Carcinoma of the apocrine glands of the anal sac in dogs: 113 cases (1985–1995)

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Objective—To characterize the signalment, clinical signs, biological behavior, and response to treatment of carcinoma of the apocrine glands of the anal sac in dogs.

Design—Retrospective study.

Animals—113 dogs with histologically confirmed carcinoma of the apocrine glands of the anal sac.

Procedure—Data on signalment, clinical signs, and staging were reviewed and analyzed along with treatment modality for potential association with survival time.

Results—Sex distribution was approximately equal (54% female, 46% male). One hundred four dogs underwent treatment consisting of surgery, radiation therapy, chemotherapy, or multimodal treatment. Median survival for treated dogs was 544 days (range, 0 to 1,873 days). Dogs treated with chemotherapy alone had significantly shorter survival (median, 212 days) than those receiving other treatments (median, 584 days). Dogs not treated with surgery had significantly shorter survival (median, 402 days) than those that underwent surgery as part of their treatment (median, 548 days). Dogs with tumors ≥ 10 cm^2 had significantly shorter survival (median, 292 days) than dogs with tumors < 10 cm^2 (median, 584 days). Hypercalcemia was identified in 27% (n = 29) of dogs, and those dogs had significantly shorter survival (median, 256 days), compared with those that were normocalcemic (median, 584 days). Dogs with pulmonary metastasis had significantly shorter survival (median, 219 days) than dogs without evidence of pulmonary metastasis (median, 548 days).

Conclusions and Clinical Relevance—Unlike most previous reports, this study revealed an approximately equal sex distribution, and results suggest a more favorable prognosis. (*J Am Vet Med Assoc* 2003;223: 825–831)

Carcinoma of the apocrine glands of the anal sac is a relatively uncommon perianal tumor in dogs. Masses consistent with **carcinoma of the apocrine glands of the anal sac (CAS)** accounted for only 16.5% of cases in 1 study[1] of 139 dogs with histologically classified perianal tumors. However, the importance of this neoplasm is its highly invasive and metastatic nature and association with paraneoplastic hypercalcemia. Carcinomas of the apocrine glands of the anal sac obliterate the anal sac, readily invade surrounding soft tissues, and frequently metastasize to regional lymph nodes and, less often, the lungs and other internal organs.[1-5] Paraneoplastic hypercalcemia is reported in approximately 25% of dogs with CAS.[5]

Several reports[3-5] describe this tumor as occurring predominantly in older female dogs. In most studies, at least 80% of affected dogs were female. Another well-documented finding in dogs with CAS is hypercalcemia.[2,4-8] Ross et al[5] found that 8 of 32 (25%) dogs with CAS were hypercalcemic and determined that hypercalcemia indicated a poor prognosis. Whereas median survival time for dogs with serum calcium concentration in reference range prior to surgery was 11.5 months, median survival time for hypercalcemic dogs was only 6 months.

Rates of metastasis vary among studies, ranging from 36[3] to 96%.[4] In most studies, the metastatic rate is at least 50%.[2,4-6] Evidence of metastasis at the time of initial diagnosis has been associated with shorter survival times, compared with survival times of dogs with tumors that were merely locally invasive. Ross et al[5] reviewed 32 cases of CAS and reported that median survival time for dogs with evidence of metastasis was only 6 months, whereas median survival time for dogs with no evidence of metastasis was 15.5 months.[5]

Presently, definitive treatment consists of surgical excision, either as the sole form of treatment or as part of multimodal treatment. Given the prevalence of local recurrence and metastasis, identification of effective adjuvant therapies seems warranted. Although the use of adjuvant chemotherapy has increased in small animal medicine during the past 20 years, only a few reports have been made on the use of chemotherapy in the treatment of CAS in dogs. Results of a recent study[6] reported a response rate of 31 and 33% in dogs with CAS treated with cisplatin and carboplatin, respectively. Median survival time for all dogs in that study was only 6 months, and no increase in survival was report-

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ed for those dogs that received chemotherapy. However, limitations exist, because the clinical studies investigating this tumor have all involved relatively small numbers of dogs (from 4 to 43 dogs), and some of those reports are now 20 years old.

