Incidence, survival time, and surgical treatment of parathyroid carcinomas in dogs: 100 cases (2010–2019)

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OBJECTIVE
To evaluate outcomes of dogs with parathyroid carcinoma (PTC) treated by surgical excision and to describe the incidence of postoperative hypocalcemia, degree of hypocalcemia, duration of hospitalization, duration of calcium supplementation, and survival time

ANIMALS
100 client-owned dogs with PTC admitted to academic, referral veterinary institutions.

PROCEDURES
In a retrospective multi-institutional study, medical records of dogs undergoing surgical excision of PTC between 2010 to 2019 were reviewed. Signalment, relevant medical history, clinical signs, clinicopathologic testing, imaging, surgical findings, intraoperative complications, histologic examination, and survival time were recorded.

RESULTS
100 dogs with PTC were included, and 96 dogs had clinical or incidental hypercalcemia. Common clinical signs included polyuria (44%), polydipsia (43%), hind limb paresis (22%), lethargy (21%), and hyporexia (20%). Cervical ultrasonography detected a parathyroid nodule in 91 of 91 dogs, with a single nodule in 70.3% (64/91), 2 nodules in 25.3% (23/91), and ≥ 3 nodules in 4 (4/91)% of dogs. Hypercalcemia resolved in 89 of 96 dogs within 7 days after surgery. Thirty-four percent of dogs developed hypocalcemia, on the basis of individual analyzer ranges, within 1 week after surgery. One dog had metastatic PTC to the prescapular lymph node, and 3 dogs were euthanized for refractory postoperative hypocalcemia. Estimated 1-, 2-, and 3-year survival rates were 84%, 65%, and 51% respectively, with a median survival time of 2 years.

CONCLUSIONS AND CLINICAL RELEVANCE
Excision of PTC results in resolution of hypercalcemia and excellent long-term tumor control. Surgical excision of PTC is recommended because of resolution of hypercalcemia and a good long-term prognosis. Future prospective studies and long-term follow-up are needed to further assess primary tumor recurrence, metastasis, and incidence of postoperative hypocalcemia.

Parathyroid carcinoma (PTC) is a rare neoplasia, typically resulting in hypercalcemia secondary to autonomous production of parathyroid hormone (PTH) by chief cells.[1–3] Historically, PTC has a reported prevalence of 5% to 10% in dogs with primary hyperparathyroidism (PHPTH) with only a small number of reported cases.[1,2,4–6] However, a higher prevalence of 15% to 25% of parathyroid nodules were reported as PTC, in recent retrospective studies.[7,8]

Dogs with PTC typically have an underlying hypercalcemia and often demonstrate mild clinical signs, which may or may not be detected by owners.[2,6,9] Nonspecific signs such as hyporexia, lethargy, and weakness, along with urinary tract signs, are reported most commonly and are indistinguishable from more common causes of PHPTH, such as parathyroid adenoma and parathyroid hyperplasia.[4,9–11] Less commonly reported clinical signs include weight loss, vomiting, diarrhea, shivering or trembling, and disorientation.[9,10]

Veterinary literature review revealed case reports[12–14] and inclusion of several instances of PTC within studies[1,2,4,5,15] documenting the diagnosis, treatment, and outcome in dogs with PHPTH. A single study by Sawyer et al,[9] specifically demonstrated the clinical signs and outcome in 19 dogs with PTC undergoing surgical excision with a reported median overall survival (OS) time of 614 days and 1-, 2-, and 3-year survival rates of 72%, 37%, and 30%, respectively. Recurrence of hy-

percalcemia, PTC recurrence, or detection of metastasis was not documented in any of the dogs in that study[9] but have been reported in the veterinary literature.[9,12,13]

The purpose of the retrospective study reported here was to further evaluate outcomes of dogs with PTC treated by surgical excision and to describe the incidence of postoperative hypocalcemia, degree of hypocalcemia, duration of hospitalization, duration of calcium supplementation, and survival time. To the authors' knowledge, this multi-institutional collaboration is the largest current compilation of dogs with PTC, and its purpose is to provide further guidance for clinical treatment and prognosis for this extremely rare neoplasia. Our hypothesis was that dogs with PTC would have good long-term survival rate with surgical excision.

Materials and Methods

Patient selection and data collection

Collaborators from 12 academic veterinary referral hospitals performed a medical record database review for surgical cases of PTC between 2010 and 2019. Affected dogs were included in the study if PTC was confirmed by histologic findings, treatment was by surgical excision, and follow-up of ≥ 2 weeks' duration was available. Board certified pathologists at the respective universities performed histologic evaluations of parathyroid nodules. Dogs were excluded from the study when they did not undergo parathyroid mass excision or when the medical record was incomplete.

