Apocrine gland anal sac adenocarcinoma in cats: 30 cases (1994–2015)

OBJECTIVE
To describe the signalment, clinical signs, biological behavior, and outcome for cats with apocrine gland anal sac adenocarcinoma (AGASACA) that underwent surgical excision.

DESIGN
Retrospective case series.

ANIMALS
30 client-owned cats.

PROCEDURES
Databases of 13 Veterinary Society of Surgical Oncology member–affiliated institutions were searched for records of cats with a histologic diagnosis of AGASACA that underwent tumor excision. For each cat, information regarding signalment, clinical signs, diagnostic test results, treatment, and outcome was extracted from the medical record. The Kaplan-Meier method was used to determine median time to local recurrence (TLR), disease-free interval (DFI), and survival time. Cox regression was used to identify factors associated with TLR, DFI, and survival time.

RESULTS
Perineal ulceration or discharge was the most common clinical sign in affected cats. Eleven cats developed local recurrence at a median of 96 days after AGASACA excision. Incomplete tumor margins and a high nuclear pleomorphic score were risk factors for local recurrence. Nuclear pleomorphic score was negatively associated with DFI. Local recurrence and a high nuclear pleomorphic score were risk factors for death. Median DFI and survival time were 234 and 260 days, respectively.

CONCLUSIONS AND CLINICAL RELEVANCE
Results indicated that, in cats, perineal ulceration or discharge should raise suspicion of AGASACA and prompt rectal and anal sac examinations. Local recurrence was the most common life-limiting event in cats that underwent surgery for treatment of AGASACA, suggesting that wide margins should be obtained whenever possible during AGASACA excision. Efficacy of chemotherapy and radiation therapy for treatment of cats with AGASACA requires further investigation. (J Am Vet Med Assoc 2019;254:716–722)
surgery followed by radiation therapy and carboplatin chemotherapy.\textsuperscript{2-5} Local recurrence\textsuperscript{6,7} and metastasis to the sublumbar lymph nodes and lungs have been reported.\textsuperscript{5,6} In the largest retrospective study,\textsuperscript{7} the MST was only 90 days. However, 29 of the 64 (45\%) cats of that study\textsuperscript{7} underwent surgical excision or debulking of the tumor, and the outcomes for cats that underwent surgical excision were not clearly reported. Thus, the outcome for cats with AGASACA that are treated with curative-intent surgical excision rather than debulking remains unclear. The purpose of the study reported here was to describe the signalment, clinical signs, laboratory and diagnostic imaging findings, treatment, outcome, and factors associated with outcome for cats with AGASACA that underwent curative-intent surgical excision of the tumor.

**Materials and Methods**

**Case selection criteria**

The study proposal was approved by the research committee of the Veterinary Society of Surgical Oncology. Participating members of the Veterinary Society of Surgical Oncology were asked to search their medical record databases for cats with a histopathologic diagnosis of AGASACA and a complete medical record. Only cats that underwent tumor excision by means of anal sacculectomy were included in the study. Cats that underwent tumor debulking or biopsy only were excluded from the study.

**Medical records review**

For each cat included in the study, information extracted from the medical record included sex, breed, body weight, age at time of surgery, clinical signs, duration of clinical signs (from date of first clinical signs to date of surgery), maximal dimension of the mass, preoperative serum total calcium concentration, staging test results, type of surgery performed, surgery date, histopathologic diagnosis, completeness of surgical tumor margins, details of adjuvant chemotherapy or radiation therapy (when administered), date and site of local recurrence or metastasis, and date and cause of death when available. Completeness of surgical tumor margins was determined on the basis of the original histopathologic report issued by the attending pathologist and was not standardized.