The purpose of the multicenter study reported here was to characterize signalment, clinical signs, and biological behavior of CAS in a large number of dogs and determine whether or not individual treatment modalities or multimodal treatments increase survival beyond that achieved historically with surgery alone.

Criteria for Selection of Cases

Detailed survey questionnaires were sent to participating Veterinary Cooperative Oncology Group institutions, including 9 colleges of veterinary medicine and 2 private veterinary practices. Dogs were included in the study only if medical records were complete, the diagnosis had been obtained by means of histologic examination, and histologic slides were available for review.

Procedures

Data were collected retrospectively via review of medical records and, when possible, follow-up conversations with pet owners or referring veterinarians. Follow-up conversations were conducted by clinicians at the participating institutions. A representative histologic sample from each case was reviewed and the diagnosis confirmed as CAS by a board-certified veterinary pathologist (JG). Information obtained from medical records included dog characteristics (breed, age, sex, and body weight); signs at referral and duration of those signs; physical examination findings including tumor size; pretreatment performance status (normal, restricted, compromised, disabled, or dead) as assessed by the clinician at the participating institution and based on modified performance status criteria[9]; results of CBC, serum biochemical analyses, urinalysis, thoracic and abdominal radiography, and abdominal ultrasonography; cytologic diagnosis; histopathologic diagnosis; type of treatment (surgery, chemotherapy, radiotherapy, phototherapy, or immunotherapy); complications; clinical response (complete response, partial response, stable disease, or progressive disease); posttreatment performance status (as for pretreatment performance status); duration of remission; date of relapse; survival time; necropsy results; and final disposition. Many dogs received multiple courses of treatment, and follow-up staging was not consistently performed with each new treatment; therefore, specific responses to individual treatments could not be determined, and survival was thus used as the main endpoint of the study.

All cases meeting inclusion criteria were included in the initial review of signalment, clinical signs, and staging. Survival times were calculated for all treated dogs and were measured from the first day of treatment until the date of death due to any cause. In addition to calculating and reporting median survival time, survival probabilities after treatment, with 95% **confidence intervals (CIs)**, were calculated.

The following factors were evaluated for association with survival: treating institution; age; sex; body weight; presence of clinical signs; tumor size and location; pretreatment performance status; leukocytosis; hypercalcemia; increased serum activity of alanine transferase, alkaline phosphatase, or aspartate aminotransferase; iliac lymphadenopathy; pulmonary metastasis; and treatment group. Abnormal laboratory values (eg, leukocytosis, hypercalcemia, and increased serum activities of alanine transferase, alkaline phosphatase, or aspartate aminotransferase) were defined as values greater than reference range at the reporting institution. Treatment groups were categorized as follows: surgery alone, radiation therapy alone, local therapy alone (consisting of surgery alone, radiation therapy alone, or the combination of surgery and radiation therapy), chemotherapy alone, surgery and chemotherapy, or the combination of surgery, radiation therapy, and chemotherapy.

The relationship between study factors and survival was examined via the Kaplan-Meier method to estimate survival distribution for each category and the log rank test to compare categories.[10,11] The 95% CIs for the Kaplan-Meier estimates were obtained by use of the method of Simon and Lee.[12] Multivariate analysis was performed on significant ($P \leq 0.05$) variables identified in the univariate analysis. The association between study factors and the use of chemotherapy was analyzed by use of the Fisher exact test.[13]

