Managing canine apocrine gland anal sac adenocarcinoma

Canine apocrine gland anal sac adenocarcinoma represents a common challenge for veterinary practitioners. This is often partly because the majority of animals diagnosed with apocrine gland anal sac adenocarcinoma show no systemic signs at the time of presentation. Moreover, rectal examinations are not frequently performed during routine physical examinations, making it difficult to diagnose a mass at an early stage. An understanding of the disease process, common metastatic sites, diagnostic modalities and multimodal treatment approaches will help practitioners achieve better clinical outcomes for animals diagnosed with apocrine gland anal sac adenocarcinoma. Furthermore, knowledge of prognostic indicators will help practitioners to set realistic expectations with their clients and improve clinician–client communication. This article focuses on the predisposition, staging, multimodal treatment therapies and outcomes of dogs presenting with apocrine gland anal sac adenocarcinoma.

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Apocrine gland anal sac adenocarcinoma (AGASAC) represents 17% of perianal tumours and 2% of all cutaneous tumours in dogs (Liptak and Turek, 2020). This tumour arises from the apocrine secretory epithelium in the anal sac gland wall (Goldschmidt and Hendrick, 2002). It is characterised by high local invasiveness and a high metastatic rate (Polton and Brearley, 2007). Furthermore, the tumour can be associated with hypercalcaemia of malignancy that causes an additional clinical challenge (Williams et al, 2003). The majority are diagnosed at a late stage, when the tumour is large and early metastasis is already established. A multimodal approach to AGASAC, including early diagnosis, surgical management, chemotherapy and radiotherapy, is associated with increased median survival time (Williams et al, 2003).

Predisposition

English Cocker Spaniels, Labradors and German Shepherds, followed by Cavalier King Charles Spaniels, were over-represented in a study of British dogs with AGASAC (Polton et al, 2006). Among those breeds, English Cocker Spaniels are reported to be genetically predisposed to AGASAC and have a mean relative risk of 7.3 compared to other breeds (Polton et al, 2006). The tumour tends to affect dogs in middle-to-old age, with 10 years being the median age at presentation. The risk of neoplasia increases in neutered dogs, especially neutered males (Polton et al, 2006). However, an approximately equal gender distribution has also been reported (Williams et al, 2003).

Clinical presentation and physical examination

Animals presenting with AGASAC can show a variety of clinical signs, with perineal swelling, a palpable perineal mass, tenesmus, licking or biting at the perineum and perineal bleeding being those most commonly reported (Williams et al, 2003). Other symptoms include hindlimb weakness, lethargy and stranguria. Faecal tenesmus, dyschezia and hindlimb weakness are frequently reported in animals with large AGASACs and large metastatic sub-lumbar lymphadenopathy (Williams et al, 2003). Rectal and abdominal examination can help detect large sub-lumbar lymph nodes which increases the index of suspicion of AGASAC. Interestingly, hypercalcaemia of malignancy has been reported in 27% of animals, but only 22% of these animals were polyuric or polydipsic (Willams et al, 2003).

AGASAC has also been reported in adult dogs more than 5 years of age (Polton et al, 2006). Therefore, digital palpation screening for anal gland sac neoplasia in older animals is recommended during physical examination. The disease process may present as unilateral or bilateral. Chambers et al (2020) reported 93% prevalence of unilateral and 7% prevalence of bilateral AGASAC. Therefore, examining both anal gland

