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Short- and long-term outcomes associated with anal sacculectomy in dogs with massive apocrine gland anal sac adenocarcinoma

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OBJECTIVE
To evaluate short- and long-term outcomes for dogs undergoing anal sacculectomy for massive (> 5 cm) apocrine gland anal sac adenocarcinoma (AGASACA).

ANIMALS
28 client-owned dogs with massive AGASACA.

PROCEDURES
A retrospective multi-institutional study was performed. Pre-, intra-, and post-operative data was collected, and variables were statistically analyzed for associations with progression-free interval (PFI) and overall survival (OS).

RESULTS
At the time of anal sacculectomy, 19 (68%) dogs underwent concurrent iliosacral lymph node extirpation, including 17 of 18 (94%) dogs with suspected nodal metastasis preoperatively. Five (18%) dogs experienced grade 2 intraoperative complications. Ten (36%) dogs experienced postoperative complications, including 1 grade 3 and 1 grade 4 complication. No dogs had permanent fecal incontinence, tenesmus, or anal stenosis. Nineteen dogs received adjuvant chemotherapy, radiation, or both. Local recurrence occurred in 37% of dogs. Dogs with lymph node metastasis at surgery were more likely than dogs without metastasis to develop new/progressive lymph node metastasis (10/17 [59%] vs 0/10 [0%]; P = .003) and distant metastasis (7/17 [41%] vs 0/10 [0%]; P = .026). Median PFI was 204 days (95% CI, 145 to 392). Median OS was 671 days (95% CI, 225 to upper limit not reached). Nodal metastasis at the time of surgery was associated with shorter PFI (P = .017) but not OS (P = .26). Adjuvant therapy was not associated with outcome.

CLINICAL RELEVANCE
Dogs with massive AGASACA experienced prolonged survival following anal sacculectomy despite a high incidence of local recurrence and metastasis. Lymph node metastasis at the time of surgery was a negative prognostic indicator for PFI but not OS.

Multiple prognostic indicators have been reported for dogs with apocrine gland anal sac adenocarcinoma (AGASACA), including disease stage, hypercalcemia, histopathologic features, and treatment performed.[1–6] Primary AGASACA tumor size is an important component of disease stage that has been associated with outcome. Reports suggest that dogs with larger tumors have worse prognoses and may be more likely to present with metastatic disease.[1,3,7–9] One study demonstrated a reduced mean survival time of 9.4 months in dogs with primary tumor diameter > 5 cm compared to 18.8 months for dogs with primary tumor diameter < 5 cm.[7] In that study, 86% of dogs with tumor diameter > 5 cm had locoregional lymph node metastases at the time of diagnosis.[7] However, data were lacking with regard to staging diagnostics and treatments performed for these dogs.[7]

Surgery is generally considered the first-line therapy for dogs with primary AGASACA. A recent study reported the overall intraoperative and postoperative complication rates for anal sacculectomy in 161 dogs with AGASACA to be 7% and 17%, respectively; self-limiting diarrhea/hematochezia, tenesmus,

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surgical site erythema/swelling not related to infection, transient fecal incontinence, urinary retention or difficulty ambulating after epidural injection, and inappetence during hospitalization were considered sequelae and not complications.[10] The most common intraoperative complication was anorectal perforation (5%), and the most common postoperative complication was surgical site infection (12%); no dogs developed permanent fecal incontinence.[10] In that study, the median primary tumor diameter was 2.4 cm and 60% of tumors were < 2.5 cm in diameter.[10] The authors found no association between primary tumor size and development of complications, though the majority of tumors were relatively small.[10]

Data on dogs with massive (> 5 cm) primary AGASACA that undergo anal sacculectomy is generally lacking, likely given the potential for poor prognosis, as previously reported, as well as a subjectively greater risk for perioperative complications (eg, rectal perforation, fecal incontinence, and infection).[1,3,7] Although larger primary tumor size has previously been correlated with an increased risk of metastatic disease, several studies have demonstrated potential for prolonged outcomes (up to several years) with lymph node extirpation in dogs with nodal metastasis.[1,5,11–13] Therefore, the potentially increased risk of metastatic disease in dogs with massive AGASACA does not necessarily result in guarded prognoses for owners that elect treatment.

The aims of our study were to evaluate the short- and long-term outcomes of dogs that undergo surgical excision of massive (> 5 cm) AGASACA. We hypothesized that dogs undergoing anal sacculectomy for massive AGASACA would have low perioperative morbidity rates and the long-term outcomes for these dogs would be comparable to those found for nonmassive AGASACA cases of similar metastatic stage at the time of surgery.

