# ANAL SAC ANAL GLAND ADENOCARCINOMA (ASAGACA): HOW COMBINATION THERAPY IMPACTS OUTCOME. THE BLADES, THE DRUGS, AND THE NUTRICEUTICALS FROM THE PERSPECTIVE OF THE SURGEON AND THE ONCOLOGIST

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## INTRODUCTION

Tumors of the anal sac are often thought of as a local disease but like all malignant conditions, the local development of the primary tumor, the behavior and spread of the tumor (grade and stage, respectively), and the outcome of intervention are all related to the systemic conditions that exist at any point during the disease process. The comprehension of any disease process, not just cancer, at this level, provides the veterinarian with a unique opportunity to intervene on many levels both providing more options for the pet parent and improving outcomes for the patient. The article will define and describe ASAGASAC, discuss traditional treatment interventions and outcomes as well as adjuvunct interventions from the perspective of functional food.

Tumors of the anal sac are uncommon and represent a small percentage of all skin tumors in dogs (< 2%). The most common malignant tumor of the perianal region is the anal sac (gland) carcinoma, accounting for 15–20% of all perianal tumors. These tumors are locally invasive and metastasize early in the course of disease. The average age of dogs diagnosed with this disease is 10–11 years, and there does not appear to be a breed or sex predilection. These tumors are often noted as an incidental finding on a routine rectal examination. If patients present with clinical signs, perianal swelling, straining to defecate, licking at the perianal region, and bleeding are the most frequently reported. It is important to measure the size of the tumor because its size is prognostic. In some cases, the only presenting signs are polyuria and polydipsia secondary to hypercalcemia. Hypercalcemia is the most common paraneoplastic syndrome seen in dogs with AGASACA and occurs in almost 30% of cases.

### Diagnostics and Staging

Standard preoperative workup includes a CBC and blood chemistry, including an ionized calcium level, and urinalysis. Imaging studies are indicated, including three-view thorax radiographs to assess for pulmonary metastasis and abdominal ultrasound to evaluate the regional lymph nodes, which are the most commonly affected with metastatic spread. Ultrasound

is superior to abdominal radiographs for assessment of the abdominal lymph nodes but if ultrasound is not available, enlarged lymph nodes can be identified on radiographs. Computed tomography of the thoracic and abdominal cavities is a superior imaging modality and offers many advantages over radiographs and ultrasound, including cost in some cases. Aspirates/biopsy of the tumor or regional lymph nodes are necessary for clinical staging and therapeutic assessment when possible.

The size of the anal sac tumor does not dictate the presence of metastatic disease. Abdominal ultrasound should be recommended in all cases of anal sac tumors to rule out metastatic disease to regional lymph nodes. Up to 50 percent of patients do have metastasis to the sublumbar nodes at the time of presentation and 10 to 20 percent of patients have lung metastasis.

If ionized hypercalcemia is identified on preoperative blood work, it needs to be corrected before anesthesia and surgery. Diuresis with 0.9% saline, furosemide, and possibly prednisone will help normalize ionized calcium concentration prior to surgery.

**Surgery**

The first stage of treatment for anal gland adenocarcinoma is surgical resection which in many cases can be curative.

The anal sac is located between the external and internal anal sphincters. Malignant tumors commonly invade these muscles. Other regional structures of interest include the pudendal artery, vein and the caudal rectal nerve. Anal sacculectomy is considered a clean-contaminated surgery and antibiotics are given at the time of induction and depending on the antibiotic, every 90-120 minutes during anesthesia. If there is not significant contamination during surgery, antibiotics are not needed in the post-operative period. Preoperative enemas are not recommended as they will liquefy the feces and contaminate the surgery site. Manual emptying of feces is often required prior to surgical prep of the surrounding skin. In the case of anal sac tumors, a purse string is not recommended because access to the anal sac duct opening is often required to obtain surgical margins. In some cases, part of the rectal wall will need to be resected and reconstructed. The patient is placed in the standard perineal position. A rolled towel is placed under the caudal abdomen and the cranial quadriceps muscles are padded against the table to prevent trauma to the femoral nerves.