Results

Data were reviewed for 113 dogs with histologically confirmed CAS, which was diagnosed from January 1985 through December 1995. There were 29 breeds of dog. Mixed-breed dogs (n = 44) were the most common, followed by German Shepherd Dogs (14), Golden Retrievers (7), and Cocker Spaniels (6). Median age at referral was 10 years (range, 5 to 15 years), and median weight was 26 kg (range, 3.6 to 59 kg). Sixty-one (54%) dogs were female; 5 were sexually intact. Fifty-two (46%) dogs were male; 8 were sexually intact. A subset (n = 6) of these cases has been published.[6]

Participating institutions or practices and the number of cases provided by each included The Ohio State University (n = 25), University of Wisconsin (19), North Carolina State University (16), Colorado State University (15), Tufts University (14), University of Minnesota (8), Purdue University (6), Southwest Veterinary Oncology, Tucson, Ariz (5), Louisiana State University (3), University of Tennessee (1), and Beltway Veterinary Referral Center, Glenn Dale, Md (1).

Perianal swelling and tenesmus were the most common signs at referral (**Table 1**). Polyuria and polydipsia, hind limb weakness, lethargy, and other individual signs were each detected in < 35% of dogs. Forty-four dogs had more than 1 of the clinical signs at the time of referral. Pretreatment performance status information was available for 110 of the dogs. Seventy-four (67%) were classified as having normal performance, 31 (28%) as having restricted activity, and 5 (5%) as having compromised performance.

Sixty (53%) dogs had a palpable perianal mass at the time of evaluation. Median tumor size in these dogs was 9 cm^2 (range, 0.5 to 400 cm^2). Tumor size was

Table 1—Clinical signs at initial evaluation in 113 dogs with carcinoma of the anal sac

Clinical sign	Proportion of dogs (%)
Perianal swelling	54/88 (61)
Tenesmus	30/89 (34)
Licking or biting at the perineum	11/37 (30)
Perianal bleeding	8/33 (24)
Polyuria-polydipsia	19/88 (22)
Scooting	7/33 (21)
Hind limb weakness	15/85 (18)
Lethargy	11/83 (13)
Stranguria	3/83 (4)

Many dogs had > 1 clinical sign. For certain dogs and clinical signs, data in the medical records were incomplete (denominator < 113).

identified as an independent predictor of overall survival in treated dogs. Median survival for dogs with tumors ≥ 10 cm^2 was 292 days, compared with 584 days in dogs with tumors < 10 cm^2 (P = 0.04; **Fig 1**). Other variables, including signalment (age and sex), body weight, presence of clinical signs, and pretreatment performance status, were not significantly related to survival.

Serum biochemical analyses were performed at the time of initial diagnosis in 108 dogs. Hypercalcemia was found in 29 (27%) dogs. Forty-six percent of these dogs had concurrent iliac lymphadenopathy. Hypercalcemia was identified as a significant (P = 0.002) independent predictor of overall survival in treated dogs. Median survival was 256 days for hypercalcemic dogs, compared with 584 days for normocalcemic dogs (**Fig 2**). Tumor size was recorded for 18 of the 29 dogs with hypercalcemia. Tumors in these dogs ranged in size from 0.5 to 100 cm^2. Eight dogs had tumors ≤ 9 cm^2. Three dogs had tumors ≤ 1 cm^2. Although 1 of these dogs weighed only 7.5 kg, the other 2 were relatively large dogs (a 29-kg Golden Retriever and 31-kg mixed-breed dog). Other laboratory variables evaluated, including leukocytosis and liver enzyme activities, were not significantly associated with survival.

Thoracic radiography and abdominal imaging (radiography, ultrasonography, or both) were performed in 104 dogs. Of these, 49 (47%) dogs had evidence of iliac lymphadenopathy at the time of initial diagnosis. Excision of iliac lymph nodes was performed in 12 of these dogs. Histologic examination of excised lymph nodes in the 9 dogs from which nodal tissue was submitted confirmed metastatic CAS in each instance. Five of these dogs were treated with surgery alone, 6 received adjuvant chemotherapy, and 1 received adjuvant radiation therapy and chemotherapy. There was no significant difference in survival time for treated dogs with iliac lymphadenopathy, compared with dogs with no evidence of lymphadenopathy (P = 0.75). Pulmonary nodules consistent with metastatic disease were identified in 8 of these dogs. Dogs with evidence of pulmonary metastasis that underwent treatment had significantly (P = 0.03) shorter survival time (219 days) than dogs without evidence of pulmonary metastasis (548 days; **Fig 3**).