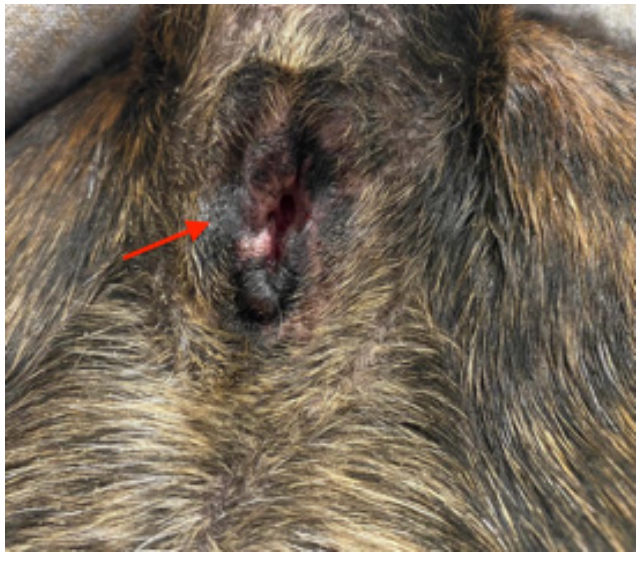

Figure 1. Unilateral, left-sided apocrine gland anal sac adenocarcinoma (red arrow) confirmed by fine-needle aspiration

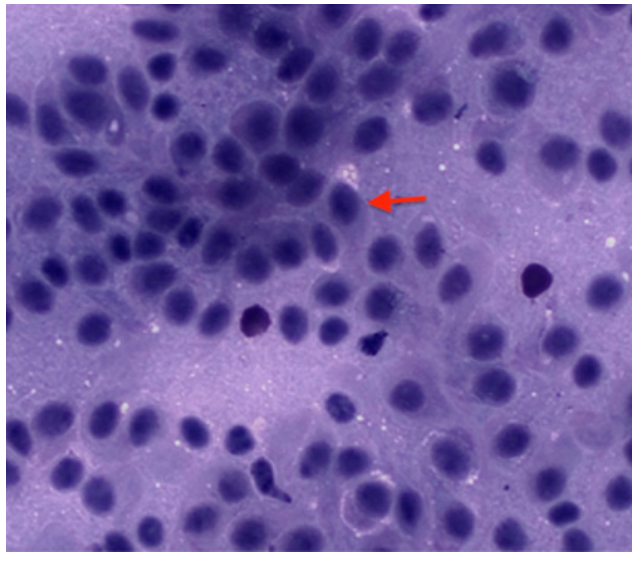

Figure 2. Cytology of apocrine gland anal sac adenocarcinoma demonstrating neoplastic cells (red arrow)

sacs is mandatory. Furthermore, initially unilateral, surgically removed neoplasia can subsequently develop contralateral AGASACs between 50 and 390 days after the initial surgery (Bowlt et al, 2013). Therefore, monitoring of the contralateral anal gland sac is recommended if bilateral anal sacculectomy is not performed.

The tumour may vary in size from a small nodule incidentally found during physical examination (*Figure 1*) to a large palpable mass. Animals presenting with a small nodule may be asymptomatic, therefore a full physical examination, a complete blood count, serum biochemistry and cytology of the mass is recommended these cases.

Staging

Classification of AGASAC is recommended for initial clinical staging (Polton and Brearley, 2007) (*Table 1*). The reported metastatic rate of AGASAC ranges from 36–72% (Williams et al, 2003; Polton and Brearley, 2007; Barnes and Demetriou, 2017). Bennett et al (2002) reported that 72% of affected dogs demonstrated sub-lumbar lymph node metastasis at the time of diagnosis. Distant metastasis sites, such as the lungs, liver, spleen, bone and, less frequently, the heart, adrenal glands, pancreas, kidneys and mediastinum, have been reported (Liptak and Turek, 2020). Staging of AGASAC includes a complete blood count, serum biochemistry including ionised calcium, urinalysis, diagnostic imaging and fine-needle aspiration of the mass (*Figure 2*) (Polton and Brearley, 2007).

Computed tomography (CT) of the thorax and abdomen (*Figures 3* and *4*) with ultrasound-guided fine-needle aspirates of any abnormal abdominal lymph nodes are recommended for screening. However, thoracic radiographs and abdominal ultrasound will suffice. The most commonly affected are the medial and internal iliac lymph nodes (Polton and Brearley, 2007).