Anal sac tumors are approached with a closed technique. The open technique will lead to contamination of the surrounding tissues with tumor cells and will not provide a clean surgical margin, often leading to local recurrence, and providing an ongoing source of metastasis and hypercalcemia. Surgery is approached with an incision directly over the palpable mass and careful dissection is used to maintain the integrity of the tumor capsule. Maintenance of the capsule is paramount to achieve local tumor control because wide resection in this area is not feasible due to the proximity of surrounding structures including the rectal nerve, anus, rectum, and sciatic nerve. If the tumor has adhered to the dermis or epidermis, it is possible and necessary to obtain a larger skin margin. If using electrosurgery, radiosurgery, or carbon dioxide laser for dissection and hemostasis, care must be taken not to damage the caudal rectal nerve, external and internal anal sphincter, and the rectal wall. Monopolar electrosurgery utilizes a grounding plate routinely placed under the patient. The energy source travels from the tip of the instrument through the local tissues, then through the body to the grounding plate, to continue the circuit. Bipolar tip attachments are preferred to minimize thermal damage as the energy only passes between the tips of the instrument. After excision is complete, new gloves and

instruments are used for local lavage and closure of the surgical wound to minimize the potential of seeding local tissues with tumor cells. External skin sutures or staples are avoided if possible as they tend to collect fecal material along the incision in the post-operative period. In the case of gross lymphadenopathy on ultrasound exam or CT, extirpation of the nodes is strongly recommended, especially in the hypercalcemic patient. The medial iliac and hypogastric lymph nodes are located in the region of the distal vena cava and bifurcation of the aorta. With mild amounts of lymphadenopathy, removal is straightforward but as the degree of lymphadenopathy increases, surrounding structures including the distal aorta, ureters, and iliac vessels can make removal more challenging. Successful lymph node resection in this location is largely dependent on adequate exposure to caudal peritoneal cavity and a thorough knowledge of the surrounding structures. The standard celiotomy incision will need to be extended caudally to the pelvic brim to allow for appropriate exposure to the region. Intraoperatively, it may be decided that the affected lymph nodes may not be resectable and are therefore biopsied prior to closure of the abdomen.

Complications include infection, fecal incontinence, and recurrence of local disease. All of which are minimized by appropriately prepping and positioning the patient, gentle tissue handling, providing meticulous hemostasis but minimizing the use of electrosurgery or laser, avoiding the use of external sutures or staples, and obtaining tumor free margins (if possible). Submit all tissues removed intact. If it is worth removing, it is worth submitting.

**Adjuvunct Therapy**

Adjuvunct intervention with radiation and/or chemotherapy may be recommended based on the presurgical staging and the postoperative histopathology report.

**Radiation Therapy**

In cases where surgery is not complete, then radiation therapy to the primary tumor site and regional lymph nodes will improve local control. Radiation therapy protocols range from 16–20 fractions on a Monday through Friday schedule. Acute side effects of radiation therapy can be moderate to severe and may result in colitis and rectal mucositis. During this time period an e-collar must be worn to prevent licking of the area. One study found dogs treated with surgery, radiation therapy (15 treatments) and chemotherapy (mitoxantrone) resulted in an overall survival of > 900 days. In non-resectable tumors, hypofractionated radiation therapy has anecdotally been useful in palliation with a relatively high rate of response noted. Side effects such as rectal stricture may occur with this type of protocol.

**Chemotherapy**

The benefits of chemotherapy for this cancer are not well characterized; however, chemotherapy is often incorporated into treatment protocols. The most commonly used chemotherapy agents include doxorubicin, carboplatin, mitoxantrone, melphalan and gemcitabine. NSAIDs are often utilized for putative anticancer effects. In a recent study assessing 42 dogs at AGASACA treated with surgery +/- chemotherapy, survival time was significantly associated with the presence of sublumbar LN and sublumbar LN extirpation, with median survival time significantly shorter for dogs with sublumbar than for those without and for dogs that underwent lymph node extirpation than for those that did not. Disease-free interval was significantly associated with the presence of sublumbar LNs, LN extirpation, and administration of platinum-containing chemotherapeutic