Median survival for all treated dogs was 544 days (range, 0 to 1,873 days; **Fig 4**). The probability of sur-

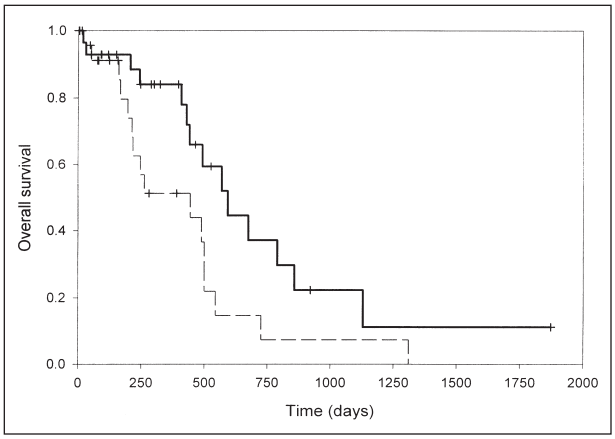

Figure 1—Kaplan-Meier survival curves for 56 dogs with carcinoma of the apocrine glands of the anal sac, grouped according to tumor size. The solid line represents 32 dogs with tumors < 10 cm^2, and the dashed line represents 24 dogs with tumors ≥ 10 cm^2. Vertical lines denote dogs that were censored from analysis.

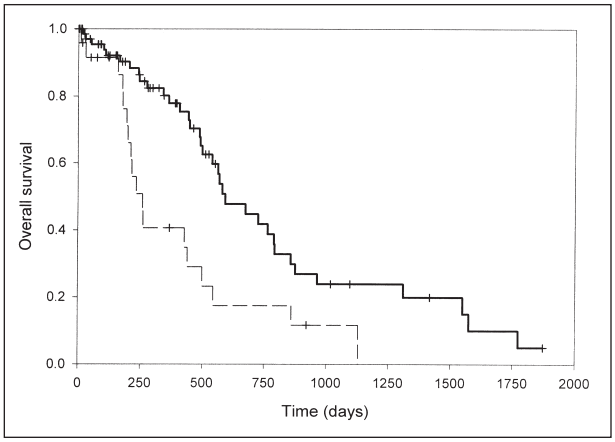

Figure 2—Kaplan-Meier survival curves for 100 dogs with carcinoma of the apocrine glands of the anal sac, grouped according to serum calcium concentration. The solid line represents 74 dogs with normocalcemia, and the dashed line represents 26 dogs with hypercalcemia. Vertical lines denote dogs that were censored from analysis.

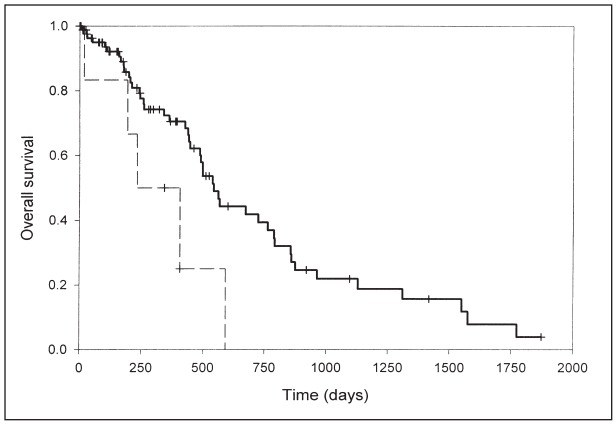

Figure 3—Kaplan-Meier survival curves for 95 dogs with carcinoma of the apocrine glands of the anal sac, grouped according to the absence or presence of pulmonary metastasis. The solid line represents 88 dogs with no evidence of pulmonary metastasis, and the dashed line represents 7 dogs with evidence of pulmonary metastasis. Vertical lines denote dogs that were censored from analysis.