**Histologic review**

When available, archived histologic slides or tissue blocks of masses excised from study cats were reviewed by a board-certified veterinary pathologist (BEP) to confirm the diagnosis and to subjectively or objectively assess various histologic criteria, which were evaluated by use of a scoring system that was arbitrarily created by the pathologist. Extent of tumor differentiation was scored on a scale of 1 to 3, where 1 = well-differentiated tumor and 3 = poorly differentiated tumor. Nuclear pleomorphism was scored on a scale of 1 to 3, where 1 = nuclei have minimal variation in size or shape, 2 = at least 25\% of nuclei were 1.5 times the expected size and at least 10\% of nuclei varied in shape, and 3 = at least 25\% of nuclei were > 2 times the expected size and at least 25\% of nuclei varied in shape. The mitotic index was scored on a scale of 1 to 3, where 1 = ≤ 15 mitotic figures/10 hpf, 2 = 15 to 29 mitotic figures/10 hpf, and 3 = ≥ 30 mitotic figures/10 hpf. The extents of scirrhous reaction, necrosis, and inflammation were also scored on a scale of 1 to 3, where 1 = severe reaction, necrosis, or inflammation, 2 = moderate reaction, necrosis, or inflammation, and 3 = mild reaction, necrosis, or inflammation. All scores were summed to create a cumulative histopathologic score, which was then categorized into 3 grades, where grade 1 = a cumulative histopathologic score ≤ 8, grade 2 = a cumulative histopathologic score between 9 and 12, and grade 3 = a cumulative histopathologic score ≥ 13. The presence or absence of squamous or sebaceous changes and local or vascular invasion was recorded but was not used in the scoring or grading scheme.

**Data analysis**

Descriptive statistics were generated. Outcomes of interest were TLR, DFI, and survival time. Time to local recurrence was defined as the time from surgery to local recurrence. For TLR analysis, cats that did not have local recurrence at the time of follow-up or were lost to follow-up were censored, whereas cats that developed local recurrence or died but did not undergo a complete necropsy were not censored. The DFI was defined as the interval between surgery and detection of local recurrence or regional (nodal) or distant metastasis. For DFI analysis, cats that were lost to follow-up, died for reasons unrelated to AGASACA, or that had not developed local recurrence or metastasis at the time of last follow-up were censored. Survival time was defined as the interval between the date of surgery and death. For survival analysis, death or euthanasia because of AGASACA-related problems was considered an event. Cats that were lost to follow-up, still alive at the time of the last follow-up, or that died for reasons unrelated to AGASACA were censored. Cats that died for an unknown reason and cats that did not undergo necropsy were assumed to have died from the disease and were not censored.

The Kaplan-Meier method was used to determine the median TLR, median DFI, MST, and 1-, 2-, and 3-year survival rates, and the log-rank test was used to compare survival curves. Cox regression analysis was used to evaluate the association between independent variables and each outcome of interest. Independent variables assessed included age, body weight, clinical signs, duration of clinical signs, maximal dimension of the mass, presence of hypercalcemia, presence of enlarged sublumbar lymph nodes preoperatively, completeness of tumor excision, administration of chemotherapy, presence of metastasis or local recurrence, histopathologic scores, and cumulative histopathologic grade. For each outcome, univariate models were assessed initially, and independent variables with a value of $P < 0.2$ were entered into a multivariable model. Multivariable Cox regression models...
were built with 2 variables at a time. Confounders were identified by the use of criteria described by Braga et al. The final multivariable Cox regression model for each outcome included only variables with values of \( P < 0.05 \). All analyses were performed with a commercial software program.

**Results**

**Cats**

Thirty cats treated at 13 institutions were enrolled in the study. The study population included 15 spayed females and 15 neutered males and had a median age of 13 years (range, 7 to 20 years) and body weight of 4.9 kg (10.8 lb; range, 2.9 to 12.7 kg [6.4 to 27.9 lb]). There were 17 domestic shorthair cats, 7 Siamese, 2 domestic longhair cats, 1 Abyssinian, 1 Burmese, 1 Maine Coon, and 1 Persian.

**Clinical signs**

The most common clinical sign recorded was perineal ulceration or discharge (22/26 [85%]). Other commonly recorded clinical signs included tenesmus or constipation (6/29 [21%]) and hyporexia (3/30 [10%]). The median duration of clinical signs prior to surgery was 34 days (range, 3 to 554 days). Fifteen cats had concurrent conditions, which included a heart murmur (\( n = 6 \)), hyperthyroidism (4), renal disease (2), and lipomas, multiple myeloma, and a history of inflammatory bowel disease (1 each).