agents, with median disease-free interval significantly shorter for dogs with sublumbar LN vs without, for dogs that underwent LN extirpation vs without, and for dogs that received platinum chemotherapy vs without. Interestingly, survival time and disease-free interval did not differ among groups when dogs were grouped on the basis of histopathologic margins (complete vs marginal vs incomplete excision). One question raised by this study in regard to chemotherapy is whether chemotherapy was utilized in the "worst cases" thus being associated with an unfavorable outcome is a study bias. In some cases, all three modalities are utilized (surgery, chemotherapy, radiation therapy) in the treatment of dogs with ASAGAC.

**Non-resectable/Metastatic Tumors**

Currently no standard of care exists for advanced, non-resectable, or metastatic tumors. There is currently some data to help guide clinicians as a result of several retrospective studies.

*Hypofractionated radiation therapy (Palliative Radiation therapy)*

One study assessed 77 dogs with measurable ASASACA; 38% of dogs experienced a partial response to RT. For dogs presenting with clinical signs related to the tumour, improvement or resolution of signs was noted in 63%. For dogs presenting with hypercalcemia of malignancy, resolution was noted in 31% with RT alone and an additional 46% with radiation, prednisone, and/or bisphosphonates. The median overall survival was 329 days (range: 252–448 days) and the median progression free survival was 289 days (range: 224–469).

A second study using a protocol of 8 × 3.8 Gy (total dose 30.4 Gy, over 2.5 weeks) was assessed in 28 dogs (15 underwent surgery, 13 underwent RT). At the time of presentation, 21% had a life-threatening obstipation and 25% were hypercalcaemia. The progression free interval and median survival time for surgery cases were 159 days and 182 days, both significantly lower than for radiation therapy cases cases with 347 days and 447 days. Surgery as well as RT led to relief of clinical signs.

**Prognosis**

There are many prognostic factors established in dogs with AGASACA. The four that are worth noting and communicating to the pet owner are the presence of hypercalcemia at the time of diagnosis or at any time during the disease process, the presence of pulmonary metastasis, primary tumor size greater than 10 $cm^2$, and if surgery is part of therapy (improved prognosis) vs. no surgery (poor prognosis).

**Novel Therapy**

Recently, unique and novel therapeutic interventions have been developed and their impact on ASAGAC assessed. Toceranib phosphate (Palladia) is an orally bioavailable, multitargeted receptor tyrosine kinase (RTK) inhibitor active against several members of the split-kinase RTK family (VEGFR, PDGFR and Kit). Although approved for use in canine mast cell tumors, due to its mechanism of action in targeting new blood vessel growth, activity in a broad range of tumors might be expected. Following approval in 2009, toceranib was used off label to treat a variety of canine cancers, most often in patients having failed multiple treatment modalities. In a recent retrospective study of 32 dogs with ASAGACA treated with toceranib, 8 dogs (25%)

experienced partial response (PR) and 20 (62.5%) experienced stable disease (SD) for a clinical benefit (CB) rate of 87.5%. The median duration of treatment for all 32 dogs treated with toceranib was 25 weeks (range, 0 to > 47 weeks).

**Integrative and Nutritional Therapy**

Humans with cancer commonly use physician recommended or self-prescribed unconventional but complementary therapy, in the form of herbs and nutritional supplements. An interesting insight into the widespread use of nutraceutical use to treat cancer in humans was described in a recent study in which investigators found that only 7% of human cancer patients used unconventional medical therapies when they were asked routine questions by their oncologist; however, when a questionnaire was given to patients across studies, it was revealed that 40%-80% of cancer patients were actually using nutraceuticals to supplement their chemotherapy or radiation therapy protocols. The high prevalence of nutraceutical use among human cancer patients further suggests that nutraceutical use in pets with cancer is likely to be as, or more, frequent. There is actually some good science behind the use of certain ocean-sourced natural ingredients, especially, purified but not chemically altered EPA and DHA sourced from fish and the naturally isolated carbohydrate component of the New Zealand green-lipped mussel.

