

# Anal Sac Adenocarcinoma; A Hidden Cancer



Tumours of the perianal region occur frequently in dogs (Bennett *et al.* 2002), with benign adenomas comprising 58-96 % of tumours at this site (Turek & Withrow 2013). In some cases these may transform to become malignant perianal adenocarcinomas, and these need to be distinguished from adenocarcinomas which derive from the apocrine secretory epithelium within the wall of the anal sacs (Polton & Brearley 2007). Neoplasia of the squamous epithelial lining of the anal sac is uncommon (Polton *et al.* 2006; Mellett *et al.* 2014). Anal gland/sac adenocarcinomas (ASA) represent 2% of all skin and subcutaneous tumours in dogs, and around 17% of all perianal malignancies (Bennett *et al.* 2002; Turek & Withrow 2013; Potanas *et al.* 2015). They are clinically important because of their high metastatic potential and association with paraneoplastic hypercalcaemia; this review will therefore focus on this tumour type (Polton *et al.* 2006.; Wouda *et al.* 2013).

## Signalment

Anal sac adenocarcinoma commonly affects older dogs, with the mean age of diagnosis being approximately 10 years (Bennett *et al.* 2002; Williams *et al.* 2003; Polton & Brearley 2007). Despite historical reports linking anal sac adenocarcinoma to older females, recent studies have not confirmed this sex predilection (Williams *et al.* 2003). Most recently, Polton *et al.* (2006), found an increased risk of disease in castrated males. The reasons behind this are unclear, but they hypothesise that absence of sex hormones may make individuals less likely to void their anal sacs and predispose to stagnation of anal gland content (Polton *et al.* 2006). Certain breeds tend to be over-represented with English Cocker Spaniels considered as high risk, but Springer Spaniels, Cavalier King Charles Spaniels and German Shepherd dogs are also over-represented. There is some suggestion in the literature of a possible underlying genetic predisposition (Bennett *et al.* 2002; Polton *et al.* 2006).

## Presentation and Clinical Signs

Although small asymptomatic nodules can be detected as incidental findings, ASA may also be associated with clinical signs. These clinical signs are related to either the physical presence of the primary anal sac mass, or secondary to substantial metastatic disease, or they may result from hypercalcaemia of malignancy (Bennett *et al.* 2002; Turek & Withrow 2013; Bowlt *et al.* 2014).

## Primary Mass

If large enough, the anal mass itself may manifest with signs associated with anal gland discomfort, for example a subcutaneous swelling around the perianal region (Figure 1 and 2), scooting behaviours, discomfort with sitting or persistent licking around the anal area. Occasionally perianal bleeding may be noted or a more ulcerative lesion eroding through the dermis (Williams *et al.* 2003; Polton & Brearley 2007; Turek & Withrow 2013; Wouda *et al.* 2013).

## Metastatic Disease

In many cases, the primary lesion may be asymptomatic and the dog presents with signs consistent with metastasis to the regional lymph nodes (medial iliac, sacral, hypogastric, pelvic etc.) (Williams *et al.* 2003; Polton & Brearley 2007; Wouda *et al.* 2013). Metastatic disease in this region can present as difficulty passing faeces, straining to defecate, abnormal posturing or altered faecal shape. Although less common, metastasis to bone can be seen. A single case report of a young dog presenting with progressive hind limb ataxia and paresis, worsening to paralysis over a short period of time, was attributed to an anal sac adenocarcinoma with metastatic spread to the vertebrae and subsequent pathological fractures (Bray 2011).



Figure 1. Right sided anal gland adenocarcinoma, dorso-lateral to anus.



Figure 2. Anal sac adenocarcinoma presenting as bulging of perineum.

## Hypercalcaemia of Malignancy

In 25-55% of cases, clinical signs are not attributable to the physical presence of a primary or metastatic tumour, but result from metabolic consequences of a paraneoplastic syndrome (Williams *et al.* 2003; Polton & Brearley 2007; Wouda *et al.* 2013). Anal sac adenocarcinoma is the second

most common cause of hypercalcaemia of malignancy after lymphoma (Messinger *et al.* 2009; Bray 2011; Turek & Withrow 2013; Potanas *et al.* 2015). Clinical signs of hypercalcaemia tend to improve after surgery, however hypercalcaemia often returns with tumour recurrence (Ross *et al.* 1991; Williams *et al.* 2003).