Materials and Methods

A retrospective multi-institutional study was performed. Dogs were included if they had a diagnosis of AGASACA > 5 cm in diameter on CT measurement and underwent anal sacculectomy. Bilateral AGASACA, disease stage, neoadjuvant radiation therapy and/or chemotherapy, and previous anal sac surgery were not considered exclusion criteria, and this information was documented. Recorded preoperative data included signalment, history, clinical signs, physical examination findings, clinical laboratory results, cytology results, diagnostic imaging and staging results, as well as neoadjuvant treatments administered. Surgical and postoperative outcomes recorded included intraoperative complications, histopathologic results, survival to discharge, postoperative complications that occurred during hospitalization and within 30 postoperative days, adjuvant treatments administered, disease progression, date of death or last follow-up, and cause of death. Primary tumor dimensions on CT were recorded, and tumor volume was subsequently determined. Complications were listed as grades 1 to 4 in accordance with the Classification for Intraoperative Complications criteria for intraoperative complications and the Accordion criteria for postoperative complications.[14]

Continuous variables were assessed for normality with Shapiro-Wilk tests. Summary statistics were reported as median (range) or number (percentage). Wilcoxon rank sum tests and Fisher exact tests were used for between-group comparisons. Progression-free interval (PFI) and overall survival (OS) time were modeled using product limit and Cox proportional hazard methods. Progression-free interval was defined as days elapsed from surgery until local recurrence, new lymph node or distant metastasis, or death of any cause. Overall survival time was defined as days elapsed from surgery until death of any cause. Subjects were censored in analyses if alive or lost to follow-up without reaching the given survival end point. Univariable associations were tested, and variables with $P < .15$ were tested for inclusion in final multivariable models. Variables were retained in multivariable models if $P < .05$ or if identified as confounders on the main effects (defined as change in hazard ratio [HR] of at least 15%). All tests were 2-sided, and $P < .05$ was considered statistically significant.

Results

Preoperative characteristics and staging

Twenty-eight dogs were included with 16 (57.1%) undergoing treatment at the University of California-Davis William R. Pritchard Veterinary Medical Teaching Hospital and 12 (42.9%) at the University of Guelph Ontario Veterinary College Health Sciences Centre. Baseline characteristics and presenting complaints are presented **(Table 1)**.

Table 1—Demographic data.

Demographic	No. (percent)
Sex	
Male castrated	22 (78.6)
Female spayed	6 (21.4)
Breed	
Mixed breed	12 (42.9)
Pure breed	16 (57.1)
Age, years	9.9 (2.8–13.1)
Weight, kg	29.8 (7.1–46.1)
Body condition score (1–9)	5 (3–9)
Clinical signs at referral presentation	
Perianal swelling	16 (57.1)
Perianal discomfort	10 (35.7)
Ribbon-like stools	9 (32.1)
Polydipsia/polyuria	8 (28.6)
Tenesmus	5 (17.7)
Hyporexia	4 (14.3)
Weight loss	4 (14.3)
Hind limb gait abnormalities	4 (14.3)
Lethargy	3 (10.7)
Dyschezia	2 (7.1)
Hematochezia	1 (3.6)
Largest estimated mass dimension on PE, cm	5.5 (3.2–10.0)
Origin of mass	
Right anal sac*	18 (64.3)
Left anal sac	10 (35.7)

*One dog had bilateral anal sac disease, with a massive tumor on the right and smaller tumor on the left.

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Two dogs had a previous history of anal sac disease (fistula in 1 dog and AGASACA in 1 dog) approximately 1 year prior, and one of these dogs had prior anal sac surgery at that time (excision of the AGASACA). Most (18/28 [64.3%]) dogs were diagnosed with a perianal mass by a referring veterinarian before being treated; 9 were asymptomatic when the mass was identified on routine exam. However, 8 of these 9 dogs developed clinical signs by the time they were treated at the referral institution. Among the 10 dogs diagnosed with a perianal mass by the referral institution, 5 had clinical signs and 5 did not. Overall, 14 of 28 (50.0%) dogs had clinical signs when the mass was initially identified by a veterinarian, and 22 of 28 (78.6%) had clinical signs when they were seen by the referral institution. At the time of presentation to the referral hospital, the median duration of clinical signs attributable to AGASACA was 32 days (range, 0 to 281 days).

Preoperative bloodwork was available for most dogs and is described **(Table 2)**. Fifteen (53.6%) dogs were hypercalcemic (defined for the study as ionized calcium > 1.4 mmol/L or total calcium above upper reference limit when ionized calcium was not performed). Preoperative perianal mass cytology was performed in 27 of 28 dogs, and results were reported as AGASACA (n = 23), (adeno) carcinoma (3), and apocrine gland neoplasia (1).