Cancer cachexia is weight loss in cancer patients despite adequate nutrient intake and is a devastating consequence of malignancy in human and veterinary patients. Alterations in resting energy expenditure and derangements in carbohydrate, protein, and lipid metabolism have been documented in dogs prior to overt signs of cachexia being observed.

**EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid)**

The omega-3 fatty acids are EPA (eicosapentaenoic acid), DHA (docosahexaenoic acid), and ALA (alpha-linolenic acid). Both EPA and DHA are found in high levels in fish oils. EPA is a potent anti-inflammatory mediator in the body while DHA has its greatest impact in the brain and spinal cord. ALA, which is found in some seeds and plants and marketed as a safe plant source of omega-3's, requires the enzyme delta-6 desaturase to convert it into EPA and DHA in the body. Unfortunately, humans, dogs, and cats have a limited (dogs and humans) to no ability (cats) to convert ALA to EPA and DHA.

In general, the omega-6 fatty acids, found in vegetable oils, corn oil, grapeseed oil, cottonseed oil, margarine, sesame oil, saturated fats, and fast food products are proinflammatory. They keep the cells, tissue, and body in a state of continued inflammation. The body needs inflammation to heal wounds and fight infection and cancer cells but too much inflammation over time leads to many systemic health conditions and diseases in dogs and cats. The body constantly strives to be in a balance between inflammation and anti-inflammation, between omega-6 and omega-3. However, the body can't produce or store omega-3 or omega-6 polyunsaturated fatty acids and therefore it can only use what it is fed.

Studies of polyunsaturated fatty acids (PUFAs), especially the omega-3's eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids, have demonstrated prevention of the development of carcinogen-induced tumors, the growth of solid tumors, and the occurrence of cachexia and metastatic disease in experimental tumor models. The proposed mechanisms in which these fatty acids elicit their effects may be related to the inhibition of cell proliferation and induction of

apoptosis. In contrast, PUFAs of the omega-6 series appear to enhance tumor development and metastases and are considered to be inflammatory in the tissues of the body. There is also epidemiologic evidence of an inverse relation between dietary omega-3 fatty acid intake and incidence of some cancers.

Some tumor cells have difficulty in using lipids as a fuel source, although host tissues continue to oxidize lipids for energy. This finding led to the hypothesis that foods moderately high in certain fats may benefit animals with cancer compared with foods relatively high in carbohydrates. Pets in North America receive most of their nutrient intake from commercial dry pet foods. In general, these foods are usually high in soluble carbohydrate and relatively low in fat. These characteristics may make some commercial kibble-based foods less optimal for nutritional management of animals with cancer.

High levels of EPA and DHA, as found in the triglyceride form of fish oil, are probably the most important nutraceutical to consider for animals with cancer. Several human epidemiologic studies have suggested that consumption of the correct form, source, and dose of EPA and DHA is a beneficial adjunct to treating many cancers. The recommendation for feeding high levels of EPA and DHA to pets with cancer is based on in vitro cell culture studies, studies in rodent models evaluating different types of cancer, clinical trials in human patients with solitary and metastatic forms of cancer, and in clinical trials in dogs treated for lymphoma and carcinoma.

Several hundred studies using laboratory models have evaluated the effects of EPA and DHA on tumorigenesis, tumor growth, metastasis, and chemotherapy. EPA & DHA administration reduces cancerous transformation of irradiated fibroblasts and inhibits proliferation and metabolism in various cancer cell lines, inhibits growth of aberrant cells, increases radiation sensitivity of cancer cells, inhibits growth of primary and metastatic tumors, demonstrates an enhanced effect of chemotherapeutic agents on cancer cells, decreases angiogenesis, reduces radiation damage to normal tissues, increases survival time when used with chemotherapy, increases disease free interval when used with chemotherapy, and increases quality of life when used with chemotherapy.

Several well-controlled clinical trials have evaluated the use of a fish oil–supplemented food in normal dogs and dogs undergoing chemotherapy for lymphoma and in a study of dogs being treated for carcinoma.