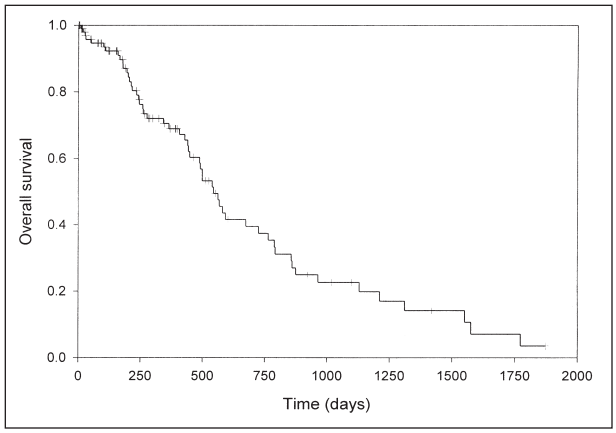

Figure 4—Kaplan-Meier curve for overall survival in 113 dogs with carcinoma of the apocrine glands of the anal sac. Vertical lines denote dogs that were censored from analysis.

viving 2 years or more was 0.37 (95% CI, 0.25 to 0.50). Among treated dogs, 50 dogs were alive at last follow-up (**Table 2**). Among these dogs, 25 (50%) dogs were reported to be in remission, and 25 (50%) dogs were alive with disease. Fifty-four dogs died; 40 (74%) were reported to have died of disease, and 14 (26%) died from unrelated causes.

There was no significant difference in survival time for dogs treated with surgery alone; radiation therapy alone; local therapy alone (consisting of surgery, radiation therapy, or the combination of surgery and radiation therapy); surgery and chemotherapy; or the combination of surgery, radiation therapy, and chemotherapy. There was, however, a survival advantage for dogs receiving any type of surgery as part of their treatment. Dogs not treated with surgery had a median survival time of 402 days, compared with 548 days for dogs that received surgery alone or in combination with other modalities ($P = 0.049$). Median survival for the 11 dogs treated with chemotherapy alone was 212 days (range, 18 to 280 days). This survival time was significantly ($P < 0.001$) shorter than that for dogs in all other treatment groups.

Chemotherapy was used in 61 dogs; it was used as an adjunct treatment in 50 dogs and as the sole treatment in 11 dogs. Agents used and the number of dogs that received each drug included cisplatin-carboplatin (n = 28), doxorubicin-mitoxantrone (27), melphalan (21), actinomycin D (6), piroxicam (2), epirubicin (1), and chlorambucil (1). Single agents were used in 39 dogs; combinations of drugs were used in 22 dogs. There was no significant difference in survival time for dogs treated with different chemotherapy regimens. Dogs with iliac lymphadenopathy were significantly ($P = 0.01$) more likely to receive chemotherapy as part of their treatment.

Treatment complications were reported in 38 (37%) dogs after treatment. Of 81 dogs undergoing surgery, 8 (10%) developed complications attributed to surgery. These included infection (n = 2) resulting in the death of 1 dog, hypocalcemia (1) following presurgical hypercalcemia, and sudden death (1) during recovery from anesthesia in the surgery-alone group; intermittent fecal incontinence (1), tenesmus (1), and the development of a perianal fistula (1) in the group treated with surgery and chemotherapy; and fecal incontinence (1) in the group treated with the combination of surgery, radiation therapy, and chemotherapy. Of 27 dogs that received radiation therapy, 9 (33%) developed complications attributed to radiation therapy, including tumor abscess formation (1) in the radiation-alone group, moist desquamation alone (3), moist desquamation with dyschezia-hematochezia (1), moist desquamation with tumor abscess formation and fistula formation (1), and moist desquamation followed by the development of an anal stricture (3) in the group treated with the combination of surgery, radiation therapy, and chemotherapy. Of 61 dogs receiving chemotherapy, 22 (36%) developed complications attributed to chemotherapy consisting of myelosuppression, gastrointestinal toxicosis, or unique toxicoses related to individual agents (cardiac toxicosis