Table 2—Preoperative clinical laboratory results.

Select preoperative CBC parameters (n = 25)	**Median (range)**
Hematocrit, %	48 (38–70)
WBC, X 10^3/µL	9.8 (5.3–18.4)
Neutrophil, X 10^3/µL	7.3 (3.4–15.4)
Band neutrophil, X 10^3/µL	0.0 (0.0–0.0)
Platelet, X 10^3/µL	300 (136–577)
Select preoperative chemistry parameters	**No. (percent)**
Albumin (n = 25)	
Below reference range	2 (8.0)
Within reference range	23 (92.0)
Above reference range	0 (0.0)
BUN (n = 26)	
Below reference range	0 (0.0)
Within reference range	25 (96.2)
Above reference range	1 (3.8)
Creatinine (n = 26)	
Below reference range	5 (19.2)
Within reference range	20 (76.9)
Above reference range	1 (3.9)
Total calcium (n = 26)	
Below reference range	1 (3.9)
Within reference range	9 (34.6)
Above reference range	16 (61.5)
Ionized calcium (n = 22)	
≤ 1.4 mm/L	7 (31.8)
> 1.4 mmol/L	15 (68.2)
Glucose (n = 23)	
Below reference range	1 (4.4)
Within reference range	19 (82.6)
Above reference range	3 (13.0)
Phosphorus (n = 24)	
Below reference range	9 (37.5)
Within reference range	15 (62.5)
Above reference range	0 (0.0)
Total protein (n = 24)	
Below reference range	1 (4.2)
Within reference range	19 (79.2)
Above reference range	4 (16.7)

All dogs had thoracic and abdominal imaging prior to surgery. Thoracic imaging consisted of radiographs (n = 21), CT (1), or both thoracic radiographs and CT (6); evidence of thoracic metastasis was not identified in any dog. Abdominal imaging consisted of ultrasound and CT in 19 dogs and CT alone in 9 dogs. Massive tumors originated from the right and left anal sac in 18 of 28 (64.3%) and 10 of 28 (35.7%) dogs, respectively; 1 dog with a massive right-sided tumor also had a 2-cm-diameter left-sided tumor. On abdominal CT, median (range) tumor measurements in centimeters were 6.3 (5.0 to 10.0) X 5.3 (3.5 to 9.0) X 4.3 (2.8 to 7.7), and the median maximal tumor measurement was 6.4 cm (range, 5 to 10 cm). Median tumor volume measured on CT was 153.7 cm^3 (range, 51.8 to 567.0 cm^3). Median tumor volume-to-body weight ratio measured on CT was 6.1 cm^3/kg (range, 1.5 to 24.4 cm^3/kg). CT findings included possible tumor invasion into the rectal wall in 15 of 28 (53.6%) dogs and enlarged (≥ 1 cm) or abnormal iliosacral lymph nodes in 18 of 28 (64.3%) dogs. Enlarged or abnormal iliosacral lymph nodes included medial iliac in 12 dogs, internal iliac in 8 dogs, sacral in 10 dogs, and undefined in 3 dogs; 10 dogs had multiple abnormal iliosacral lymph node sites. Enlarged or abnormal lymph nodes were ipsilateral to the massive AGASACA in 6 dogs, contralateral in 1 dog, and bilateral in 5 dogs, and the laterality was not defined in 6 dogs. Two dogs with enlarged iliosacral lymph nodes also had lesions in other abdominal lymph nodes (n = 1) and adjacent vertebrae (1). The remaining 10 dogs were not considered to have lesions overtly suspicious for metastatic disease on CT, though metastatic disease could not be ruled out. In most cases lymph nodes were not sampled for cytology prior to surgery; in 4 dogs, cytology was performed and confirmed metastatic disease. Overall, 18 of 28 (64.3%) dogs were considered to have suspicion for metastasis at the time of surgery (all to iliosacral lymph nodes ± vertebrae) and 10 of 28 (35.7%) dogs were considered not to have definitive metastasis.