**Diagnostic findings**

The maximal dimension of the primary mass was reported for 21 cats, and the median maximal dimension was 2 cm (range, 0.3 to 6 cm). Cytologic examination of an aspirate sample of the mass was performed for 9 cats, and the cytologic interpretations were carcinoma (\( n = 3 \)), AGASACA (2), suspected epithelial tumor (2), unspecified malignancy (1), and nondiagnostic sample (1). An incisional biopsy specimen was obtained from 13 cats. Histologic results of the biopsy specimen were available for 9 of those cats and included findings consistent with AGASACA (\( n = 7 \)), solid undifferentiated carcinoma (1), and carcinoma (1).

The serum total calcium concentration was within the reference range for 24 of 27 (89%) cats and slightly increased from the reference range for the remaining 3 cats. Among the 24 cats with a clinically normal serum total calcium concentration, the serum ionized calcium concentration was available for only 3. The serum ionized calcium concentration was within the reference range (1.00 to 1.40 mmol/L) for 2 of those cats and slightly increased for the other (1.43 mmol/L).

Diagnostic techniques used for initial staging of the AGASACA included 3-view thoracic radiography (\( n = 25 \)), abdominal ultrasonography (19), and abdominal CT (1); no staging tests were performed for 5 cats. Evaluation of the 3-view thoracic radiographs revealed no evidence of lung metastases (\( n = 23 \)), a solitary nodule in the left caudal lung field (1), and an increase in opacity of unknown importance in the right cranial lung field (1). Abdominal ultrasonography revealed substantial sublumbar lymphadenopathy in 5 cats. The lymphadenopathy was bilateral in 2 of those cats; the sublumbar lymph node dimensions were 15 X 10 mm and 15 X 5 mm in one cat and 15 X 14 mm and 20 X 13 mm in the other. The enlarged lymph nodes were aspirated in one of those cats, but cytologic examination of the aspirate samples yielded nondiagnostic results. Other ultrasonographic findings included a soft tissue mass ventral to the sacrum (dimensions not recorded; \( n = 1 \) cat), minimally enlarged sublumbar lymph nodes (1), an enlarged medial iliac lymph node (dimensions, 3.7 X 4.8 mm) ipsilateral to the AGASACA (1), changes consistent with chronic renal disease (1), an abnormally small right kidney (1), and an abnormally thickened small intestinal wall (1). Two cats (1 with substantial bilateral sublumbar lymphadenopathy and 1 with minimally enlarged sublumbar lymph nodes) underwent sublumbar lymphadenectomy, and histlogic evaluation of the extirpated lymph nodes was indicative of metastatic carcinoma for both cats. For the cat that underwent abdominal CT, evidence of abnormally enlarged inguinal and jejunal lymph nodes was observed, but those lymph nodes were not sampled or removed.

**Treatment**

All 30 cats underwent surgical excision of the primary mass, which included anal sacculectomy. Unilateral anal sacculectomy was performed in 26 cats, and bilateral anal sacculectomy was performed in 4 cats. Of the 4 cats that underwent bilateral anal sacculectomy, 2 had a unilateral mass, and the extent of the mass was not specified for the other 2 cats. A portion of the rectal wall was removed in 3 cats. One cat had an internal obturator muscle flap performed concurrently because of the presence of a perineal hernia following tumor excision. Sublumbar lymphadenectomy was performed in 2 cats. No surgical complications were reported.

Surgical tumor margins were interpreted as complete for 14 cats, incomplete for 14 cats, and not reported for 2 cats. Maximal tumor dimension was available for only 19 of the 28 cats (8 with complete tumor excision and 11 with incomplete tumor excision) with information available regarding surgical margins. The mean ± SD maximal tumor dimension (1.3 ± 0.8 cm) for the 8 cats with complete tumor excision did not differ significantly (\( P = 0.30 \)) from that (2.1 ± 1.5 cm) for the 11 cats with incomplete tumor excision. Archived slides of tumor specimens for 26 cats were available for review and histologic grading. The median cumulative histopathologic score was 11 (range, 4 to 15), and 6, 13, and 7 cats were assigned a histopathologic grade of 1, 2, and 3, respectively. Metastatic AGASACA was histologically confirmed in both cats that underwent tumor removal with concurrent sublumbar lymphadenectomy.
Nine cats received adjuvant chemotherapy. Tumor margins were classified as incomplete and complete for 5 and 2 of those cats, respectively; tumor margins were unavailable for the remaining 2 cats. Both cats with histologically confirmed sublumbar lymph node metastasis were treated with adjuvant chemotherapy. Chemotherapy protocols included single-agent carboplatin (n = 4), mitoxantrone (1), and toceranib phosphate (1) or multiple-agent protocols in which carboplatin was followed with doxorubicin (1) or mitoxantrone (1). One cat continued to receive prednisone and melphalan for multiple myeloma, which was diagnosed prior to AGASACA. Recorded complications associated with chemotherapy included diarrhea and hematuria after receiving 1 dose of carboplatin (n = 1), vomiting after receiving 1 dose of carboplatin (1), and worsening of chronic renal failure after receiving 1 dose of mitoxantrone (1). Chemotherapy was discontinued in all 3 cats that developed complications.