Although abdominal ultrasonography is an effective screening test for iliosacral lymphadenopathy, CT is more sensitive at detecting lymphadenomegaly and is recommended, especially if additional metastatic sites are suspected (Palladino et al, 2016). Three-view inflated thoracic radiographs may be used for the detection of pulmonary metastasis, although it has been shown that radiography is less sensitive than CT at detecting pulmonary nodules (Armbrust et al, 2012). The sensitivity of radiography in detecting pulmonary nodules varies between 71% and 95%, depending on the diagnostic imaging specialist reading the films (Armbrust et al, 2012).

In cases where CT is not available, a combination of three-view inflated thoracic radiographs, abdominal radiography and abdominal ultrasonography is recommended (Polton and Brearley, 2007). Abdominal radiography may demonstrate lytic bony

Table 1. Clinical staging of apocrine gland anal sac adenocarcinoma

Clinical stage	Primary tumour (T)	Regional lymph node (N)	Distant metastasis
Stage 1	<2.5 cm max diameter	None	None
Stage 2	<2.5 cm max diameter	None	None
Stage 3a	Any T	Present <4.5 cm max diameter	None
Stage 3b	Any T	Present >4.5 cm max diameter	None
Stage 4	Any T	Any N	Present

Adapted from Polton and Brearley (2007)

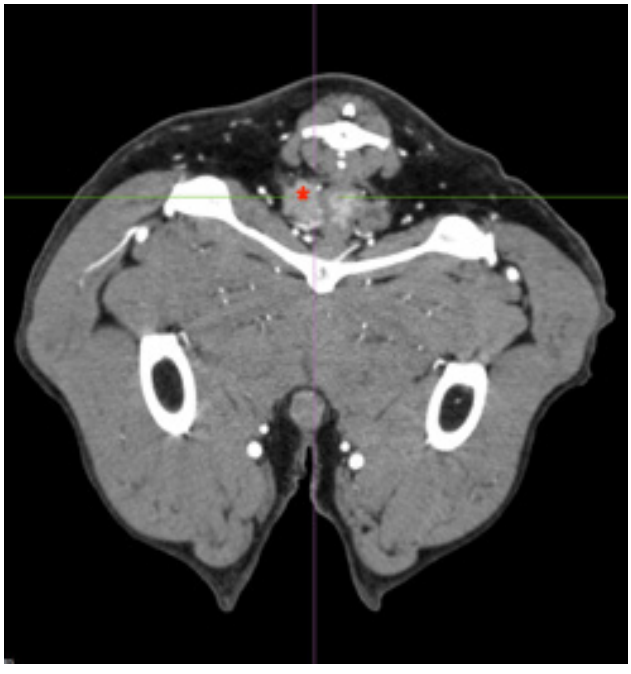

Figure 3. Transverse computed tomography projection demonstrating heterogeneous, contrast-enhancing anal gland sac mass (red star)

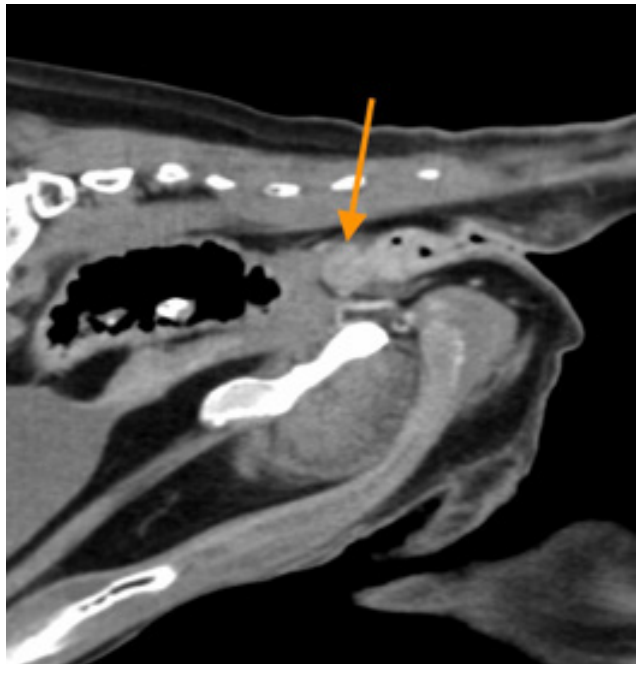

Figure 4. Sagittal computed tomography projection demonstrating anal gland sac mass (orange arrow)