Medical records were retrospectively reviewed, and data collected included signalment, relevant medical history, clinical signs, clinicopathologic test results, diagnostic imaging findings, surgical findings and procedure performed, intraoperative complications, duration of hospitalization, histologic findings, and survival time. Methods (eg, serial clinicopathologic test results and cervical ultrasonographic finding) for determining progression-free survival (PFS) time were included when available. Referring veterinarians and owners were interviewed by telephone where follow-up information was incomplete.

Serum ionized calcium (iCa) concentrations at each university were measured by use of analyzers with established reference ranges as follows: University of Florida, 1.18 to 1.35 mmol/L; Colorado State University, 1.12 to 1.4 mmol/L; Cornell University, 1.18 to 1.37 mmol/L; North Carolina State University, 0.91 to 1.32 mmol/L; Oklahoma State University, 1.24 to 1.45 mmol/L; The Ohio State University, 4.9 to 5.8 mmol/L; University of Missouri, 1.22 to 1.4 mmol/L; Iowa State University, 1.25 to 1.45 mmol/L; Texas A&M University, 4.92 to 5.4 mmol/L; University of Wisconsin, 1.16 to 1.4 mmol/L; University of Georgia, 1.17 to 1.43 mmol/L; and Michigan State University, 3.6 to 5.4 mmol/L.[16]

Statistical analysis

Descriptive statistics (median, mean, range, SD, and frequency) were used to report the characteristics of dogs with PTC. Available information that varied by case and sample size was adjusted to reflect the number of dogs with available data for each category. The study endpoints included PFS and OS times. The PFS time was defined as time in days from surgery to recurrence of hypercalcemia or primary tumor, development of metastasis, or death from any cause. The OS time was defined as time in days from surgical excision to death of any cause. The PFS and OS times were estimated by use of the Kaplan-Meier product limit method. Dogs were censored if alive (for OS time) or alive and progression free (for PFS time), lost to follow-up, and at time of data analysis. Kaplan-Meier analysis was performed by use of a computer software program (JMP version 14; SAS Institute Inc).

Results

One hundred and five cases of small animals (ie, cats and dogs) undergoing surgical excision of PTC with histologic evaluation of the lesion and available follow-up of 2 weeks duration were identified. One hundred dogs with PTC met inclusion criteria for the study with 5 animals being excluded. Reasons for exclusion included feline cases with PTC (n = 2), radiation treatment as sole treatment modality (1), diagnosis on necropsy with no surgery performed (1), and surgical biopsy as sole treatment (1).

Signalment, clinical signs, and diagnostics

Ninety-six of 100 dogs had clinical signs of hypercalcemia or incidental hypercalcemia diagnosed by referring veterinarians. Four of 100 dogs did not have clinical signs of hypercalcemia but only 1 of these dogs had documented preoperative determination of calcium concentration. Two dogs underwent further evaluation of previously diagnosed neoplasia (transitional cell carcinoma [n = 1]; mandibular mass of unknown etiology [1]). An additional 2 dogs had clinical signs of weight loss, lethargy, vomiting, and diarrhea, concerning for underlying neoplasia. Median age was 11 years (range, 4 to 18 years) and median weight of 23.3 kg with a range of 3.4 to 52 kg. There was sex predilection with 45% (45/100 spayed females; 0/100 sexually intact females) being female and 55% (51/100 castrated males; 4/100 sexually intact males) being male. Mixed breeds were most prevalent at 24% of dogs ([24/100]), followed by Beagles (7% [7/100]), Golden Retrievers (6% [6/100]), Dachshunds, Siberian Huskies, Shih Tzus (5% each [5/100]), Australian Shepherds (3% [3/100]), Labrador Retrievers (2% [2/100]), and other various purebred dogs 43% (1 of each breed (43/100]). Median duration of clinical signs was 105 days (range, 2 to 730 days) for 78 of 100 dogs. Seventy-seven percent (74/96) of the dogs with hypercalcemia had clinical signs of hypercalcemia. Clinical signs prior to hospital admission are summarized **(Table 1)**. Median preoperative serum iCa concentration was 1.82 mmol/L (range, 1.117 to 2.94 mmol/L; n = 97), with 99% (96/97) of dogs with

Table 1—Clinical signs of 100 dogs with parathyroid carcinoma.

