogs were discharged from the hospital the day following surgery. Other dogs were discharged from the hospital on the second (n = 6), third (4), fourth (2), and seventh (1) day after surgery. The median duration of hospitalization was 3 days.

Eleven dogs developed transient hypocalcemia during the immediate postoperative period (median ± SD serum calcium concentration, 1.06 ± 0.1 mm/L; reference range, 1.2 to 1.5 mm/L). Postoperative hypocalcemia was detected via serum ionized calcium analysis because affected dogs did not have clinical signs of the condition. All of these dogs returned to a normocalcemic state with appropriate calcitriol treatment with or without supplemental calcium administration in the immediate postoperative period. Use of calcitriol or a vitamin D analog was based on clinician preference. Of the 11 dogs that became hypocalcemic in the immediate postoperative period, 7 had had both parathyroid glands removed, and 3 had had one of their parathyroid glands reimplanted; parathyroid gland tissue had been preserved in 1 dog. Low serum ionized calcium concentrations (reference range, 1.2 to 1.5 mm/L) were detected 3 days after surgery in 10 dogs and 7 days after surgery in 1 dog. Another dog, in which no parathyroid gland tissue was preserved, remained normocalcemic throughout the immediate postsurgical period, but developed mild hypocalcemia (serum ionized calcium concentration, 0.99 mm/L) after an initial adjuvant dose of carboplatin 3 weeks after surgery, which necessitated resuming oral administration of calcium carbonate after demonstration of normocalcemia following weaning of postoperative calcitriol and calcium carbonate treatment. Another dog received calcitriol in the immediate postoperative period and remained normocalcemic in the immediate postoperative period yet developed hypocalcemia (serum ionized calcium

concentration, 0.8 mm/L) 8.5 weeks after surgery. This dog had been weaned off supplemental calcitriol at 3.5 weeks after surgery, but the hypocalcemic episode required resumption of calcitriol administration.

Serum total thyroxine concentrations, as assessed at the end of the immediate postoperative period per clinician discretion, were low (< 0.5 µg/dL) in 4 dogs, within reference range in 4 dogs (2.95, 2.57, and 1.2 µg/dL in 3 dogs; in 1 dog, value was 4.4 µg/dL [reported as within reference limits by another laboratory; reference range not recorded in medical record]), and high in 2 dogs (5.4 and 5.9 µg/dL). Serum total thyroxine concentrations in 5 dogs were not determined.

All dogs had TGCs (confirmed via histologic examination following surgery). Seven tumors were solid TGCs, 7 tumors were follicular TGCs, and 1 tumor was a mixed solid-follicular TGC. Evidence of lymphatic or vascular invasion (or both) by tumor cells was also found during histologic examination of tumor tissue from 9 dogs; those dogs included all 6 dogs that had grossly visible tumor thrombi at time of tumor excision. Three of the 9 dogs did not receive adjuvant chemotherapy; 1 of these 3 dogs remained free of metastasis 24 months after surgery. Six of the 9 dogs with tumor cell invasion received adjuvant chemotherapy. One of those 6 dogs received an initial dose of carboplatin, but treatment was discontinued because of toxic effects of the chemotherapy (assessed on the basis of the Veterinary Co-operative Oncology Group consensus statement[18] as grade 2 clinical hypocalcemia, grade 3 neutropenia, grade 3 anorexia and dehydration, and grade 2 vomiting); however, that dog had not developed metastatic disease at 7.4 months after surgery. Five of the 9 dogs received a complete course of chemotherapy (either doxorubicin only [5 doses] or doxorubicin alternated with carboplatin [6 cumulative doses total]); these dogs were free of metastasis at 4.3, 5.3, 6.1, 14.0, and 22.6 months after surgery.

None of the dogs that had gross tumor thrombi for which follow-up data were available (1 dog was lost to follow-up) had developed metastasis or local tumor recurrence at 4.3, 5.3, 5.7, 6.1, and 22.6 months after surgery, and 4 of them received adjuvant chemotherapy. One of the dogs had an extremely large tumor thrombus in the left caudal thyroid vein that extended to the level of the thoracic inlet but remained disease free for 5.3 months after surgery and after receiving a full course of adjuvant chemotherapy.