Clinical signs of hypercalcaemia most commonly include polydipsia and polyuria, nausea, vomiting, anorexia and constipation. Lethargy, weakness and muscle tremors can also be noticed. Occasionally total calcium may be normal and ionised calcium may be required to assess the true calcium levels in the body (Boag 2007).

In ASA, hypercalcaemia is commonly caused by the production of a parathyroid hormone-related protein (PTH-rp). This protein, produced by the tumour cells, mimics the natural action of parathyroid hormone and leads to increased serum calcium concentrations (Bray 2011; Turek & Withrow 2013). Not all anal sac adenocarcinomas will produce PTH-rp, and its production does not seem to be linked to tumour size or to correlate with biological behaviour of the tumour (Williams *et al.* 2003).

### Diagnosis

Preliminary diagnosis of ASA is primarily achieved by clinical examination, sometimes by visual inspection of the perianal region, but more usually by rectal examination. The majority of anal gland masses are unilateral, bilaterally affected glands occur less frequently, in fewer than 10% of reported cases (Emms 2005; Potanas *et al.* 2015). Rectal examination typically reveals a thickened or irregular area within the anal gland. Often the primary tumour is small, and can be just millimetres in diameter (Polton & Brearley 2007). It can be noticed as an incidental finding on routine rectal examination or routine emptying of anal sacs, with as many as 39% of tumours recognised in this way (Williams *et al.* 2003; Bray 2011; Turek & Withrow 2013). Recognition of clinical signs as being suspicious for ASA is very important so that a thorough clinical examination can then be performed.

Definitive diagnosis must be made by cytology or histopathology. Fine needle aspirates can be safely performed by positioning the mass against the skin using rectal palpation with the non-dominant hand and inserting the needle through the perianal skin. Cytology typically shows sheets or clusters of polyhedral cells with uniform round or oval nuclei and a moderate amount of greyish-blue granular cytoplasm (Figure 3). Common features of malignancy may be subtle but include a high and variable nuclear:cytoplasmic ratio, anisokaryosis and prominent nucleoli (Turek & Withrow 2013). Malignant characteristics are usually visible but may not be as obvious as carcinomas of other origins (Bray 2011).

### Staging

Following definitive or presumptive diagnosis clinical staging is recommended to assess the extent of tumour spread to regional lymph nodes and distant sites. Staging is vital to determine whether metastasis has occurred and to tailor treatment options accordingly. A staging system categorising

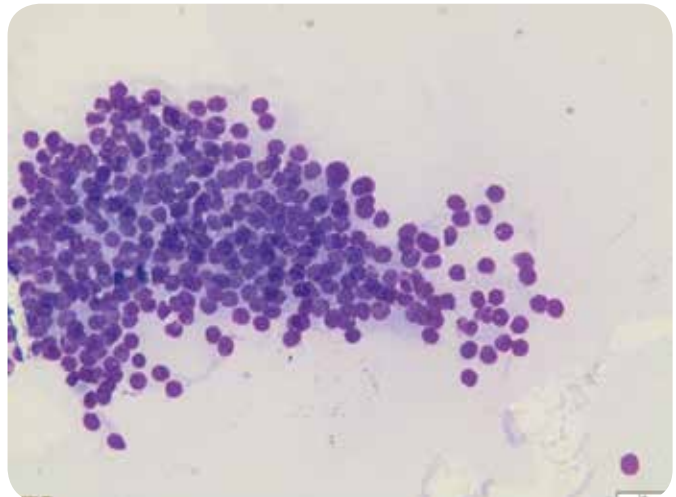


Figure 3. Typical cytology of anal sac adenocarcinoma, showing rafts/clusters of malignant epithelial cells.

anal gland adenocarcinomas into four clinical stages based on tumour size, regional lymph node size, and presence or absence of distant metastasis, has been described (Figure 4) (Polton & Brearley 2007).