Surgical treatment and complications

All dogs underwent closed anal sacculectomy to remove the primary tumor. Two dogs, including 1 with bilateral tumors, underwent bilateral closed anal sacculectomy. Rectal perforation was observed during surgery in 3 of 28 (10.7%) dogs. Nineteen (67.9%) dogs also underwent iliosacral lymph node extirpation, including 14 dogs with enlarged abnormal lymph nodes on CT, 3 dogs with cytology-confirmed metastatic lymph nodes, and 2 dogs with normal-appearing iliosacral lymph nodes on CT. Among the 9 dogs that did not have lymph node surgery, 8 were not considered to have suspicion for metastasis and 1 had cytology-confirmed metastatic iliosacral lymph nodes. Overall, 17 of 18 (94.4%) dogs with concern for lymph node metastasis preoperatively underwent

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lymph node extirpation at the time of anal sacculectomy. Extirpated lymph nodes included medial iliac in 10 dogs, internal iliac in 9 dogs, sacral in 5 dogs, and undefined in 7 dogs; 9 dogs had multiple iliosacral lymph nodes extirpated. Extirpated lymph nodes were ipsilateral to the massive AGASACA in 10 dogs, bilateral in 3 dogs, and the laterality was not defined in 6 dogs. Lymph node extirpation was performed laparoscopically in the 2 dogs with normal-appearing lymph nodes on CT and in 2 dogs with enlarged abnormal lymph nodes; no additional abdominal procedures were performed in dogs undergoing laparoscopic lymph node extirpation. Of the 4 dogs that underwent laparoscopic iliosacral lymph node extirpation, all had extirpated medial iliac lymph nodes ipsilateral to the massive AGASACA. Both dogs with normal-appearing lymph nodes on CT had nonmetastatic lymph nodes on histologic evaluation; all other dogs that underwent lymph node extirpation had evidence of nodal metastasis on histology. Iliosacral lymph node extirpation was performed via open laparotomy in 15 dogs, and of these, 7 dogs had additional procedures: 3 dogs had liver biopsies, 1 dog had a splenectomy and liver lobectomy, 1 dog had a splenectomy alone, 1 dog had liver and omental biopsies, and 1 dog had a prostatic biopsy. One dog had exploratory laparotomy and liver biopsy without additional abdominal procedures. Two dogs had additional skin masses excised.

Overall, 5 dogs experienced intraoperative complications. Four dogs experienced grade 2 complications during anal sacculectomy. These included 3 dogs with rectal perforation requiring surgical closure and 1 dog with hemorrhage necessitating intervention. In addition, 1 dog experienced a grade 2 intraoperative complication during iliosacral lymph node extirpation, characterized by hemorrhage necessitating intervention. No other intraoperative complications were reported. Median anal sacculectomy surgical time was 105 minutes (range, 55 to 235 minutes). Median total surgical time including anal sacculectomy plus any other procedures was 198 minutes (range, 70 to 425 minutes).

Histopathology was performed on all tumors, but detailed reports were not available for many dogs. Completeness of tumor excision was described in histopathology reports as complete in 2 dogs, incomplete in 17 dogs, and was not reported in 9 dogs. Vascular or lymphatic invasion was described in histopathology reports as present in 12 dogs, not present in 7 dogs, and was not reported in 9 dogs. Invasion of tumor cells beyond the anal sac capsule was described in histopathology reports as present in 12 dogs, not present in 7 dogs, and was not reported in 9 dogs.

Based on the criteria described by Polton and Brearley, at the time of surgery 10 (35.7%) dogs had stage 2 disease, 11 (39.3%) dogs had stage 3a disease, and 7 (25.0%) dogs had stage 3b disease.[1] Hypercalcemia occurred in 6 of 10 (60.0%) dogs with stage 2 disease, 6 of 11 (54.5%) dogs with stage 3a disease, and 3 of 7 (42.9%) dogs with stage 3b disease, which did not differ significantly ($P > .89$). Neither tumor size ($P = .38$) nor left/right side ($P = .63$) was associated with intraoperative complications.

Dogs were treated and monitored variably in the postoperative period, with 13 dogs receiving postoperative antibiotic prophylaxis. The median duration of postsurgical hospitalization was 2 days (range, 1 to 5 days). Five dogs experienced postoperative complications during the hospitalization period. Four dogs experienced grade 1 complications, as follows: 1 dog had grade 1 regurgitation and grade 1 fecal incontinence, 1 dog had grade 1 fecal incontinence and grade 1 tenesmus, 1 dog had grade 1 inappetence, and 1 dog experienced a grade 1 complication of hypocalcemia requiring pharmacologic correction. One dog experienced a grade 4 complication of acute respiratory distress resulting in death. All other dogs (27/28 [96.4%]) were discharged from the hospital.