changes affecting the lumbar vertebral body. or even pathological compression fractures to the vertebrae (Brisson et al, 2004). In the animals diagnosed with AGASAC or lymphoma, radiographic identification of sub-lumbar lymphadenopathy increased the suspicion of neoplastic infiltration of the lymph nodes (Murphy et al, 2020), but not being able to see the tumour does exclude mild-to-moderate enlargement. Therefore, ultrasonography of the sub-lumbar lymph nodes is recommended.

A common cause of hypercalcaemia in dogs with AGASAC is the production of parathyroid hormone-related protein by the tumour cells (Williams et al, 2003). This protein behaves in a similar way to the parathyroid hormone leading to high serum calcium concentration (Williams et al, 2003). Not all dogs with AGASAC will develop hypercalcaemia, because hormones secreted by the tumour are dependent on a certain degree of cell differentiation, so poorly differentiated cells are less likely to be functional (Meuten et al, 1981).

Hypercalcaemia of malignancy has been reported in 27% of animals with AGASAC (Willams et al, 2003). Therefore, the presence or lack of hypercalcaemia cannot be the single criterion for determining whether the mass is malignant or not. The main differential diagnoses for paraneoplastic hypercalcaemia include canine lymphoma, multiple myeloma, tumours with bone metastasis and parathyroid tumours, with AGASAC being the second most common cause of hypercalcaemia of malignancy.

Diagnosis of AGASAC is achieved by fine-needle aspiration biopsy. In a study by Simeonove (2012), 88.7% agreement between cytological and histopathological diagnosis of canine cutaneous and subcutaneous masses was reported. In diagnosing neoplasia, cytology has a sensitivity of 90% and a specificity of 97% (Simeonove, 2012). Therefore, the final diagnosis must be confirmed based on the histopathological examination.

Treatment

Therapy for AGASAC often involves a multimodal approach (Barnes and Demetriou, 2017). The mainstay of therapy is surgical removal of the primary mass wherever possible, together with excision of any metastatic lymph nodes. Local reoccurrence and high metastasis rate, mean that adjuvant radiation and chemotherapy are often necessary (Williams et al, 2003).

Preoperatively, electrolyte and acid-base abnormalities should be corrected (Radlinsky, 2013). Animals suffering from hypercalcaemia of malignancy require presurgical management of the calcium levels. This involves promoting diuresis by placing the patient on intravenous saline solution and potentially the administration of frusemide, although this should only be performed in a well hydrated, non-azotaemic patient (Radlinsky, 2013). Additional therapy to decrease the level of calcium includes the administration of prednisolone and bone resorption inhibitor agents (bisphosphonates) such as pamidronate disodium (Radlinsky, 2013).

The remission of hypercalcaemia is reported following surgical removal of AGASAC (Williams et al, 2003). Common signs associated with hypercalcaemia include polyuria or polydipsia, lethargy and weakness; the latter of which are believed to be caused by decreased neuronal membrane permeability to sodium, leading to a reduction of neuronal depolarisation events (Lucas et al, 2007). Furthermore, hypercalcaemia may lead to renal tubular damage, which manifests in the azotaemia and the isosthenuria (Lucas et al, 2007). Renal dysfunction is initially reversible, although prolonged hypercalcaemia may lead to oliguria and irreversible chronic renal failure (MacPhail, 2013). Gastrointestinal signs related to hypercalcaemia are non-specific and include nausea, anorexia, vomiting, constipation and weight loss. It is rare that medical management will correct hypercalcaemia without removing the