Eleven dogs received thyroid hormone treatment (ie, levothyroxine), and 13 dogs received calcitriol with or without oral administration of calcium carbonate in the immediate postoperative period. Two dogs were discharged from the hospital without any thyroid or parathyroid hormone replacement therapy. One of these dogs continued to do well and did not require any form of supplement throughout its life; the other dog reportedly continued to do well and required no supplements at time of last follow-up (6.1 months after surgery). At the end of the last study follow-up, 8 of the 11 dogs that were initially administered levothyroxine continued to receive supplemental levothyroxine, 1 dog did not require supplemental levothyroxine, and the remaining 2 dogs were lost to follow-up. Also, at the last study follow-up, 3 dogs required supplemental calcitriol, 1 dog was being treated with calcium carbonate, 3 dogs required supplemental calcitriol and calcium carbonate (2 of these dogs had reimplanted parathyroid glands); calcitriol and calcium supplementation was discontinued for 3 dogs. Three dogs that had received supplemental calcitriol and calcium were lost to follow-up. With the exception of 2 dogs lost to long-term follow-up, routine long-term monitoring of ionized calcium and thyroid hormone concentrations was performed in all dogs, with excellent owner compliance, although such monitoring was directed by clinician discretion and was not standardized at the study institution.

The latest date at which follow-up information was obtained was June 30, 2010, and statistical analyses performed included data up to that date. The follow-up period ranged from 128 to 2,311 days (median, 507.5 days). Twelve of 15 dogs had a follow-up period of at least 4 months.

Kaplan-Meier survival analyses revealed that the overall censored median survival time was 38.3 months (range, 0.33 to 73.67 months; **Figure 1**). Kaplan-Meier survival analyses revealed that thyroid hormone replacement therapy had a significant effect on overall survival time; median survival time was 38.3 months among dogs that received levothyroxine and 17.5 months among dogs that did not receive levothyroxine (P = 0.025; **Figure 2**). Otherwise, there were no significant effects of chemotherapy or administration of supplemental calcitriol or calcium among the dogs. The overall median survival time for dogs that did not receive chemotherapy was 38.3 months (range, 0.33 to 72.2 months). Five of the 6 dogs that received chemotherapy were alive at time of follow-up, and the overall median survival time had not been reached (median survival time, > 19.2 months; range, 4.3 to 19.2 months). No significant (P = 0.157) difference in survival time was detected between the dogs that did and those that did not receive chemotherapy. Three dogs

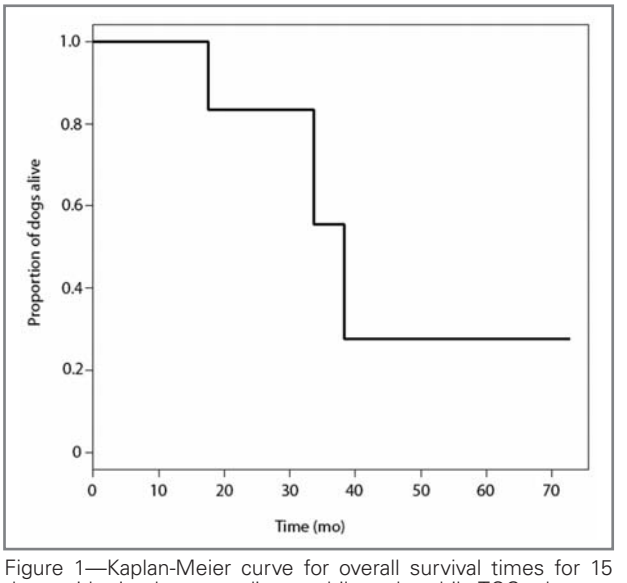

Figure 1—Kaplan-Meier curve for overall survival times for 15 dogs with simultaneous discrete bilateral mobile TGCs that underwent bilateral thyroid lobectomies.