Three cats received adjuvant radiation therapy to the perineum. Because of the retrospective nature of the study, it was not possible to determine whether the sublumbar nodal bed was also irradiated in those cats. Only 1 of those 3 cats also received adjuvant chemotherapy. That cat received carboplatin, but the exact protocol was not specified. The tumor margins were classified as complete in 1 cat, incomplete in 1 cat, and not reported in the remaining cat. The radiation therapy protocols administered included 4 fractions of 6 Gy for a total of 24 Gy (n = 2) and 10 fractions of an unknown dose (1). The cat that received adjuvant chemotherapy in addition to four 6-Gy fractions of radiation developed local tumor recurrence within the radiated field with metastasis to the sublumbar lymph nodes and was euthanized 93 days after surgery because of pelvic limb paralysis. The other cat that received four 6-Gy fractions of radiation was alive and disease free at 1,390 days after surgery. The cat that received 10 fractions of an unknown radiation dose had local recurrence near the surgical scar at 146 days after surgery and was euthanized 165 days after surgery because of local recurrence and a urethral stricture, which was presumed to be a radiation therapy–associated complication.

Outcome

The median duration of follow-up after surgery was 167 days (range, 0 to 1,390 days). Eleven cats had local tumor recurrence in the perianal area, and the median TLR was 96 days (range, 23 to 347 days) for those cats. Of the 11 cats with local recurrence, tumor margins were classified as complete for 3 and incomplete for 7 and were not reported for 1. For the 3 cats that had a portion of the rectal wall removed during surgery, tumor margins were classified as complete and local recurrence had not occurred at the time of last follow-up at 145, 260, and 356 days after surgery. Variables assessed for inclusion in the multivariable Cox regression model for TLR included NPS, vascular and lymphatic tumor invasion, completeness of histologic tumor margins, chemotherapy, and body weight. The final multivariable for TLR included completeness of histologic tumor margins (hazard ratio, 3.63; 95% CI, 1.09 to 14.6; P = 0.03) and NPS (hazard ratio, 3.53; 95% CI, 1.20 to 12.53; P = 0.03). Incomplete histologic tumor margins and a high NPS were risk factors for local recurrence. The median TLR for cats with complete tumor margins (555 days) was significantly (P = 0.01) longer than the median TLR for cats with incomplete tumor margins (196 days; Figure 1).

The median DFI 234 days (range, 0 to 1,039 days). For 3 cats, regional metastasis was histologically confirmed in the inguinal and sublumbar lymph nodes at 0, 36, and 100 days after anal sacculectomy. Metastasis to the lungs was suspected for 1 cat on the basis of evaluation of thoracic radiographs obtained 156 days after surgery. Variables assessed for inclusion in the multivariable model for DFI included body weight, completeness of histologic tumor margins, chemotherapy, tumor differentiation score, NPS, cumulative histopathologic score, and duration of clinical signs. Nuclear pleomorphic score was the only variable included in the final multivariable model for DFI; NPS was negatively associated with DFI (hazard ratio, 2.95; 95% CI, 1.12 to 9.03; P = 0.04).