Clinical signs	No. of affected dogs
Polyuria and polydipsia	44
Hind limb paresis	22
Lethargy	21
Hyporexia	20
Weight loss	19
Vomiting	12
Incontinence	10
Tremors	9
Urolithiasis	8
Anxiety	4
Diarrhea	2
Other signs*	7
No clinical signs	22

*Other clinical signs present in 1% of dogs include polyphagia, weight gain, alopecia, forelimb lameness, collapse, hematuria, stranguria, recurrent urinary tract infections, and constipation.

preoperative hypercalcemia. Median preoperative serum PTH concentration was 4.9 pmol/L (range, 1.2 to 432, n = 89) with 46% (41/89) of values being above the reference range.

Cervical ultrasonography detected a parathyroid nodule in 91 of 91 dogs; a single nodule was identified in 64 of 91 (70.3%) dogs, 2 nodules in 23 of 91 (25.3%) dogs, and ≥ 3 nodules in 4 of 91 (4.4%) dogs. Ninety-four nodules from 90 dogs were measured (2 dogs had bilateral PTC). The median PTC nodule size was 5.5-mm-diameter (range, 2- to 20.7-mm-diameter). A cervical mass was palpable in 2 dogs. Location of the mass correlated with site of surgical removal. Findings on histologic examination of nodules ensured that measurements were representative of only PTC lesions. Seventy-five percent (94/125) of nodules that were removed following detection by cervical ultrasonography were consistent with PTC on the basis of histologic examination findings.

Evidence of metastasis was detected on thoracic radiography of a single patient (1/79 dogs) prior to surgery. Of 85 dogs that underwent abdominal imaging, urolithiasis was detected in 37 (44%), adrenal gland abnormalities in 18 (21%), liver abnormalities in 15 (18%), nephrocalcinosis in 13 (15%), additional urinary tract abnormalities in 8 (9%), and no clinically relevant abnormalities in 20 (24%) dogs.

Surgical treatment, postoperative management, and complications

Surgical excision was pursued for treatment in 100 dogs with PTC. Calcium diuresis was performed in 22 dogs before surgery and included parenteral administration of saline (0.9% NaCl) solution (n = 19), lactated Ringer solution (1), buffered crystalloid solution (1), furosemide (5), prednisone (3), and calcitonin (1). Surgical procedure was chosen on the basis of appearance of parathyroid tissue at surgery and either parathyroidectomy alone (n = 61) or parathyroidectomy with unilateral thyroid lobectomy (38) was elected. One dog had a second unilateral thyroid lobectomy because of persistent hypercalcemia following initial parathyroidectomy with unilateral thyroid lobectomy.

Intraoperatively, 76 of 100 dogs had a single parathyroid gland nodule and 24 dogs had 2 parathyroid gland nodules. Thirteen of 100 dogs had an irregular thyroid texture with multiple small (2- to 3-mm-diameter) nodules. No evidence of gross vascular invasion was noted in surgical reports and the median size of 43 nodules submitted for histologic examination was 5-mm-diameter (range, 1- to 85-mm-diameter). Postoperative serum iCa concentrations during initial hospitalization (range, 1 to 13 days) and time to resolution of hypercalcemia are summarized **(Table 2)**. Duration of hospitalization, type of supplementation after surgery, and duration of supplementation after surgery are summarized **(Table 3)**.

Minor intraoperative complications occurred in 52 of 100 dogs and included hypotension (n = 46), intermittent ventricular premature complexes (4), bradycardia (1), and hypoxia (1). No major intraoperative complications occurred. Thirty-four percent (33/96) of dogs developed hypocalcemia within 1 week after surgery. Median preoperative serum iCa concentration for 63 dogs that were normocalcemic and hypercalcemic after surgery was 1.8 mmol/L (range, 1.17 to 2.94 mmol/L) and median preoperative serum iCa concentration for 33 dogs that were hypocalcemic after surgery was clinically equivalent at 1.9 mmol/L. Only 10 of 33 hypocalcemic dogs demonstrated clinical signs of hypocalcemia during hospitalization including muscle tremors (n = 4), facial itching and twitching (4), and weakness (2). Six of the 10 dogs had received calcium, vitamin D, or both supplementations prophylactically. Three dogs were euthanized at 2 weeks (n = 2) and 1.5 months (1) after surgery because of persistent uncontrollable hypocalcemia. Six dogs were rehospitalized within 2 weeks of discharge because of clinical signs of hypocalcemia. One dog was rehospitalized 2 months after surgery for clinical signs of hypocalcemia secondary to iatrogenic hypoparathyroidism. This dog was discharged from the hospital and had a survival time of 880 days. Hypercalcemia was confirmed to resolve within 7 days after surgery in 89 of 96 dogs with preoperative hypercalcemia. Of the 7 dogs without resolution of hypercalcemia, 5 were prophylactically receiving calcium supplementation. Of the 5 dogs, 2 dogs were documented to have serum iCa concentrations within reference range after discontinuation of calcium supplementation and 1 dog was documented to be hypocalcemic and required hospitalization after discontinuation of calcium supplementation. Four dogs did not have long-term serum iCa concentration follow-up available, including 2 of the 5 dogs that received calcium supplementation and 2 that did not receive supplementation.