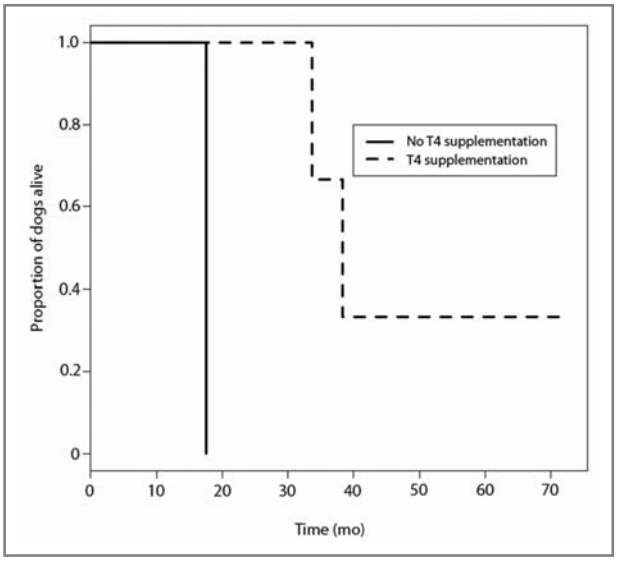

Figure 2—Kaplan-Meier curve for overall survival times for the dogs in Figure 1 that were (dashed line; n = 11) or were not (solid line; 4) administered supplemental levothyroxine following surgery. T4 = Thyroxine.

were lost to follow-up, 4 dogs died, and 8 dogs were alive at final follow-up (4.3, 5.3, 5.7, 6.1, 14, 22.6, 24, and 77 months [median, 15.8 months; mean ± SD, 18.8 ± 19.8 months] after the initial surgery). None of the dogs had local tumor recurrence or de novo distant metastasis. However, 1 dog had presumed pulmonary metastasis before surgery (detected during radiographic evaluation). This dog had had thyroid gland cancer 3 years previously and did not receive any adjuvant treatment for any condition, but died as a result of an unrelated mammary gland tumor 16.3 months following thyroidectomy. Serial follow-up thoracic radiographic views were not obtained, and a postmortem examination was not performed. Overall, cause of death was unrelated to TGCs for 4 dogs: 1 dog died as a result of cardiac disease, 2 dogs died as a result of another unrelated cancer (a nasal tumor and the aforementioned mammary gland tumor), and 1 dog died as a result of natural causes at an advanced age.

Discussion

To our knowledge, there are no previously published reports in which the outcome of dogs undergoing bilateral thyroid lobectomies for treatment of simultaneous bilateral discrete mobile TGCs has been evaluated, nor publication of any guidelines for surgical intervention in such cases. Analysis of data in the present study revealed that resection is a viable treatment option for dogs with simultaneous bilateral discrete mobile TGCs, even when no parathyroid gland tissue can be preserved, and that a good prognosis can be expected. Minimal intraoperative and postoperative morbidity was observed, and even in dogs that underwent total parathyroidectomy, hypocalcemia was readily managed with oral administration of appropriate supplements. Bilateral thyroid lobectomies resulted in acceptable survival times, an absence of local tumor recurrence, and low metastatic rates in the dogs assessed in the present study.

The most important accepted criterion determining successful thyroid gland tumor surgical resectability is palpable mobility of the tumor.[12] Additional traditional criteria include lack of tumor invasion of the surrounding tissues such as the trachea, recurrent laryngeal nerve, or esophagus[12,13]; tumor length < 7 cm[13]; presence of a unilateral thyroid gland tumor[12]; and no evidence of gross metastasis.[12] Further guiding principles recommend preservation of at least 1 parathyroid gland in the event that patients require bilateral thyroidectomies,[13] and that patients with bilateral thyroid gland tumors should receive adjuvant chemotherapy.[12] In the present study, we found that palpability of discrete, mobile, bilateral thyroid gland tumors was the most important criterion for determining feasibility of resection and that the size of these tumors did not impact resection or patient survival, nor was preservation of parathyroid gland tissue critical.

Overall median survival time for the dogs in this retrospective case series was considered long, comparable with or better than some of the previously reported survival times (> 36 months,[9] 22 months,[7] and 7 months[11]), bearing in mind that those studies did not exclusively involve dogs that underwent bilateral thyroid lobectomies. The study by Klein et al[9] revealed one of the more favorable historical survival rates (> 36 months), but only 4 of the 20 study dogs had bilateral thyroid gland tumors. In the dogs in the present study, survival time was comparable with that determined for dogs with resectable unilateral thyroid gland tumors, which challenges the historical view that bilateral discrete thyroid gland tumors are associated with a worse prognosis, compared with that for unilateral thyroid gland tumors.[10]