Survival

The MST was 260 days (range, 42 to 1,390 days), and the 1-, 2-, and 3-year survival rates were 42%, 27%, and 18%, respectively. Sixteen cats were uncensored and were euthanized because of a poor quality of life after local recurrence (n = 8), anemia and respiratory distress (1), lethargy and inappetence (1), pulmonary metastases (1), right pelvic limb paralysis

![Figure 1](image-url) —Kaplan-Meier curves for TLR for 28 cats with AGASACA from which the tumor was excised with complete (rightmost curve; n = 14) and incomplete (leftmost curve; 14) histologic margins. The median TLR for cats with complete margins (555 days) was significantly (P = 0.01) longer than that for cats with incomplete margins (196 days). Dots represent cats that were censored (ie, cats that did not have local recurrence at the end of the observation period or were lost to follow-up).
(1), and urethral stricture after initiation of radiotherapy (1) or were euthanized for unknown reasons and did not undergo a necropsy (3). Fourteen cats were censored; 5 were lost to follow-up, and 9 were alive at the time of the last follow-up. Variables assessed for inclusion in the multivariable Cox regression model for survival included completeness of histologic tumor margins, chemotherapy, NPS, local recurrence, and vascular or lymphatic tumor invasion. The final multivariable for survival included local recurrence (hazard ratio, 8.18; 95% CI, 2.15 to 42.86; \( P = 0.001 \)) and NPS (hazard ratio, 9.56; 95% CI, 2.28 to 59.05; \( P = 0.001 \)); both were risk factors for death. The NPS was 1, 2, and 3 for 3, 12, and 15 cats, respectively. The MST for cats with an NPS of 2 (909 days) was significantly \( (P = 0.005) \) longer than the MST for cats with an NPS of 3 (187 days; Figure 2). Nuclear pleomorphic score was a confounder in the assessment of the association between local recurrence and survival.

**Discussion**

For the cats of the present study, the presence of perineal ulceration or discharge was the most common clinical sign (22/26 [85%]) associated with AGASACA. That finding was consistent with the results of the other large retrospective study \(^7\) of cats with AGASACA. In that study, \(^7\) 18 of 64 (28%) cats with AGASACA had perineal ulceration or a purulent or hemorrhagic discharge. For cats, perineal ulceration or discharge might lead to a suspicion of anal sac abscess and delay diagnosis of neoplasia. Benign anal sac disease, such as impaction or abscession, is less common in cats than in dogs. \(^9\) Consequently, the presence of perineal discharge or ulceration in a cat should prompt a rectal examination and, if indicated, a fine-needle aspirate or biopsy to facilitate diagnosis of AGASACA as early as possible.

Paraneoplastic hypercalcemia was reported in 29 of 108 (27%) dogs with AGASACA in another study \(^10\) and is associated with the production of PTHrp by neoplastic cells. \(^11\) Mild hypercalcemia was reported in 1 of 5 cats with AGASACA in another retrospective study \(^7\) and 3 of 27 cats of the present study. Unfortunately, serum concentrations of ionized calcium, parathyroid hormone, and PTHrp were not measured in any of those cats; therefore, the cause of the hypercalcemia was unidentified. To our knowledge, an association between paraneoplastic hypercalcemia and serum PTHrp concentration has not been described in cats with AGASACA. However, on the basis of the results of the present study, further investigation of hypercalcemia in cats with AGASACA is warranted.

Many veterinary oncologists recommend that dogs with AGASACA undergo adjuvant chemotherapy following surgical excision of the tumor owing to the high frequency of metastatic disease. Nevertheless, the survival advantage for dogs that undergo surgery and chemotherapy over that for dogs that undergo surgery alone remains controversial. \(^12\) The efficacy of chemotherapy for cats with AGASACA has not been investigated. In the present study, 3 cats developed locoregional metastases and 1 cat was suspected to have lung metastases, which suggested that, in cats, AGASACA has metastatic potential and chemotherapy might be beneficial in an adjuvant or neoadjuvant setting. Only 9 cats of the present study received some form of adjuvant chemotherapy, and it did not appear to provide them with a survival benefit. However, the number of cats that received adjuvant chemotherapy was small, and type II error was possible. Further research is necessary to assess the efficacy of chemotherapy in cats with AGASACA.

In dogs with AGASACA, adjuvant radiation therapy to the perineal area is used to slow progression of local disease \(^13-15\) and the longest MST (956 days) was reported for dogs that underwent a combination of surgery, radiation therapy, and chemotherapy. \(^15\) The efficacy of radiation therapy for the treatment of AGASACA in cats is unknown. Only 3 of the cats of the present study underwent radiation therapy (different protocols), and 2 of the 3 developed local tumor recurrence within the radiation field. Additional research is warranted to determine the efficacy of radiation therapy in cats with AGASACA.