Histopathologic findings

The median nodule diameter was 5 mm (range, 1- to 85-mm-diameter; 90 nodules recorded) and median number of mitotic figures were 1 (range, 0 to 30;

Table 2—Postoperative serum ionized calcium (iCa) concentrations (mmol/L) during hospitalization categorized by analyzer reference ranges (ie, 0.9 to 1.45 mmol/L and 3.6 to 5.8 mmol/L) and time to resolution of preoperative hypercalcemia in dogs with parathyroid carcinoma treated by surgical excision.

Variable	No. of dogs	Measurement
Postoperative serum iCa (RR, 0.9–1.45 mmol/L)	69	
		1.27 (0.68–2.48)*
		1.29 ± 0.21†
Postoperative serum iCa (RR, 3.6–5.8 mmol/L)	27	
		5.69 (3.8–8.7)*
		5.8 ± 0.91†
Postoperative serum iCa concentrations‡	96	
Normocalcemic dogs		57
Hypocalcemic dogs		33
Hypercalcemic dogs		6
Serum iCa (RR, 0.9–1.45 mmol/L) during postoperative hypocalcemia§	30	
		1.08 (0.68–1.23)*
		1.06 ± 0.1†
Postoperative time to resolution of preoperative hypercalcemia (d)	89	
		1 (0–7)*
		1.67 ± 1.30†
Breakdown of postoperative time to resolution of preoperative hypercalcemia	89	
< 24 h		2
1 d		53
2 d		22
3 d		7
4–5 d		1
6–7 d		4

Unless otherwise specified, values represent number of dogs.

*Values reported as median (range). †Values reported as mean ± SD. ‡Patient serum iCa concentrations were compared with the established analyzer reference range at the university laboratory. §Patients from universities with an analyzer reference range for serum iCa concentration of 3.6 to 5.8 mmol/L were not documented to be hypocalcemic after surgery.

RR = Reference range.

Table 3—Duration of hospitalization and type and duration of supplementation after surgery in 100 dogs with parathyroid carcinoma.

Variable	No. of dogs	Measurement
Duration of hospitalization (d)	100	
		4 (2–13)*
		4.5 ± 1.93†
Postoperative calcium supplementation‡	100	
Not supplemented		42
Supplemented		58
Clinical reasoning for supplementation	58	
Supplemented because of hypocalcemia		33
Prophylactic supplementation		25
Type of calcium supplementation	58	
Calcitriol (vitamin D)		55
Calcium carbonate		32
Calcium gluconate (during hospitalization)		10
Calcium supplementation combinations	58	
Calcitriol (vitamin D) and calcium carbonate		29
Calcitriol (vitamin D) only		26
Calcium carbonate only		3
Duration of calcium supplementation (d)	28	
		45 (8–1,230)*
		150 ± 291†

‡One patient was supplemented with pamidronate (bisphosphonate) for 5 months before surgery.

See Table 2 for remainder of key.

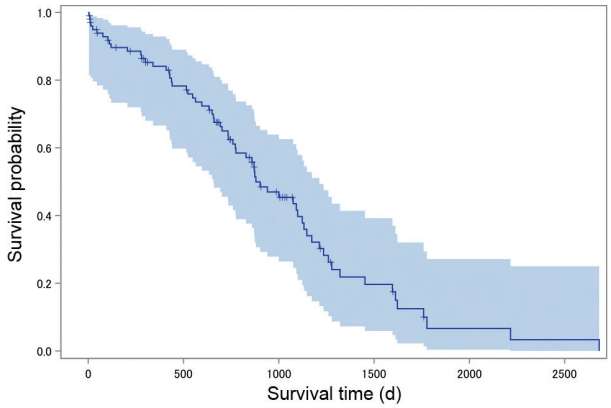

Figure 1—Kaplan-Meier survival curve detailing overall survival times of 100 dogs with parathyroid carcinoma treated with surgical excision. Vertical marks represent censored data (lost to follow-up). Blue shading = 95% CI.