In the present study, the rate of local tumor recurrence was lower than a previously reported rate (7/23 [30.4%] dogs).[7] The rate of metastasis was also lower than previously reported rates (9/23 [39%] dogs[7] and 7/25 [28%] dogs[10]), despite the fact that dogs in the present study had at least 1 poor prognostic predictor of metastasis: bilateral thyroid gland tumors.[10] Five of the 8 dogs for which tumor volumes were measured in the present study also had an apparent increased risk factor for metastasis: tumor volume > 21 cm^3.[8] Only 1 of the 15 (6.7%) dogs in the study reported here had suspected metastatic disease initially, compared with 5 of 14 (35%) and 8 of 21 (38%) dogs reported to already have gross metastasis at time of diagnosis in other studies.[2,11] Excluding the dog with probable pulmonary metastatic disease at the time of diagnosis in the present study, none of the dogs developed de novo metastasis during the study period. This finding was considered favorable in contrast to that of a study by Theon et al,[10] in which the risk for metastasis with bilateral TGCs was 16 times that of metastasis with unilateral TGC. In the present study, 6 of the 15 dogs had evidence of tumor thrombi; tumor invasion into the cranial and caudal thyroid veins with thrombi formation reportedly increases the risk of metastasis.[11] None of the dogs that had gross tumor thrombi for which follow-up data were available had developed metastasis or local tumor recurrence at 4.3, 5.3, 5.7, 6.1,

and 22.6 months after surgery, and 4 of them received adjuvant chemotherapy. One of the dogs had an extremely large tumor thrombus in the left caudal thyroid vein that extended to the level of the thoracic inlet but remained disease free for 5.3 months after surgery and after receiving a full course of adjuvant chemotherapy. In the present study, it should be noted that some of the owners whose dogs had a long follow-up period elected to discontinue routine radiographic examinations for metastatic disease and instead relied primarily on the lack of clinical signs and physical examination abnormalities (as determined by the referring veterinarians) as an indicator of the absence of disease. Despite poor compliance with routine radiographic examinations in the present study, it is our institution's practice to recommend that thoracic radiography (3 views) is performed at 1 month after surgery, at 2- to 3-month intervals thereafter for the first year, and subsequently at 6-month intervals. Data from the present study supported the observation that good local tumor control may be achieved with marginal resection of mobile thyroid gland tumors[9] and also reinforced another observation that good local tumor control might decrease metastatic risk.[10] Tumor volume may also not be as accurate a predictor of metastasis as was originally thought.

The age and sex distributions of the dogs in the present study were similar to those among dogs with thyroid gland tumors in previous studies.[2–5,11] The conventional criterion of palpable tumor mobility was applied to the cases in this study when successful resectability of thyroid gland tumors was assessed. However, in these dogs, bilateral tumors were considered resectable, as long as the tumors appeared to be mobile on palpation and, if available, imaging results indicated that they had not excessively invaded surrounding structures. Size of the tumor was not necessarily a limiting factor in determining resectability; 3 dogs had tumors > 7 cm, yet none of them had intraoperative complications that were due to large tumor size. One of the dogs in the present study was suspected to have preexisting pulmonary metastasis at the time of surgery, but this dog did not have complications related to the TGC or metastatic disease after surgery as reported by the owner, and it did not receive any thyroid hormone supplementation or adjuvant therapy. The dog eventually died as a result of an unrelated mammary gland tumor at 16.3 months after its thyroidectomy. This dog was considered an anomaly with regard to the stability of its probable metastatic disease in the absence of adjuvant chemotherapy; however, the possibility exists that the pulmonary metastasis was an inadvertent radiographic misdiagnosis.

In the present study, none of the owners elected to pursue adjuvant radiation therapy for their dogs; however, over the long period in which cases accumulated for inclusion in this study, a compelling need for adjuvant radiation therapy could not be identified and ceased to be recommended. Not all clients elected to pursue adjuvant chemotherapy for their dogs. Dogs that did not undergo adjuvant chemotherapy did not appear to have decreased survival time, compared with dogs that received chemotherapy. However, this comparison may be biased by the fact that most dogs that received chemotherapy were the more recent cases, with 3 of them undergoing thyroidectomies in 2010. Regardless, this lack of significant difference in survival time between dogs that did or did not receive chemotherapy is noteworthy and highlights the need for more definitive studies on the role of adjuvant chemotherapy in the treatment of TGCs in dogs. Vascular and lymphatic invasion by tumor cells (detected during histologic examination of excised tissues) suggests that these affected dogs would conceptually benefit from adjuvant chemotherapy because such tumors may have a higher risk of metastasis. However, 1 of the 9 dogs with vascular invasion, lymphatic invasion, or both in the present study had a 24-month disease-free interval without adjuvant chemotherapy, but a statistical comparison of survival time was not made because of inadequate sample size. Interestingly, only 1 dog included in the present case series had definitively clean surgical margins (as determined via histologic examination), and incomplete margins traditionally have dictated the need for adjuvant treatments. However, there was no significant difference in survival time for dogs that did and dogs that did not receive adjuvant chemotherapy. Potentially, clean surgical margins were present for more of these dogs because the dissection plane was immediately adjacent to the thyroid tumor capsule, a fascial structure that was sufficiently thin to possibly escape detection during histologic evaluation. Even if this were not the case, local tumor recurrence and development of de novo metastasis did not develop in dogs in which marginal excision was performed.