Follow-up of at least 10 days was obtained in all dogs, at least 30 days in 24 dogs, and at least 90 days in 22 dogs. The median duration of follow-up for all discharged dogs was 225 days (range, 10 to 1,400 days). Postoperative complications were reported within 30 days of hospital discharge in 7 of 27 (25.9%) dogs. Grade 1 complications were reported in 4 dogs, consisting of self-limiting fecal incontinence in 2 dogs; diarrhea, hematochezia, vomiting, and tenesmus in 1 dog (this dog also had intraoperative rectal perforation); and minor wound dehiscence in 1 dog (this dog also had intraoperative rectal perforation). Grade 2 postoperative complications were reported in 2 dogs, consisting of a urinary tract infection in 1 dog and superficial surgical site infection in 1 dog. A grade 3 postoperative complication occurred in 1 dog 10 days postoperatively, consisting of deep surgical site infection and rectocutaneous fistula associated with dehiscence of the surgically repaired rectal wall; this dog also experienced fecal incontinence and regurgitation during hospitalization. The owner of this dog declined further treatment and the dog was lost to follow-up immediately following diagnosis of the complication.

Overall, 10 dogs (35.7%) experienced a postoperative complication in hospital or up to 30 days postoperatively; 2 of these dogs had different complications within each postoperative period (during hospitalization and after discharge within 30 days postoperatively). No dog in the study had long-term fecal incontinence, tenesmus, or anal stenosis.

Adjuvant therapy

Following surgery, 19 dogs received adjuvant therapy, including 15 dogs that received chemotherapy, 1 dog that received radiation therapy, and 3 dogs that received both chemotherapy and radiation therapy. Nine dogs were treated with carboplatin for a median of 5 doses (range, 2 to 7 doses); 6 dogs were treated with mitoxantrone for a median of 3 doses (range, 1 to 6 doses); 1 dog was treated sequentially with mitoxantrone, carboplatin, gemcitabine, toceranib, melphalan, and meloxicam; 1 dog was treated sequentially with mitoxantrone, carboplatin, and toceranib; and 1 dog was treated with toceranib. Three dogs underwent postoperative radiation therapy of the anal sac surgical site following surgery at doses of 16 X 3 Gy, 4 X 6 Gy, and 4 X 2.4 Gy. One dog had local tumor recurrence approximately 60 days postoperatively and was treated with surgery followed by radiation therapy (8 X 3 Gy) to the anal sac tumor site.

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Follow-up, disease progression, and survival outcomes

At the time of data collection, 18 dogs were lost to follow-up, including 10 dogs following documented disease progression, and 10 dogs had died. The median duration from anal sacculectomy to death or loss to follow-up was 222 days (range, 1 to 1,400 days). Dogs that did not receive any adjuvant therapy were lost to follow-up significantly sooner than dogs that did receive adjuvant therapy (median, 30 days vs 473 days; P = .013).

Disease progression was evaluated in 27 dogs that survived hospital discharge. Local tumor recurrence was reported in 10 of 27 (37.0%) dogs at a median of 319 days (range, 36 to 1,100 days) postoperatively and was not associated with disease stage at the time of surgery (P = .27). The overall incidence of new/recurrent lymph node metastasis postoperatively was 10 of 27 (37.0%). New/recurrent lymph node metastasis occurred in 10 of 17 (58.8%) dogs with lymph node metastasis at the time of anal sac surgery and 0 of 10 (0.0%) dogs without lymph node metastasis at the time of anal sac surgery; this difference was significant (P = .003). The median time to new/recurrent lymph node metastasis was 183.5 days (range, 36 to 651 days) postoperatively. Seven of 27 (25.9%) dogs developed lesions that were categorized as possible distant metastasis; all 7 dogs also had lymph node metastasis at the time of surgery. Distant metastatic lesions occurred in 7 of 17 (41.2%) dogs with lymph node metastasis at the time of surgery and 0 of 10 (0.0%) dogs without lymph node metastasis at the time of surgery; this difference was statistically significant (P = .026). These included 1 dog that developed an AGASACA in the contralateral anal sac, 4 dogs that developed multifocal pulmonary nodules consistent with metastasis, 1 dog that developed a cranial mediastinal mass and subsequently pulmonary nodules, and 1 dog that developed undefined distant metastatic disease identified via abdominal ultrasound. In 2 cases, metastatic AGASACA was confirmed via histopathology (anal sac mass in 1 dog and pulmonary metastases confirmed via necropsy in 1 dog), whereas tissue diagnosis was not obtained in the other 5 dogs such that distant metastatic AGASACA was not definitively determined.

Nine dogs experienced > 1 type of disease progression. Four dogs developed local recurrence, new lymph node metastasis, and distant metastasis; 3 dogs developed local recurrence and new lymph node metastasis; and 2 dogs developed new lymph node metastasis and new distant metastasis.