Table 2—Survival probabilities for 104 dogs treated for carcinoma of the anal sac

Treatment (No. of dogs)	Survival probability (95% confidence interval) 6 months	1 year	2 years	3 years	Median (d)	*P* value
Surgery alone (31)	0.90 (0.77, 1.00)	0.65 (0.43, 0.88)	0.29 (0.06, 0.53)	—	500	0.936
Radiation therapy alone (10)	0.85 (0.61, 1.00)	0.79 (0.52, 1.00)	0.38 (0.04, 0.74)	—	657	0.822
Local therapy alone (43)	0.91 (0.81, 1.00)	0.76 (0.60, 0.92)	0.37 (0.17, 0.57)	0.23 (0.06, 0.41)	544 days	0.999
Chemotherapy alone (11)	0.67 (0.35, 0.99)	—	—	—	212	< 0.001
Surgery and chemotherapy (35)	0.86 (0.73, 0.99)	0.69 (0.50, 0.87)	0.36 (0.12, 0.59)	0.14 (0.00, 0.32)	540	0.964
Surgery, radiation, and chemotherapy (15)	0.86 (0.68, 1.00)	0.80 (0.59, 1.00)	0.56 (0.27, 0.85)	0.35 (0.05, 0.66)	742	0.098
Any surgery (81)	0.87 (0.79, 0.96)	0.72 (0.60, 0.84)	0.39 (0.25, 0.54)	0.28 (0.14, 0.42)	548	0.0495
Any radiation therapy (27)	0.88 (0.76, 1.00)	0.84 (0.69, 0.98)	0.48 (0.26, 0.70)	0.24 (0.04, 0.44)	719	0.164
Any chemotherapy (61)	0.85 (0.75, 0.95)	0.65 (0.51, 0.79)	0.38 (0.22, 0.55)	0.19 (0.05, 0.34)	539	0.999

— = No survivors.

secondary to doxorubicin administration or sterile hemorrhagic cystitis secondary to cyclophosphamide administration). Myelosuppression was reported in 2 of 11 dogs in the chemotherapy-alone group, 12 of 35 dogs in the group treated with surgery and chemotherapy, and 2 of 15 dogs treated with the combination of surgery, radiation therapy, and chemotherapy. Signs consistent with gastrointestinal toxicosis were reported in 2 of 11 dogs in the chemotherapy-alone group, 8 of 35 dogs in the group treated with surgery and chemotherapy, and 1 of 15 dogs treated with the combination of surgery, radiation therapy, and chemotherapy.

Discussion

Consistent with earlier studies,[3-5] we found that CAS is frequently occult. Only 61% of the dogs in our study had initially been evaluated because of a noticeable perianal swelling; in 39% of dogs, the tumor was an incidental finding on physical examination. Signs referable to perianal irritation or anal-rectal obstruction were even less common. Thus, this tumor may be easily missed in its early stages.

The median age (10 years) at initial evaluation in this study was consistent with that in earlier reports.[1-7] However, it is worth noting that in our study as in others,[3,5] CAS was identified in dogs as young as 5 years of age. The potential for occurrence of this tumor in young adult dogs suggests that palpation of the anal sacs and perianal region should be a routine part of the physical examination in every adult dog.