EPA and DHA supplementation were found to decrease or eliminate the metabolic alterations seen in dogs with stage IIIa and IVa lymphoma treated concurrently with doxorubicin chemotherapy, providing a significantly longer disease-free interval, longer survival times, and improved quality of life for these dogs. It is extremely important to note that specifically increasing the serum DHA content in dogs was associated with longer disease-free intervals and survival times in dogs with stage III lymphoma. This is key because only the triglyceride form of fish oil provides superior absorption, bioavailability, and cell membrane saturation of DHA.

Another controlled and randomized clinical trial evaluated the effect of fish oil supplementation on the acute effects of radiation injury in dogs with nasal tumors. Dogs fed the supplemented food had higher serum concentrations of EPA and DHA compared with values from control dogs. Higher serum levels of EPA and DHA were associated with lower plasma lactic acid

concentrations, lower tissue concentrations of inflammatory mediators, improved quality of life scores, and a lesser degree of histologic damage to normal tissues from radiation therapy.

**Matrix metalloproteinases (MMP's)**

MMP's are a family of zinc-dependent enzymes that play a key role in degrading basement membrane components and extracellular matrix. MMP's are proinflammatory, tissue destructive, and thought to be involved in chronic inflammation and some neoplastic conditions. MMP activity is detectable in canine and feline neoplastic tissue and in the serum of tumor-bearing animals. MMP activity is higher in tumor tissue than in unaffected stromal tissue, indicating that MMP may be involved in the pathogenesis of angiogenesis and tumor growth and metastasis. MMP's have been identified to be significantly higher in naturally developing malignant mammary gland tumors in dogs and most carcinomas compared with activities in normal tissues, and activities of tissue inhibitors of MMP's were lower in tumor tissue.

MMP's also play a significant role in the early and late inflammatory destruction of irradiated tissues. A study of dogs with osteosarcoma found that patients with activated levels of plasma MMP's had a significantly shorter survival time than dogs without activated plasma MMP's. New Zealand Green Lipped Mussels (GLM) that are extracted as adults from the ocean and immediately processed by cold live extraction methods, maintain the glycoprolex (glycogen-protein complex) component of the mussel which contains the active ingredient necessary for significant inhibition of the activation of MMP.

Together, these studies suggest that feeding a diet supplemented with a natural triglyceride (chemically unaltered) form of EPA and DHA and supplementation with the appropriate form (isolated carbohydrate) of a GLM extract, increases survival time of dogs undergoing single-agent cancer chemotherapy, increases the survival time of a subset of dogs undergoing single-agent cancer chemotherapy by more than 30% compared with the survival time of similar dogs consuming an unsupplemented food, reduces the severity of some acute phases of radiation therapy, thereby improving the quality of life for dogs with cancer, suppresses the clinical signs of cancer for longer intervals, and counteracts persistent metabolic changes found in many canine cancer patients.

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[Captions]

Figure 1. Dog with right sided ASAGAC. The patient is in sternal recumbency with the pelvic limbs hanging over the back edge of the surgery table. Towel pads are placed on the edge of the table supporting the cranial and proximal surface of the pelvic limbs to prevent injury to the femoral nerves. The surgery table is tilted in the Trendelenburg position (head tilted down) to prevent the patient from sliding off of the back end of the table and to allow the surgeon to comfortably stand during the procedure. A large clip and prep area have been created and the draping margin is wide allowing for any unexpected alterations in the surgical plan as commonly occurs with surgical oncology cases. A moistened laparoromy pad, 4inch X 18 inch, has been gently placed in the rectum (for smaller patients, a tampon works well) to prevent gross fecal contamination of the surgical site. There is ulceration of the skin and the surgical plan should include excision of the skin, using an elliptical incision, with appropriate margins and should include the anal sac and duct in an en bloc excision.

Figure 2. Patient from figure 1 after an elliptical skin incision was performed to obtain skin margins from an ulcerated ASAGAC. The skin, subcutaneous tissues, and anal sac were removed en bloc.