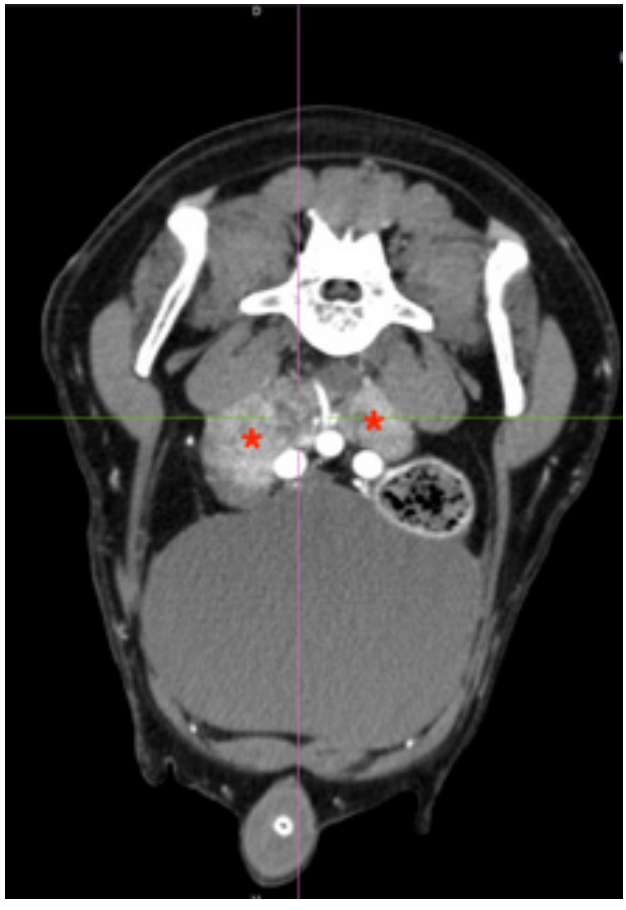

Figure 5. Transverse computed tomography projection showing a heterogeneous contrast-enhancing markedly enlarged metastatic sub-lumbar lymph node (red star)

causative tumour. Dogs with metastatic lymph nodes will often remain hypercalcaemic if only the primary anal sac tumour is removed, and all neoplastic disease must be removed to achieve normo-calcaemia.

Surgery

Surgery involves excision of the AGASAC and any metastatic lymph nodes. To the best of the authors' knowledge, there is no current consensus on whether bilateral sacculectomy is recommended for unilaterally located AGASACs, or whether unilateral sacculectomy is sufficient. Nevertheless, 174 dogs that had undergone anal sacculectomy were evaluated for the treatment of AGASAC (Chambers et al, 2020). In this study, 162 animals underwent unilateral anal sacculectomy for the treatment of a unilateral tumour, and 12 dogs underwent bilateral anal sacculectomy for a bilateral tumour.

The anal gland sacs are located between the external and internal sphincter muscles. As the tumour tends to be locally invasive, removing a portion of the external sphincter muscle might be necessary. Removing 50% of the sphincter muscle of one side is possible without causing permanent faecal incontinence (Radlinsky, 2013). Surgery can be challenging, especially when the tumour is large and invades the surrounding tissue. Pre-surgical administration of an intravenous prophylactic antibiotic is advisable. Before the surgery, manual evacuation of faecal material from the rectum is recommended.