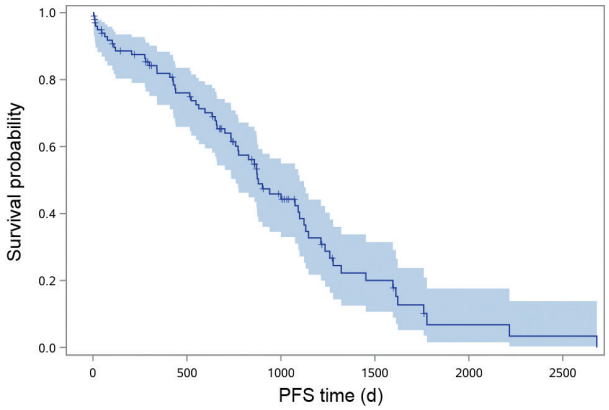

Figure 2—Kaplan-Meier survival curve detailing progression free-survival (PFS) times of 100 dogs with parathyroid carcinoma treated with surgical excision. **See** Figure 1 for key.

98 nodules recorded). Most dogs had nodules with capsular invasion (84%, [84/100]), nuclear atypia (84%, [84/100]), fibrous trabeculae (62%, [62/100]), and a trabecular growth pattern (62%, [62/100]). Less dogs had nodules with extracapsular invasion (29%, [29/100]), hemorrhage (16%, [16/100]), vascular invasion (15%, [15/100]), macronuclei (15%, [15/100]), and necrosis (14%, [14/100]). Several cases of multiple endocrine neoplasia (MEN) were rarely reported with a single case of multiple endocrine neoplasia type I (MEN1; 1% [1/100]), 3 cases of multiple endocrine neoplasia type II (MEN2; 3%, [3/100]), and 3 cases of MEN syndrome variants (3%, [3/100]).

Most dogs had 1 parathyroid gland affected by PTC (n = 96), with 2 parathyroid glands (3) and 3 parathyroid glands (1) being affected in the minority of dogs. Parathyroid carcinomas were found in ectopic locations in 2 patients, both being in adipose tissue near the thyroid gland. Margins were recorded for 75% of dogs, with complete excision in 50 dogs and incomplete excision in 25 dogs. None of the dogs were taken back to surgery because of incomplete margins.

Survival time and outcome

Metastasis of PTC to the prescapular lymph node was documented in a single dog. Five other dogs demonstrated evidence of suspected metastasis (ie, lung, kidney, bladder) at the time of euthanasia but were unable to be evaluated for metastatic PTC, because of lack of necropsy. Recurrence of hypercalcemia was documented in 1 dog on routine blood work; at that time, cervical ultrasonography was performed with no recurrence of the primary tumor found. This patient was euthanized 1,173 days after surgery at 14 years of age; a specific reason for euthanasia was not documented. Sixty-five dogs were deceased at the time of study and 6 were lost to follow-up. Six dogs were euthanized for PTC-related causes including the following: persistent uncontrollable hypocalcemia (n = 3), iatrogenic hypoparathyroidism (1), pathological fracture secondary to chronic hypercalcemia (1), and metastasis of PTC (1). Twelve dogs were euthanized because of intercurrent disease and 47 of 65 died of causes that were not definitively diagnosed. Twenty-nine dogs were alive at last follow-up. Median OS time was 735 days (range, 4 to 2,681 days; **Figure 1**). The 1-, 2-, and 3-year survival rates were 84%, 65%, and 51%, respectively. Median PFS time was 718 days (range, 4 to 2,681 days; **Figure 2**). The 1-, 2-, and 3-year PFS rates were 81%, 63%, and 39% respectively.

Discussion

In the present study, medical record review at 12 academic institutions between 2010 and 2019 yielded 100 cases of PTC in dogs, providing further support that the overall occurrence in dogs is rare. Results of the present study support our hypothesis as excision of PTC resulted in resolution of hypercalcemia in 95% of dogs and excellent long-term tumor control. On the basis of review of the literature, this is the largest study evaluating outcomes of dogs with PTC treated with surgical excision.