Overall PFI was 204 days (95% CI, 145 to 392). Adjusting for sex, lymph node metastasis at the time of surgery was the only factor significantly associated with PFI on multivariable analysis. Dogs with lymph node metastasis had a 12.6 times greater hazard of disease progression compared to dogs without lymph node metastasis at the time of surgery (HR, 12.60; 95% CI, 1.56 to 101.56; P = .017). Age, body weight, hypercalcemia, largest mass dimension on CT, adjuvant chemotherapy, and adjuvant radiation therapy were not associated with PFI nor identified as confounders on the main effects **(Table 3)**.

Table 3—Statistical analysis findings of factors evaluated for association with progression-free interval.

	Univariable			Multivariable		
Variable	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Age, y	1.22	0.91–1.66	.18	—	—	—
Body weight, kg	1.02	0.97–1.06	.47	—	—	—
Male sex	12.06	1.54–94.71	.018	7.63	0.89–65.42	.06
Hypercalcemia	0.85	0.33–2.18	.74	—	—	—
Largest mass dimension, cm	1.18	0.86–1.62	.31	—	—	—
Lymph node metastasis at surgery	20.80	2.56–168.88	.005	12.60	1.56–101.56	.017*
Adjuvant chemotherapy	0.76	0.26–2.21	.62	—	—	—
Adjuvant radiation therapy	1.32	0.43–4.04	.63	—	—	—

*Statistically significant result.
HR = Hazard ratio.

Table 4—Statistical analysis findings of factors evaluated for association with overall survival.

	Univariable		
Variable	**HR**	**95% CI**	***P* value**
Age, y	1.04	0.78–1.39	.77
Body weight, kg	1.00	0.95–1.07	.89
Male sex	4.18	0.53–32.99	.18
Hypercalcemia	0.84	0.25–2.77	.77
Largest mass dimension, cm	1.24	0.88–1.74	.22
Lymph node metastasis at surgery	2.15	0.57–8.04	.26
30-day postoperative complication	0.36	0.08–1.68	.19
Adjuvant chemotherapy	0.35	0.09–1.32	.12
Adjuvant radiation therapy	0.80	0.17–3.73	.77
Local recurrence	0.36	0.10–1.29	.12
Metastatic progression	1.01	0.31–3.36	.98

See Table 3 for key.

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Overall survival time was 671 days (95% CI, 225 to upper limit not reached). Age, body weight, sex, hypercalcemia, largest mass dimension on CT, lymph node metastasis, 30-day postoperative complication occurrence, adjuvant chemotherapy, adjuvant radiation therapy, local recurrence, and metastatic progression were not associated with OS **(Table 4)**. Due to incomplete data in histopathology reports, histologic criteria (such as completeness of excision, lymphovascular invasion, and mitotic index) could not be modeled for disease outcomes.

Discussion

In this cohort, dogs with massive primary AGASACA that underwent anal sacculectomy overall had good outcomes with an acceptable incidence of major complications and relatively prolonged PFI and OS. However, consistent with prior reports demonstrating a greater incidence of metastatic disease with larger primary tumors, nodal metastasis was common in this population and the majority of dogs (64.3%) had stage 3 disease at the time of surgery. In addition, the majority (53.6%) of dogs in this cohort were hypercalcemic preoperatively. Therefore, multiple previously reported negative prognostic indicators were present in this study population, though overall outcomes were relatively good.