Eleven of the 30 cats of the present study developed local tumor recurrence, which appeared to be the main life-threatening factor. Local recurrence was significantly associated with incomplete histologic tumor margins and a high NPS. One option for obtaining wider tumor margins and thereby decreasing the risk for local recurrence is to perform a more extensive surgery. Local recurrence of AGASACA was reported following surgical excision of the primary tumor for 5 of 11 dogs of one study \(^16\) and 1 of 19 dogs of another study. \(^17\) In the latter study, \(^17\) an extensive surgical approach that included removal of a portion of the external anal sphincter and rectal wall was used, which might have contributed to the low lo-
Small Animals

The present study had several limitations. The standardized form sent to participating practices for data collection did not inquire about specific details regarding postoperative complications; therefore, it is likely that most postoperative complications went unreported. Tumor-staging techniques and follow-up visits were not standardized or consistently performed. Thus, local recurrence and regional or distant metastases might have been missed, and the true incidence of local recurrence or metastatic disease was likely higher than what was reported. The cause of death was unknown for 4 cats because necropsies were not performed. We assumed those cats died from AGASACA-related complications and did not censor them from our analyses, which could have artificially decreased the MST and median DFI. Only 30 cats were enrolled in the study, despite the fact that cases were recruited from multiple institutions over a period of 21 years. This underscored the fact that AGASACA is uncommon in cats, but it also limited the power of the study to detect significant differences and may have increased the probability of type II errors.

In the present study, local recurrence following surgical excision was the most common reason cats with AGASACA were euthanized. Risk factors for local recurrence included a high NPS and incomplete surgical margins. Consequently, during excision of AGASACAs, wide surgical margins should be obtained when possible to minimize the risk of local recurrence. The roles of adjuvant chemotherapy and radiation therapy in the treatment of cats with AGASACA warrant further investigation.

Acknowledgments

The authors thank Henrik Stryhn for assistance with statistical analysis and Michelle Oblak, Kristina Jores, Courtney Zwahlen, Tara Britt, Mary Lafferty, Laura Hinton, Kathleen Mullins, and Shannon Parfitt for contributing cases to the study.

Footnotes


References

10. Williams LE, Gliatto JM, Dodge RK, et al. Carcinoma of the
Small Animals


From this month’s *AJVR*

**Pharmacokinetics after subcutaneous administration of a single dose of cefovecin sodium in African lions (Panthera leo)**

Kelly P. Flaminio et al

**OBJECTIVE**

To determine the pharmacokinetics of cefovecin sodium after SC administration of a single dose to African lions (*Panthera leo*).

**ANIMALS**

3 adult (9 to 10 years old; 1 male and 2 females) and 3 juvenile (2 years old; 1 male and 2 females) African lions.

**PROCEDURES**

A crossover study was conducted. A single dose of cefovecin was administered SC at 4 mg/kg (half dose) and 8 mg/kg (full dose) to African lions. Blood samples were collected daily for 14 days after cefovecin injection. Plasma drug concentrations were determined by use of high-performance liquid chromatography with UV detection.

**RESULTS**

Cefovecin had first-order elimination kinetics for doses of 4 and 8 mg/kg. Mean ± SD maximum plasma concentration was 9.73 ± 1.01 µg/mL and 18.35 ± 0.94 µg/mL after doses of 4 and 8 mg/kg, respectively. Time to maximum plasma concentration was approximately 4 hours for both doses. Mean elimination half-life was approximately 111 and 115 hours after doses of 4 and 8 mg/kg, respectively.

**CONCLUSIONS AND CLINICAL RELEVANCE**

Cefovecin was detected in lion plasma for 336 hours after administration at both 4 and 8 mg/kg at concentrations greater than the reported minimum inhibitory concentration (0.06 µg/mL) for common bacterial organisms in domestic cats. These results indicated that cefovecin administered at 4 mg/kg SC reached therapeutic concentrations for an extended period in African lions. (*Am J Vet Res* 2019;80:230–234)