For dogs in the present study, presenting clinical signs, older signalment, lack of gender predilection, and clinicopathologic data resemble those previously reported for PHPTH.[2,9,10,17] Concurrent with Sawyer et al,[9] the present study did not identify any Keeshondens with PTC, despite documented autosomal dominant inheritance of PHPTH in this breed.[18] Similar to previous studies[2,4,10,19] evaluating PHPTH, clinical signs of dogs in the present study were consistent with hypercalcemia, with polyuria and polydipsia being the most prevalent. Although Sawyer et al[9] found weakness and an abnormal gait to be more prevalent in dogs with PTC, in that study[9] and our study, polyuria and polydipsia, paresis, lethargy, and hyporexia were still the most commonly reported clinical signs of dogs with PTC. In the present study, hypercalcemia was documented in 96 of 97 dogs tested, and serum PTH concentrations were elevated or inappropriately within reference range in all 89 dogs tested. This inappropriate physiologic response between hypercalcemia and serum PTH concentration is consistent

with previous reports describing varying causes of PHPTH.[1,9,11] Systemic effects of hypercalcemia, such as urolithiasis and nephrocalcinosis, were discovered on abdominal ultrasonography in half the dogs in the present study. These findings are consistent with previous reports of dogs and humans with PTC.[9,20] Pathological long bone fracture was documented in 1 dog in the present study, which has been previously reported in a dog with PHPTH but is more commonly reported in humans with PHPTH.[4,20]

In the present study, cervical ultrasonography was an excellent imaging modality for detection of parathyroid nodules, as nodules were detected in all 91 dogs evaluated with cervical ultrasonography. The median PTC nodule diameter was 5.5 mm (n = 94 nodules, 90 dogs with nodule measurements, and 2 dogs with bilateral PTC), which is smaller than in other reported[7,9,21] cases of PTC and supports 4-mm-diameter as a cutoff for differentiating parathyroid neoplasia (ie, adenoma, adenocarcinoma) from hyperplasia. However, 14 of 94 ultrasonically detected PTC nodules in the present study would have been excluded on the basis of 4-mm-diameter as a differentiating cutoff. Our findings support historical findings that parathyroid hyperplasia, adenomas, and adenocarcinomas have been challenging to differentiate by ultrasonography alone.[22] Histologic examination of surgically excised nodules in the present study, visualized before surgery on cervical ultrasonography, demonstrated evidence of not only PTC, but also normal parathyroid glands, parathyroid hyperplasia, thyroid carcinoma, and branchial, thyroid, and parathyroid cystic structures. Our findings support previously reported[9,22,23] limitations in specificity for diagnosis of PTC before surgery as only 75% (94/125) of nodules were consistent with PTC histologically. However, a recent study[7] demonstrated a correlation between heterogenous echotexture and detection of PTC, which has also been documented in a human PTC case report.[24] As heterogenous echotexture was not documented in medical records of PTC in the present case series; therefore, evaluation of this characteristic was unable to be performed but remains an avenue for future comparison. Furthermore, few patients in the present study were evaluated with CT (4% [4/100]) and mass size varied widely (range, 3- to 50-mm-diameter). Additional studies with larger sample size are needed to further evaluate the relationship between CT detected nodule size and cause of PHPTH.

After surgical treatment for PTC, a third of dogs in the present study became hypocalcemic, which is similar to other reported causes of PHPTH.[4,25–27] This data suggests that dogs with PTC are not more likely to become hypocalcemic than dogs with parathyroid adenoma or parathyroid hyperplasia. Furthermore, the degree of hypocalcemia was not more severe in dogs with PTC, compared with other causes of PHPTH.[19] Additionally, differences in degree of preoperative hypercalcemia were not clinically significant between groups. Median preoperative serum iCa concentrations were similar between dogs that developed hypocalcemia (1.9 mmol/L) and those that did not (1.8 mmol/L) after surgery, which is consistent with several recent studies but in contrast to others.[4,8,19,25,26] Median duration of hospitalization following surgery (4 days) did not differ between dogs with PTC and the commonly recommended 3 to 5 days for other causes of PHPTH. In the present study, hypercalcemia resolved in most dogs within 48 hours after surgery, which is similar to other surgically treated dogs with PHPTH.[1,5,8,25] These findings support the difficulty in differentiating PTC from other causes of PHPTH prior to histologic examination.