In marked contrast to all but the most recent study, almost 50% of the dogs in our study were male. The reason for this apparent increase in the prevalence of CAS in male dogs is unknown. Perhaps in some earlier studies, a percentage of CAS in male dogs was categorized as the more common perianal (hepatoid) gland tumor, which is much more common in males than in females.[1] It is also possible that hormonal factors play a role in tumor development and that the sex distribution observed in our study was a reflection of an increased frequency and earlier age of neutering in recent years. Regardless, the often-occult nature of this tumor and the approximately equal sex distribution found in our study group suggest the need for careful palpation of the anal sacs and perianal area in older dogs of either sex during routine physical examination.

Hypercalcemia was found in 27% of the dogs for which serum biochemical results were available. This finding is consistent with a previous report[5] in which 25% of dogs with CAS were hypercalcemic. In both studies, there was a disparity between the number of dogs found to be hypercalcemic and those with clinical signs of hypercalcemia. For example, although 27% of the dogs in our study were hypercalcemic, only 22% of all dogs had polyuria-polydipsia at referral. In another study,[8] polyuria-polydipsia was found in only 68% of 40 dogs with hypercalcemia from various causes. Other signs of hypercalcemia, such as weakness, vomiting, twitching or shaking, and muscle wasting, were less common.[8] Thus, not all dogs with hypercalcemia had clinical signs.

As in a previous study,[5] the dogs in our study that were hypercalcemic at referral had a shorter median survival time than normocalcemic dogs. Serum calcium concentrations should be evaluated in all dogs suspected of having CAS because of complications (renal dysfunction, gastrointestinal motility disturbances, or cardiac arrythmias) that may develop in affected dogs and also for its prognostic value. In hypercalcemic dogs with CAS, serum calcium concentration typically decreases after excision of the tumor and increases with recurrence of the tumor.[4,5,7] Although not evaluated in our study, periodic measurement of serum calcium concentration has been suggested as a useful tool for monitoring a dog for tumor recurrence.

A common cause of hypercalcemia in dogs with CAS is the production of **parathyroid hormone-related protein (PTHrP)** by the tumor cells.[14,15] This protein behaves in a biologically similar way to parathyroid hormone, increasing the serum calcium concentration. Rosol et al[15] detected that canine CAS cells produce PTHrP and that a significant linear correlation exists between circulating PTHrP and serum calcium concentrations in dogs with CAS. Not all dogs with CAS will develop hypercalcemia. Meuten et al[4] proposed 2 possible explanations for this: hormone secretion by the tumor cells may require a certain degree of cell differentiation, so poorly differentiated tumors may be nonfunctional, and the amount of hormone secreted by the tumor may be so small that the tumor may need to be quite large in order to produce biologically active quantities of hormone. The first explanation suggests that dogs with poorly differentiated (ie, nonfunctional) tumors survive longer than dogs with more differentiated (ie, functional) tumors. This seems contrary to what is known regarding other canine tumors, in which poorly differentiated tumors are associated with a poorer prognosis.[16-20] However, if correct, this somewhat unexpected result may be a reflection of the clinical impact of paraneoplastic hypercalcemia. When present, hypercalcemia and its associated complications may be more important than histologic differentiation. Reduction in serum calcium concentration after excision of the tumor supports the second possibility. However, the fact that 9 of 18 hypercalcemic dogs with known tumor size in our study had tumors < 9 cm^2, including 3 with tumors ≤ 1 cm^2, argues against the second possibility unless metastatic tumors in the iliac lymph nodes were the primary source of PTHrP. Forty-six percent of dogs in this study with hypercalcemia had concurrent iliac lymphadenopathy.

Iliac lymphadenopathy was detected in 47% of the dogs in our study. Aspiration cytology or biopsy of the enlarged lymph nodes was not performed in most dogs. However, one may speculate that iliac lymphadenopathy indicates metastasis of the CAS on the basis of the documented behavior of this tumor.[4] Although not specifically evaluated in our study, iliac lymphadenopathy can often be identified on rectal palpation.[3-7] As metastasis may already have occurred by the time of initial evaluation, rectal palpation and diagnostic imaging of the pelvic canal and caudal portion of the abdomen should be performed in dogs suspected of having CAS.