A deep purse-string suture is placed cranial to the anal sac duct. Tumours tend to be very vascular, so meticulous haemostasis is crucial. An effort should be made to remove the tumour with minimal trauma to the sphincter muscle if possible. A wide surgical excision of the neoplasia is rarely possible because of the proximity of the tumour to the rectal wall. Therefore, the vast majority of AGASACs are removed via marginal surgical excision. Achieving a tumour-free margin is often not feasible unless the tumour is very small in size. Following the excision of the tumour, the surgical site is thoroughly lavaged and the dead space closed up using an absorbable monofilament such as polydioxanone, polyglyconate or poliglecaprone 25. It is necessary to submit the excised mass for histopathology to confirm the diagnosis and establish clean margins. The survival time for animals with stage 1 or 2 AGASAC is 1205 days and 722 days, respectively (Polton and Brearley, 2007), and there is currently no treatment option other than surgery for these animals.

Sub-lumbar lymph nodes include the sacral, medial and internal iliac lymph nodes. These lymph nodes are located proximally to the aorta trifurcation, in the caudal abdomen (Liptak and Turek, 2020) (*Figures 5* and *6*).

A longer survival time was reported following metastatic iliac lymphadenectomy in animals with AGASAC (Hobson et al, 2006). Therefore, surgical excision is recommended (Hobson et al, 2006). The risk of significant intraoperative bleeding is high because of the proximity of the lymph node to the major abdominal vessels. As a result, meticulous surgical technique and presurgical blood typing is advisable. Surgical removal of the sub-lumbar lymph node is not always possible, especially if the metastatic lesion involves the aortic branches. It is likely that the mass will continue to grow and lead to tenesmus and obstipation in these circumstances.

The complication rate following the surgical removal of AGASAC varies from 0–20% and the risks include surgical site infection, wound dehiscence, recto-cutaneous fistula formation, suture reaction, faecal incontinency and tenesmus (Barnes and Demetriou, 2017). Although hypocalcaemia has been reported in the literature as a complication following sacculectomy for the removal of AGASAC, it is not a complication commonly encountered (Barnes and Demetriou, 2017). Complications following sub-lumbar lymphadenectomy vary from 0% to 12% and include intra-operative bleeding, lymph node rupture and abdominal wall dehiscence (Liptak and Turek, 2020).

Chemotherapy

Although the maximum tolerated dose of adjuvant chemotherapy has been traditionally recommended for the treatment of AGASAC because of the high risk of metastasis, the literature lacks evidence to support it (Liptak and Turek, 2020). Various different chemotherapeutic agents have been investigated for both adjuvant and palliative management of AGASAC, including cisplatin (Bennett et al, 2002), carboplatin (Wouda et al, 2016), mitoxantrone (Turek et al, 2003), actinomycin-D (Hammer et al, 1994), doxorubicin (Williams et al, 2003), melphalan