Studies of PHPTH in humans have also demonstrated that degree of preoperative hypercalcemia was not predictive of postoperative serum calcium concentrations.[28,29] The etiology for hypocalcemia following parathyroidectomy has not been definitively defined, and studies in human medicine have suggested aggressive calcium uptake by bone as a possible etiology.[30] On the basis of this potential etiology, pretreatment with bisphosphonates has been implemented in several studies of humans[28,31] with PHPTH with promising results. One dog in our study was pretreated with pamidronate for several months prior to parathyroidectomy. This patient demonstrated hypocalcemia after surgery; however, pamidronate was last given 1 month prior to surgery. Furthermore, reports of generalized osteopenia resulting in pathological fractures, commonly seen in humans,[32] are rare in dogs with PHPTH.[1,4] Only 1 dog in our case series demonstrated pathological fracture, suggesting a potential difference in the predominant source of calcium reuptake between species. However, the veterinary literature currently lacks a definitive method for predicting postoperative hypocalcemia following parathyroidectomy.[4,8,19,25,26] Additionally, bisphosphonates have a prolonged mechanism of action as osteoclast inhibitors and the duration of action following canine parathyroidectomy is currently unknown.[6] The authors suggest further pharmacokinetic evaluation of bisphosphonates is warranted before preoperative administration can be recommended in this canine population.

Of the one-third of dogs that developed hypocalcemia after surgery in the present study, only 30% of those dogs had clinical signs. Hypocalcemic patients demonstrated muscle tremors, weakness, and facial twitching and itching, which are consistent with other reported clinical signs of hypocalcemia.[1,6] Three percent of dogs with PTC were euthanized for refractory postoperative hypocalcemia outlining the rarity of this severe complication. Six percent of dogs were rehospitalized within 2 weeks of discharge because of clinical signs of hypocalcemia. Although rare that patients are severely clinically affected, these findings confirm the necessity of extensive postoperative monitoring in this patient population. Six of the hypocalcemic dogs demonstrated hypocalcemia despite prophylactic supplementation with calcium, vitamin D, or both. These findings are consistent with studies

that demonstrated lack of attenuation of postoperative serum iCa concentrations in a population supplemented with vitamin D, calcium, or both following parathyroidectomy.[8,9] Furthermore, clinical decision making for calcium supplementation, as well as duration and type of supplementation varied widely in the present study and is consistent with a lack of consensus in the veterinary literature.[1,8,9,19,26]

In the present study, most dogs undergoing surgery for PTC were treated with parathyroidectomy alone and experienced excellent long-term tumor control. Despite 84% of dogs demonstrating capsular invasion, 29% of dogs demonstrating extracapsular invasion, 15% of dogs demonstrating vascular invasion, and 25% of dogs having incomplete excision on histologic examination, only a single dog was reported to have metastasis to a prescapular lymph node. This diagnosis was confirmed via histologic examination, demonstrating the uncommon potential for PTC to spread to local lymph nodes.[12,13] A single dog had recurrence of hypercalcemia, but no dog demonstrated local recurrence of primary tumor depicting the unusual benign behavior of this rare carcinoma.

It is widely recognized in both human and veterinary literature that histopathologic diagnosis of PTC can be difficult.[9,20,33,34] Definitive criteria of malignancy including metastasis, local invasion, or vascular invasion, are not present in all cases of PTC.[20,33,35] Less definitive criteria for PTC have been proposed by varying pathologists such as fibrosis, trabecular growth pattern, necrosis, nuclear atypia, and increased mitotic activity.[36–38] On the basis of varying presence of definitive criteria and overlapping histologic features of parathyroid adenoma, multiple classification systems are frequently used by pathologists.[9,33,34] In the present study, 84% of dogs with PTC demonstrated capsular invasion, 29% demonstrated extracapsular invasion, and 15% demonstrated vascular invasion, supporting a definitive diagnosis of PTC. The most common histopathologic feature was capsular invasion, which is consistent with Sawyer et al[9]; however, nuclear atypia and extracapsular invasion were more prevalent in the present study. Interpretation by varying pathologists and a larger sample size may explain the variation between studies on PTC. Recent application of immunohistochemistry for parafibromin is being used in human medicine for a more accurate diagnosis of PTC.[39] Parafibromin is a protein product of the cell division cycle 73 gene (*CDC73*), which is downregulated because of mutation in familial and sporadic forms of PHPTH in humans.[39] A recent study demonstrated a negative predictive value of 98% for the ability to rule out PTC in the presence of a positive parafibromin stain.[39] The relevance of parafibromin and *CDC73* in a canine PTC population is unknown at this time, and further exploration is necessary to determine whether application could improve accuracy of PTC diagnosis.