Intraoperative complications (all grade 2) associated with the anal sacculectomy procedure were reported in 14.3% dogs, and 1 (3.6%) additional dog experienced a grade 2 complication associated with lymph node extirpation. Importantly, rectal wall perforation occurred in only 3 (10.7%) cases, whereas CT revealed possible rectal wall invasion in 15 (53.6%) dogs. This finding suggests that although many dogs with massive AGASACA may have concern for possible rectal wall invasion based on CT, true determination of rectal wall invasion and any intervention required is based on surgical findings. Digital rectal examination findings should also be considered relative to risk for rectal wall invasion, as mobility of the rectal wall over the anal sac tumor generally implies a lack of gross invasion of the rectal wall and unlikely indication for rectal wall excision and repair. (However, these data were generally lacking in many physical examination reports and were unable to be assessed in the current retrospective study.) Importantly, rectal perforation/resection appears to be required in only a small proportion of cases with massive AGASACA, despite features concerning for rectal invasion on CT in a majority of cases. However, of the 3 dogs that had surgical perforation of the rectum requiring repair, all developed postoperative complications including 3 grade 1 complications and 1 grade 3 complication (in a dog that also experienced a grade 1 complication). The grade 3 complication was directly related to the rectal repair, as this dog developed dehiscence and a rectocutaneous fistula. The only other reported intraoperative complication during anal sacculectomy was hemorrhage requiring intervention, which highlights the importance of being prepared to manage significant hemorrhage given the potential for extensive neovascularization of these tumors and close association with large vessels such as the caudal rectal branch of the internal pudendal. One additional patient experienced hemorrhage requiring intervention during iliosacral lymphadenectomy, a procedure which reportedly has been associated with a relatively higher risk of hemorrhage. A recent study on 136 dogs that underwent metastatic iliosacral lymph node extirpation reported an overall complication rate of 26% and hemorrhage in 18% of cases (with nearly half of these dogs requiring a blood transfusion), emphasizing the important consideration of the risk for hemorrhage in iliosacral lymphadenectomy.[15] Overall, the incidence of intraoperative complications was relatively low and no grade 3 or 4 intraoperative complications occurred despite the massive nature of these tumors, their robust vascular supply, and proximity to important surrounding structures. It is important to consider, however, that these have the potential to be challenging procedures, and the results of this study were obtained in a setting of 2 academic tertiary referral centers with surgeries performed by board-certified surgeons and surgical residents.

Postoperative complications were reported in 10 (35.7%) dogs overall, including during hospitalization for 5 dogs (4 grade 1 and 1 grade 4) and after discharge within 30 days of surgery for 7 dogs (4 grade 1, 2 grade 2, and 1 grade 3). The majority of postoperative complications reported were grade 1, and many of these would have been classified as sequelae, or generally anticipated and self-limiting outcomes of these procedures, in the recent Sterman et al study.[10] In addition, the grade 4 complication that occurred during hospitalization (acute respiratory distress syndrome and subsequent death) was unlikely to be associated with the surgical procedure itself and was considered more likely related to postanesthetic complications or systemic disease. Of the postdischarge complications, one of the grade 2 complications (urinary tract infection) was likely unrelated to the surgical procedure itself. Therefore, only 2 postoperative complications above grade 1 were definitively attributed to the surgical procedure: 1 grade 2 postoperative complication (superficial surgical site infection) and 1 grade 3 postoperative complication (deep surgical site infection and rectocutaneous fistula). The overall incidence of dogs that experienced postoperative complications was relatively low, and the incidence of dogs that experienced grade 2+ postoperative complications overtly associated with the surgical procedure (both characterized as surgical site infections) was only 7.1%. Therefore, there appears to be a low risk of major postoperative complications associated with anal sacculectomy in dogs with massive primary AGASACA, though surgical site infection is possible.

Importantly, no dogs were reported to have long-term fecal incontinence, tenesmus, or anal stenosis/stricture postoperatively. Given the massive nature of the primary tumor, nearly 50% circumference of anal sphincter may have been surgically traumatized for many of these dogs. The finding that no dogs developed permanent

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fecal incontinence supports the general statement that permanent fecal incontinence is exceedingly rare following unilateral anal sacculectomy, even in the presence of massive AGASACA and substantial dissection of the external anal sphincter. It has been reported that trauma to > 50% of the external anal sphincter or bilateral iatrogenic damage to the caudal rectal nerves can result in fecal incontinence; therefore, unilateral surgery should not result in permanent incontinence, unless underlying disease of the contralateral side exists.[10] In addition, transient fecal incontinence was reported in only 4 (14.3%) dogs postoperatively, including prior to discharge in 2 dogs and following discharge up to 30 days postoperatively in 2 dogs. Therefore, although fecal incontinence risk should be discussed with owners, findings of this study suggest that permanent incontinence following anal sacculectomy is rare. The overall incidence of major intra- and post-operative complications associated with anal sacculectomy for massive primary AGASACA in dogs appears to be low and not substantially different from that reported for smaller tumors.[10]

In considering local disease recurrence following anal sacculectomy, the reported recurrence rate in this cohort of dogs with massive AGASACA was relatively high (37.0%). However, this is within the range of recurrence rates reported previously (12% to 45%).[4,10,13,16] The only risk factor that has been previously associated with local recurrence is the presence of lymphovascular invasion, and histologically incomplete or narrow excision of the anal sac tumor has not been associated with local disease recurrence to date.[10] Due to inconsistent reporting of variables on histology reports in this cohort, histologic findings such as lymphovascular invasion or completeness of excision were unable to be assessed in association with recurrence. Regardless, this study demonstrated a relatively high rate of local disease recurrence following anal sacculectomy for massive AGASACA, though good outcomes still occurred. The median time to documented local recurrence was 319 days for these dogs, demonstrating generally slow local disease progression and prolonged time to recurrence.