Currently, because of the lack of empirical evidence on the efficacy of systemic chemotherapy in extending disease-free interval in dogs with TGCs, the protocols used are based on a small number of studies[19,20] evaluating the response of the primary thyroid gland tumor to chemotherapeutic agents such as doxorubicin. There is a similar lack of evidence of good efficacy of systemic chemotherapy in humans with metastatic TGCs,[21] although doxorubicin is cited as one of the more effective agents.[22] The chemotherapeutic agents that have been evaluated for the treatment of thyroid gland tumors in humans are generally those with an efficacy that parallels the rate of cell division. Thus, these agents, such as doxorubicin, that target the dividing cell may inherently not be particularly effective against thyroid gland tumors, whose growth rate is slow, compared with that of other solid tumors.[22] Further investigation of chemotherapy regimens for treatment of dogs with thyroid gland tumors is clearly needed. Administration of thyroid hormone supplements has also been suggested as an adjunct treatment with the assumption that such supplements would suppress secretion of thyroid-stimulating hormone, which may serve as a growth factor to tumor cells that have functional thyroid-stimulating hormone–binding sites. Use of thyroid hormone supplementation as an adjunctive treatment has not been tested in dogs to date, to our knowledge.[1] At our institution, the need for adjuvant chemotherapy for a given patient is discussed with the client and is recommended when gross tumor thrombi are detected during surgery or vascular or lymphatic invasion (or both) is identified via histologic examination of excised tissues.

The rate of complications in the present study was low; only 4 dogs had intraoperative hemorrhage, which resulted in transfusions for 2 of the dogs, and none needed corrective laryngeal surgery or tracheostomy tube placement after thyroidectomy. This is in comparison with results of a previous study by Klein et al,[9] in which the morbidity rate was high, especially in the dogs for which tumor excision with wide margins was performed. In contrast, the tumors in the dogs in the present case series were all marginally resected at the plane adjacent to the tumor capsule, which contributed to the low number of complications, especially those related to esophageal, tracheal, and recurrent laryngeal nerve damage. Presurgical and postsurgical laryngeal examinations were noted in the records of only 5 dogs, but this was most likely a result of recording failure rather than an actual failure to perform the laryngeal examinations. Four dogs reportedly had unilateral recurrent laryngeal nerve damage because the nerve was incorporated within the TGC and could not be peeled off prior to tumor removal; however, at follow-up, none of the owners reported long-term complications such as unilateral loss of laryngeal function. This suggests that with careful dissection to minimize damage, tumor removal associated with high risk of disturbing a single recurrent laryngeal nerve is not a contraindication to resection.

Postoperative hypocalcemia was subclinical, transient, and readily corrected with administration of appropriate supplement and dose adjustments in 11 dogs in the present study. These dogs did not develop long-term problems with calcium regulation. One of the dogs that did not have any preserved parathyroid gland tissue developed hypocalcemia after its first carboplatin treatment (administered 3 weeks after surgery). The hypocalcemia was aggravated by chemotherapy-induced anorexia (assessed on the basis of the Veterinary Cooperative Oncology Group consensus statement[18] as a grade 3 gastrointestinal adverse event associated with chemotherapy), which resulted in a decrease in dietary calcium intake that had been, up to this time, sufficient for calcium homeostasis in this dog. For another dog, administration of supplemental calcitriol had been discontinued at 3.5 weeks after surgery because of stable serum ionized calcium concentrations; however, that dog developed hypocalcemia 5 weeks after calcitriol supplementation ceased, and administration of calcitriol and calcium supplements was prescribed. At this dog's last follow-up, administration of supplemental calcitriol was maintaining a stable serum ionized calcium concentration within the reference range. In this dog, both parathyroid glands had been removed, and the hypocalcemic episode 8.5 weeks after surgery may be an isolated idiopathic event.