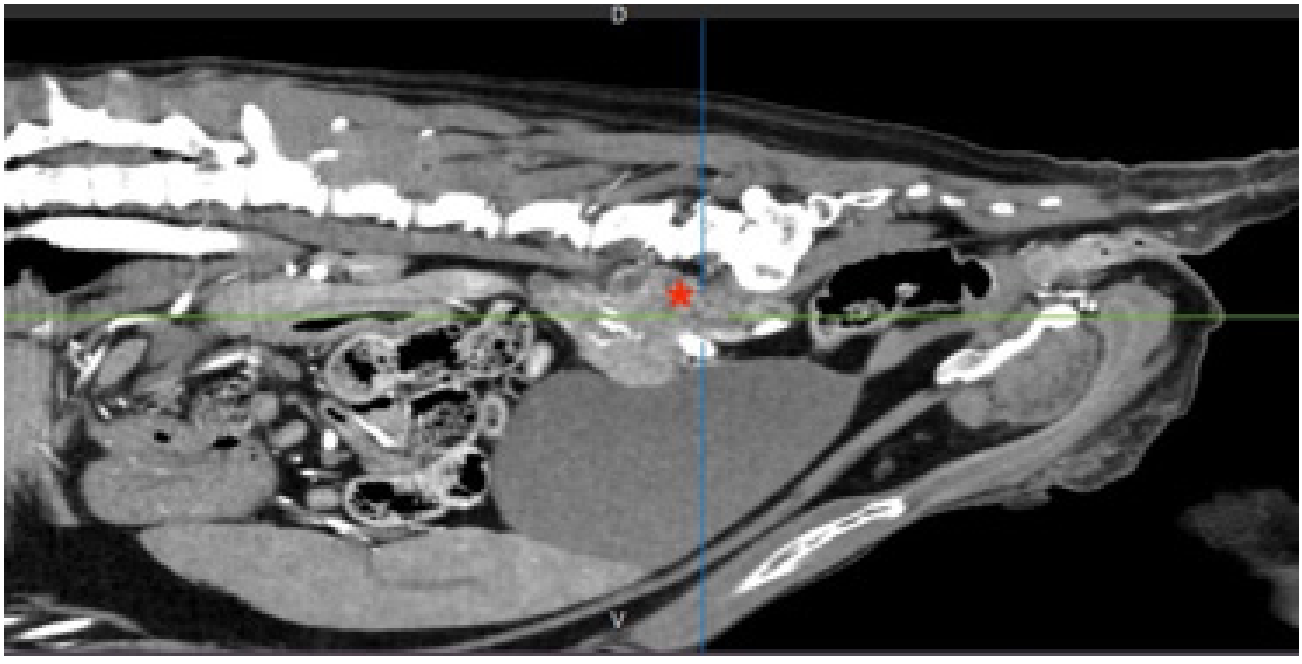

Figure 6. Sagittal computed tomography projection demonstrating a heterogeneous, contrast-enhancing, lobulated metastatic sub-lumbar lymph node (red star)

(Emms, 2005) and, more recently, the tyrosine kinase inhibitor toceranib phosphate (Heaton et al, 2020). Toceranib phosphate is a commonly used chemotherapeutic agent for the treatment of AGASAC (Heaton et al, 2020). Toceranib's mechanism of action results from competitive blockade of the ATP-binding site of tyrosine kinase receptors, impairing phosphorylation and downstream signalling (Lemmon and Schlessinger, 2010).

Clinical benefits from toceranib treatment have been reported in 69% of dogs with gross disease, with 20.7% of dogs responding partially and 48.3% of dogs experiencing stable disease (Heaton et al, 2020). The most common side effects associated with toceranib phosphate treatment include vomiting, diarrhoea, decreased/loss of appetite, weight loss, lameness and blood in the stools (Zoetis, 2015). Conversely, the most common laboratory abnormalities include neutropenia, thrombocytopaenia, hypoalbuminaemia increased alanine aminotransferase, decreased haematocrit and increased creatinine (Zoetis, 2015).

Currently, the only real evidence to support the use of toceranib is for dogs that have stage 4 disease. Historically, these dogs have shown a short survival of 70–80 days (Polton and Brearley, 2007). However, a recent study reported a median survival of nearly 300 days using toceranib (Elliott, 2019). Further work is needed to clarify the use of chemotherapy in the adjuvant setting.

Radiotherapy

Radiotherapy may be advised with a palliative or multimodal curative intent (Liptak and Turek, 2020). Improvement following radiotherapy has been demonstrated in 38–75% of dogs with gross disease treated with hypofractionated or fractionated protocols (Liptak and Turek, 2020). Radiation therapy is recommended for non-resectable tumours, incompletely removed tumours or metastatic lymph node involvement (Unterer, 2017). Definitive radiation therapy is recommended for the treatment of microscopic disease following incomplete surgical removal of the primary tumour to prevent recurrence (Unterer, 2017).

Side effects associated with radiotherapy are divided into acute and chronic. Acute side effects are seen in rapidly dividing cells and appear shortly after radiotherapy is initiated. The most common acute toxicities are skin erythema and dry/moist desquamation.