With regard to outcomes, these dogs with massive AGASACA overall had prolonged PFI and OS. However, disease stage was significantly associated with PFI, and dogs with suspected nodal metastasis at the time of surgery had a 12.6 times greater hazard of disease progression compared to dogs without definitive nodal metastasis at the time of surgery. This is consistent with clinical impressions and prior literature, in which dogs with nodal metastasis at the time of surgery are anticipated to develop progressive metastatic disease postoperatively. In addition, the findings of this study support the notion that metastatic disease progression occurs through the iliosacral lymph nodes prior to distant metastasis, as potential distant metastasis was only documented in dogs with concurrent/prior nodal metastasis. However, the OS of dogs in this study was relatively long (671 days), and disease stage was not significantly associated with OS in this cohort. One possible explanation for this is the inclusion criteria of the study in which all dogs underwent surgery, and 17 of 18 dogs with suspicion for metastatic lymph nodes preoperatively underwent concurrent extirpation of their metastatic locoregional lymph nodes. Prior studies have demonstrated enhanced outcomes and survival times with extirpation of metastatic lymph nodes in dogs with AGASACA.[1,5,11–13] Therefore, although the majority (64.3%) of dogs in this cohort had stage 3 disease at the time of surgery, their survival times were similar to or improved relative to prior studies on dogs with similar disease stage. For instance, Polton and Brearley reported that in dogs with stage 3 disease, the median survival times ranged from 294 to 492 days for dogs treated via a variety of modalities.[1] The present study highlights the potential for prolonged survival times in dogs undergoing anal sacculectomy for massive AGASACA despite a high incidence of metastatic disease at presentation, and concurrent lymph node extirpation may play an important role.

In addition, adjuvant therapy was not found to be associated with PFI or OS in these dogs. Despite the multitude of negative prognostic indicators of dogs in this study (large primary tumor size, high incidence of metastatic disease, and high incidence of hypercalcemia), adjuvant chemotherapy was not found to be associated with improved outcomes. This is consistent with prior studies, which have generally not demonstrated a definitive benefit of chemotherapy in dogs with AGASACA. However, although 16 dogs of this study received adjuvant chemotherapy, the protocols were highly variable and the rationale for adjuvant chemotherapy administration or protocol prescribed was not well characterized. Therefore, although this study does not support a role for adjuvant chemotherapy postoperatively in dogs with massive AGASACA, controlled prospective trials with specific protocols and inclusion criteria are required to further assess a potential role of chemotherapy. Similarly, despite the relatively high incidence of local disease recurrence postoperatively, adjuvant radiation therapy was not found to improve outcomes in these dogs, though prospective clinical trials are needed.

This study had several limitations. First, due to the retrospective nature, complete clinical information was lacking for some patients and several patients were lost to follow-up. In addition, although all dogs had staging with abdominal/perianal CT preoperatively, postoperative staging was variable. However, the requirement of CT preoperatively is considered to be a strength of the study, as CT has been demonstrated to be more accurate in identifying abnormal-appearing lymph nodes compared to ultrasonography, and CT is considered the gold standard for primary tumor size measurement with potential for variability in reported measurements on rectal examination and formalin-fixed tissues.[8,17] In addition, variable adjuvant treatments were performed, resulting in small subgroups of patients that received or did not receive these adjuvant treatments, such that there was relatively poor power to identify potential differences between these groups. Finally, selection bias may have occurred because all cases were contributed by academic institutions and all owners elected advanced diagnostics and surgical treatment. All cases included

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were deemed to be surgical, and no stage 4 dogs were included in this study. Based on the inclusion criteria, no comparisons can be made between dogs with massive AGASACA that underwent surgery for treatment and those that did not undergo surgery.

Ultimately, although these dogs with massive primary AGASACA had multiple previously described poor prognostic indicators, prolonged survival was achieved despite a high incidence of metastatic disease progression and local recurrence. Lymph node metastasis at the time of surgery was a negative prognostic indicator for PFI but not OS in these dogs. Incidence of intraoperative and postoperative complications were relatively similar to those previously reported for anal sacculectomy of smaller tumors. Therefore, on the basis of results of this study, surgery (including anal sacculectomy and possible lymph node extirpation for dogs with stage 3 disease) should be considered a mainstay treatment in dogs with massive primary AGASACA amenable to surgical excision.

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