Survival times were not significantly different between dogs with evidence of iliac lymphadenopathy

and those without obvious lymphadenopathy at referral. One plausible explanation is that diagnostic imaging may be a fairly insensitive indicator of metastasis. The metastatic potential of this tumor is well established. Meuten et al[4] reported the clinical and histologic findings in 36 dogs with CAS. Histologic features of malignancy were identified in every tumor, and in 23 dogs evaluated for metastasis, 22 dogs had evidence of metastasis to regional lymph nodes. In a study by Ross et al[5] of 32 dogs with CAS, 3 dogs had no signs of a perianal mass, but CAS was diagnosed histologically via excisional biopsy of enlarged iliac or lumbar lymph nodes. This scenario suggests that metastasis to regional lymph nodes occurs early with this tumor. A percentage of the dogs in our study with no radiographic evidence of iliac lymphadenopathy may therefore have had early metastasis that went undetected in the absence of histologic examination.

Consistent with earlier studies, we found this tumor to have high metastasis and mortality rates. However, our survival times were more favorable than those reported in previous studies,[5,6] which ranged from 6 to 8.3 months. In contrast, median survival time for the dogs in this study was 544 days (18 months). This improvement may be due to earlier recognition and more aggressive surgical and adjuvant treatment of this tumor as a result of earlier studies. It is also possible that dogs are simply living longer with their disease, possibly because of improved efforts at palliative care.

In our study, median survival time was measured from the first day of treatment until the date of death due to any cause, because it is not always known whether death due to other or unknown causes may in actuality have been due to the tumor. Dogs alive at last follow-up were censored in the survival analysis. This system errs on the side of shorter survival times, so the reality of long-term survival may be more promising than our results indicate.

Dogs in this study who underwent surgery as part of their treatment had a survival advantage, compared with dogs not treated with any surgery. Given the retrospective nature of this study, 1 plausible explanation for this observed difference is selection bias, in which dogs with lower-stage tumors may have been considered more amenable to surgery and treated accordingly, in contrast to dogs with more advanced disease in which surgery was not recommended.

The use of adjuvant chemotherapy did not result in significantly longer median survival time for dogs in this study. It may be that there is truly no difference in survival among the types of treatment administered. However, it is also possible that these data underestimate the benefit of chemotherapy in prolonging survival in dogs with CAS. In our study, dogs with more advanced disease were more likely to receive adjuvant chemotherapy. As Ross et al[5] indicated, the presence of metastasis substantially decreases the median survival time. Thus, one may argue that the similar survival times achieved in dogs with more advanced disease suggest that chemotherapy is of potential benefit. Prospective evaluation by use of uniform diagnostic tests and staging, standardized treatment protocols, and consistent and careful monitoring of treatment responses are needed to answer this question.

It is also possible that our failure to detect significant differences among treatment groups was due to the number of censored cases and the multiple variations in diagnostic tests and treatments among the different institutions. The problems encountered in this study are not unique and are inherent in large, multicenter retrospective studies. For example, data were originally collected on individual treatments, which were defined as any treatment or combination of treatments initiated during the same 21-day period. Unfortunately, response rates and remission durations to individual treatments were often not available, so our study endpoint subsequently changed to an evaluation of overall survival. This meant combining individual treatments into general categories and limiting our evaluation of the role of different treatment modalities and individual chemotherapeutic agents. Bias was also introduced by relying on overall survival, which is often client-driven and subject to greater variability than clinically measurable remission.

More research into the responses of CAS to various chemotherapeutic agents and radiation therapy is needed. Nevertheless, our findings suggest that long-term survival for dogs with this highly malignant tumor may be better than previously reported.

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