Evaluation of the data collected in the present study suggested that reimplantation of the parathyroid glands may not be as crucial in dogs undergoing bilateral thyroidectomies as previously thought.[1,13] Of the 4 dogs that underwent parathyroid gland reimplantation, 3 had hypocalcemic episodes after surgery, and 2 required long-term continuation of supplemental calcitriol and calcium administration, with 1 dog lost to follow-up. Some dogs that underwent total parathyroidectomy did not appear to have any increased difficulty in maintaining calcium homeostasis, whereas other dogs in which parathyroid glands were reimplanted still developed hypocalcemia. Similar observations have been made in humans following total parathyroidectomy with or without parathyroid gland autotransplantation.[23] In 5 of the dogs that underwent total parathyroidectomy in the present study, serum ionized calcium concentrations stabilized within reference range with appropriate calcium or calcitriol supplementation or both. In addition, one of the dogs that had both parathyroid glands removed remained eucalcemic and did not require calcium supplementation until after its first carboplatin treatment triggered clinical hypocalcemia. Two other dogs that had both parathyroid glands removed did not require long-term administration of supplemental calcium or calcitriol and received levothyroxine only at the time of follow-up. In humans, parathyroid hormone concentration can persist after total parathyroidectomy; in those individuals, it is presumed that residual parathyroid gland cells may be present as ectopic tissue.[23,24] The 2 dogs that underwent total parathyroidectomies that did not need long-term supplementation potentially had such residual ectopic parathyroid gland cells that contributed to stable circulating calcium concentrations. However, there is a lack of evidence in the veterinary medical literature to support the theory that aberrant embryonic migration of parathyroid gland tissue may produce ectopic cell populations capable of maintaining calcium homeostasis in the face of total parathyroidectomy. The parathyroid gland tissue should be salvaged when possible during bilateral thyroid lobectomies, although its preservation is not critical and failure to do so does not predict a poorer clinical outcome for the patient.

In humans, appropriate postsurgical and long-term supplementation with vitamin D analogs contributed to the success of total parathyroidectomy without autotransplantation of parathyroid gland tissue.[23–25] Just as in veterinary medicine, hypocalcemia is a concern in humans following total parathyroidectomy, and postsurgical monitoring includes serial assessments of serum ionized calcium concentration. Oral administration of calcium carbonate and vitamin D analogs such as calcitriol or cholecalciferol[21,23–25] is commenced in the immediate postoperative period and continued long term to decrease the risk of hypocalcemia. In veterinary patients, calcium carbonate is most commonly used for calcium supplementation because it contains the highest percentage of available elemental calcium.[26] Several vitamin D analogs such as calcitriol, cholecalciferol, and ergocalciferol are available. In the present study, calcitriol was commonly preferred for administration to dogs that underwent total parathyroidectomy because it has the shortest half-life and the fastest onset of action.[26]

Five of the 15 dogs in the present case series had another tumor unrelated to the TGC, a finding that corresponds to the finding that 12 of 37 dogs with thyroid gland tumors also developed other distinct tumor types reported by Rebhun et al.[27] This association of TGCs with an additional primary tumor emphasizes the need for thorough tumor staging in patients. Advanced imag-

ing techniques such as positron emission tomography may prove to be invaluable in detecting not only aggressive metastatic thyroid gland disease, but also additionally distinct tumors; such information is crucial for optimizing comprehensive treatment planning. None of the dogs in the present study had additional neoplasms that were associated with multiple endocrine neoplasia, such as pheochromocytoma, parathyroid adenoma, insulinoma, and pituitary tumors. In contrast, a third of human medullary TGCs are associated with multiple endocrine neoplasia type 2.[21]

In the present study, a thyroid gland isthmus was identified in 2 dogs (1 during preoperative CT evaluation and 1 during surgery), consistent with the anatomic description of an infrequently present isthmus between discrete thyroid lobes in adult dogs.[16] This brings up the interesting discussion of whether bilateral thyroid gland tumors are a result of local metastasis from one side to the other or whether they are bilateral synchronous tumors illustrating the concept of field cancerization,[28] also known as field carcinogenesis. To our knowledge, there is no published evidence advocating one theory over another regarding development of bilateral thyroid gland tumors in dogs. Leav et al[8] noted that when bilateral TGCs were present in dogs in their study, the neoplastic process was extensive, leading to the conclusion that it was not possible to determine whether the tumors were synchronous or had metastasized from one thyroid lobe to the other. In essence, unless molecular analyses are performed on the peritumoral tissue and surgical margins, presence of a field lesion cannot be definitively determined. The long survival time in the present case series argues against a locally aggressive metastasis from one side to the other. However, the relatively low rate of recurrence in unilaterally treated thyroid tumors is not a hallmark of the field cancerization theory.