Radiation of the rectum and descending colon will frequently result in acute colitis and proctitis, which can cause discomfort in passing stools and haematochezia. Treatment for acute side effects involves administering supportive therapy and they usually resolve within 10–14 days, as the tissue is repaired. Chronic or late radiation toxicity affects non-replicating or slow replicating tissue and may appear months or years after radiotherapy. These side effects involve skin fibrosis, hyperpigmentation and alopecia. Of more significance, is the risk of chronic rectal stricture. Late radiation toxicity is permanent.

For animals with stage 3a and 3b AGASAC, iliac lymphadenectomy is associated with longer survival time and is currently recommended (Hobson et al, 2006). Although, if surgery is not feasible, radiation therapy of the primary tumour site and metastatic lymph nodes is associated with progression-free intervals of 347 days and median survival time of 447 days (Meier et al, 2017).

Prognosis

The outcomes following treatment for AGASAC reported in the literature are variable. Therefore, it is difficult to accurately predict the prognosis for individual animals with AGASAC. Prognoses are stage-dependent and animals diagnosed with an early stage tumour have a good prognosis when treated with surgery alone (Williams et al, 2003). Animals with advanced, inoperable tumours have worse prognoses. Radiotherapy is advocated for animals with incompletely removed tumours and is associated

Table 2. Median survival time of animals affected by apocrine gland anal sac adenocarcinoma

Clinical stage	Median survival time
Stage 1	1205 days
Stage 2	722 days
Stage 3a	492 days
Stage 3b	335 days
Stage 4	71 days
Polton and Brearley (2007)	

with increased survival time (Williams et al, 2003). A simplified summarised median survival time based on tumour staging (*Table 2*) was suggested by Polton and Brearley (2007).

It is crucial to understand that median survival time depends on the stage and the type of treatment that an individual patient receives, especially in the advanced stages of the disease. Negative prognostic indicators for survival time include the presence of distant metastasis, lymph node metastasis, primary tumour size, lack of therapy (and the presence of presurgical hypercalcaemia (Ross et al, 1991; Polton and Brearley, 2007).

Although this staging scheme is commonly used at the moment, a recent study by Tanis et al suggested that the number of metastatic lymph nodes may be more important than the size (Polton and Brearley, 2007; Tanis et al, 2022).

KEY POINTS

- Canine apocrine gland anal sac adenocarcinoma represents a common challenge for veterinary practitioners due its local invasiveness, high metastatic rate and hypercalcaemia of malignancy.
- Diagnosis is achieved by fine-needle aspiration of the mass that shows 88% compatibility with histopathological diagnosis, therefore the final diagnosis must be based on the histopathological examination.
- The sub-lumbar lymph nodes are a common metastatic site for apocrine gland anal sac adenocarcinoma, whereas distant metastatic sites include the lungs, liver, spleen, bones and, less frequently, the heart, the adrenal glands, pancreas, kidneys and mediastinum.
- Appropriate staging of apocrine gland anal sac adenocarcinoma is essential to achieve a superior outcome for the patient and includes a complete blood count, serum biochemistry including ionised calcium, urinalysis, fine-needle aspiration of the mass, imaging of the thorax and abdomen and ultrasound-guided aspiration of the abnormal sub-lumbar lymph node. Computed tomography is a gold standard for imaging of the thorax and abdomen and is recommended, although thoracic and abdominal radiography can be used when computed tomography is not available.
- Although pre-operative correction of hypercalcaemia is very important, it is rarely achieved by medical management. Therefore, surgical removal of the causative tumour is necessary to achieve normocalcaemia.
- Treatment involves a multimodal approach, including surgical removal of the primary mass, abnormal sub-lumbar lymph node, chemotherapy and radiotherapy, when necessary.

Conclusions

Although AGASAC is a highly invasive and metastatic tumour, early diagnosis, appropriate staging and a multimodal approach to the disease are associated with satisfactory long-term survival. The most important aspect of the management of AGASACA is clear clinician-client communication and establishing realistic expectations with regards to prognosis.

Conflicts of interest

The authors declare no conflict of interest.

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