Histologic examination suspected the concurrent finding of MEN in several dogs with PTC in the present study. The MEN syndromes are characterized in humans by occurrence of hyperplasia or neoplasia in 2 or more endocrine glands.[40] Four forms have been recognized and are caused by an inherited autosomal dominant mutation within the RET proto-oncogene.[41–43] Two patterns of MEN syndromes involve the parathyroid gland with parathyroid hyperplasia and adenoma most commonly reported.[42] Most commonly, MEN1 consists of tumors of the parathyroid gland, pancreatic islets, anterior pituitary gland and less commonly, adrenal cortical tumors.[44] Most commonly, MEN2 (previously MEN2A) consists of medullary thyroid carcinoma, pheochromocytoma, and parathyroid tumors.[45] Parathyroid carcinoma has rarely been described in MEN syndrome in the human literature with 15 cases of MEN1 and 3 cases of MEN2 to date.[43,46,47] Currently, few case reports describe MEN syndromes in veterinary patients, with MEN2 being most commonly reported.[48–52] The present study demonstrates 3 dogs suspected of meeting criteria for MEN2 syndrome and 1 dog meeting the criteria for MEN1 syndrome. To the authors' knowledge this is the first veterinary study to report concurrent PTC in suspected MEN1 and MEN2 syndromes in a canine population. Multiple case studies[52–57] in the veterinary literature have demonstrated variants of MEN syndrome but few cases have fit into the 4 MEN syndrome classifications. Three MEN syndrome variants were found in the present study to include variants of PTC and follicular thyroid carcinoma. Six similar cases of thyroid follicular carcinoma and parathyroid adenoma were reported in a study[58] evaluating MEN syndrome in 63 dogs with thyroid tumors, but our study differed because of the presence of PTC.

Another MEN syndrome variant demonstrated an interstitial cell testicular tumor, which has been previously reported in the veterinary literature,[53,56] but has not previously been reported with concurrent PTC. One dog in the present study, falling into the MEN2 syndrome classification, demonstrated 4 concurrent neoplasias, PTC, bilateral medullary thyroid carcinoma, and unilateral follicular cell carcinoma and concurrent parathyroid gland hyperplasia, demonstrating the highest prevalence of concurrent endocrine neoplasia. The division of cases fitting into MEN syndrome classifications and MEN syndrome variants supports previous literature suggesting that this classification system may not be suited for direct application to veterinary populations.[52] Additionally, 18 dogs were found to have adrenal abnormalities on abdominal ultrasonography, which could have underrepresented the number of pheochromocytoma, adrenal cortical tumors, and pituitary tumors detected in this population; therefore, potentially underdiagnosing additional dogs with MEN1 and MEN2. On the basis of current knowledge of MEN syndrome in dogs, further genetic analysis is required to determine whether familial neoplastic syndromes occur in canine populations or whether concurrent endocrine neoplasias are incidental findings in an aging population.[52,58]

The retrospective nature, multi-institutional case management, and nonstandardized follow-up are lim-

itations to the present study. Multi-institutional case management was necessary because of the rarity of PTC in a canine population. However, this factor introduced differences in data collection, follow-up, and case treatment on the basis of clinician discretion and varying institutional protocols. Serial follow-up and necropsy were not standardized, which if performed, may have increased the detection of metastasis, return of hypercalcemia, and local tumor recurrence. Furthermore, authors cannot comment on adjunctive treatments such as radiation or chemotherapy, as these treatments were not used for dogs in the present study. However, these adjunctive treatments have not demonstrated high levels of treatment success in humans with PTC.[59] Alternative treatment options for parathyroid tumors such as percutaneous ultrasound-guided ethanol and radiofrequency heat ablation are available,[5,60–62] but were not investigated in the present study. These modalities demonstrate varying degrees of success and adverse effects.[5,60–62]

In conclusion, for dogs of the present study clinical signs and clinicopathologic data are similar to other causes of PHPTH, including parathyroid hyperplasia or adenoma. Cervical ultrasonography appears to be an excellent imaging modality for detection of parathyroid nodules, and surgical excision is an effective treatment modality for PTC. Surgical excision of PTC is recommended because of resolution of hypercalcemia, good long-term prognosis, and excellent long-term tumor control, with a median survival time of 2 years. Our study, as the largest current compilation of dogs with PTC, serves to provide guidance for clinical treatment and prognosis for this extremely rare neoplasia. Retrospective findings support a favorable outcome following the current treatment standard of surgical excision similar to those reported by Sawyer et al.[9] However, future follow-up to include serial monitoring for hypercalcemia, repeat imaging, and necropsy is needed to further assess the degree of primary tumor recurrence and metastasis.

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