The present study did not include dogs that received external beam radiation therapy as a primary procedure for local tumor control, and none of the dogs' owners elected adjuvant radiation therapy. Interestingly, the few veterinary studies[10,29–31] evaluating the use of radiation in dogs with unilateral or bilateral TGCs do not consistently cite hypoparathyroidism and hypocalcemia as acute or late effects of the radiation therapy. Brearley et al[31] noted clinical signs of hypoparathyroidism in 1 of 13 dogs at 32 weeks after radiation therapy, and that dog was effectively managed with thyroid hormone supplementation. Theon et al[10] suspected radiation-induced hypothyroidism in 2 of 25 dogs at 13 and 29 months after therapy, with 1 of these dogs also developing hypoparathyroidism. A single case report[32] described hypothyroidism in a dog as a sequela of unilateral thyroidectomy and radiation therapy. This apparently low incidence of radiation-induced hypothyroidism and hypoparathyroidism raises questions about the ablative dose delivered and whether ectopic parathyroid tissue provides adequate compensation. In the human medical literature, radiation-induced thyroid gland dysfunction is well documented, with subclinical hypothyroidism being common.[33–35] However, there is limited information regarding the effects of radiation therapy on circulating ionized calcium concentrations in people with head and neck cancers.[36] It is likely that veterinary patients, similar to their human counterparts, develop subclinical radiation-induced thyroid gland dysfunction and that the reported low incidence is largely a function of a lack of detection. Measurements of serum thyroid hormone concentrations do not appear to be standard of care after radiation therapy; Brearley et al[31] reported that thyroid hormone concentrations were not measured before or after radiation therapy for the dogs in that study.

On the basis of the information collected in the present study, it appears that there is a highly favorable prognosis for dogs with simultaneous discrete bilateral thyroid gland tumors that undergo bilateral thyroid lobectomies. Even though the number of cases evaluated was small, the observations made may influence the therapeutic approach and management of dogs with bilateral TGCs. The good long-term outcomes such as the long median survival times for the dogs in the present study suggested that there should be less hesitancy about performing bilateral thyroid lobectomies if there is judicious case selection and confidence in appropriate postsurgical management. Bilateral tumors, as discrete masses, do not preclude surgery as a treatment option, although the role of adjuvant chemotherapy in this patient population was not definitively established.

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Appendix 1

World Health Organization clinical classification system for thyroid gland tumors in dogs.

Category	Description
T	
T_0	No evidence of tumor (microscopic residual disease)
T_1	Maximum tumor diameter < 2 cm
T_2	Maximum tumor diameter 2–5 cm
T_3	Maximum tumor diameter > 5 cm
Substage a	Tumor freely movable
Substage b	Tumor fixed to surrounding structures
N	
N_0	No evidence of lymph node involvement
N_1	Ipsilateral lymph node involvement
N_2	Bilateral lymph node involvement
Substage a	Lymph node freely movable
Substage b	Lymph node fixed
M	Distant metastasis
M_0	No evidence of distant metastasis
M_1	Distant metastasis detected

M = Distant metastasis. N = Regional lymph node. T = Primary tumor.

(Adapted from Owen LN. *TMN classification of tumors in domestic animals.* Geneva: World Health Organization, 1980;52. Reprinted with permission.)

Appendix 2

World Health Organization staging system for thyroid gland tumors in dogs.

Staging group	Primary tumor	Regional lymph nodes	Distant metastases
I	T_1 a,b	N_0	M_0
II	T_0	N_1	M_0
	T_1 a,b	N_1	M_0
	T_2 a,b	N_0 or N_1 a	M_0
III	T_3	Any N	M_0
	Any T	N_1 b or N_2 b	M_0
IV	Any T	Any N_2	M_1

See Appendix 1 for key.