Clinical Stage	Tumour (size)	Lymph Node involvement	Distant metastasis
1	<2.5cm	None	None
2	>2.5cm	None	None
3a	Any	<4.5cm nodal diameter	None
3b	Any	>4.5cm nodal diameter	None
4	Any	Any	Any

Figure 4. Staging table (modified from Polton & Brearley 2007).

Anal sac adenocarcinomas have high metastatic potential with 46-90% of tumours metastasising by the time of diagnosis to regional lymph nodes and/or distant sites (Figure 5) (Ross *et al.* 1991; Williams *et al.* 2003; Bray 2011; Turek & Withrow 2013; Potanas *et al.* 2015).



Figure 5. Still ultrasound image of 2.4cm diameter nodule in the body of the spleen.

Abdominal radiographs may be sufficient to see evidence of advanced disease and regional lymph node enlargement; however abdominal ultrasound is superior for evaluating regional lymphadenomegaly (Figures 6 + 7) (Turek & Withrow 2013). Lymph node size is the primary marker of neoplasia (Llabrés-Díaz 2004; De Swarte *et al.* 2011) with other changes in lymph node shape or echogenicity shown to be unreliable indications of metastasis.



Figure 6. Still ultrasound image of enlarged right medial iliac lymph node (1.3cm diameter). The node appears heterogenous with hypoechoic areas.



Figure 7. Still ultrasound image of an enlarged peri-aortic lymph node with mottled echogenicity and heterogenous appearance, indicative of metastasis.

Thoracic radiography allows assessment of the lungs for pulmonary metastasis and evaluation of the presteral and mediastinal lymph nodes, which drain the cranial abdomen. Pulmonary metastases are rare, occurring in 20% of dogs presenting with ASA (Figure 8) (Bray 2011).



Figure 8. Multiple well-defined rounded soft tissue nodules present in the caudal right lung lobes, at the level of the 6th and 7th rib, indicative of pulmonary metastasis.

A full staging work-up would also include a complete blood count, biochemistry (including an ionised calcium level), and urinalysis to assess for the presence of concurrent or paraneoplastic disease. Hypercalcaemia, in particular, can affect renal function (Aronson 2012) with renal calcification seen microscopically in around 90% of hypercalcaemic cases (Capen 2001). Evaluation of renal parameters is therefore important in these cases.

## Treatment

### Surgery

Surgical excision of the primary tumour (anal saccullectomy), and also regional metastases if present, is the treatment of choice for ASA (Bennett *et al.* 2002; Williams *et al.* 2003; Emms 2005; Turek & Withrow 2013; Wouda *et al.* 2013). Although surgery is recommended, it does incur relatively high morbidity and mortality (Ross *et al.* 1991; Bennett *et al.* 2002). Extensive local surgery around the anus carries the risk of faecal incontinence if there is trauma to the anal sphincter or caudal rectal nerves during surgery, and is more likely to occur if removing the primary tumour necessitates partial anoplasty (Aronson 2012). Faecal incontinence has been reported in 33% of dogs undergoing surgery (Aronson 2012), although more recent studies have found the incidence to be lower (Hill & Smeak 2002; Charlesworth 2014). Anal stricture due to scar tissue, rectal prolapse and the inherent risk of infection due to wound location are also important morbidity factors.

Sublumbar lymph nodes are often situated close to major blood vessels and the risk of intra-operative haemorrhage is high (Bennett *et al.* 2002; Bray 2011; Wouda *et al.* 2013). Access to the regional lymph nodes can be difficult and may require a pelvic osteotomy (Emms 2005). Close proximity to the local nerves can mean that aggressive surgical techniques carry a risk of sciatic nerve paralysis and urinary incontinence

following surgery has also been reported (Ross *et al.* 1991; Emms 2005). Recent studies have shown low complication rates with surgical excision of the primary tumour, however higher complications associated with lymph node extirpation (Bennett *et al.* 2002; Wouda *et al.* 2013; Potanas *et al.* 2015). Despite this, aggressive primary surgery remains the treatment of choice. In many cases, surgery alone is inadequate at controlling disease, with 20-50% of dogs showing evidence of local recurrence following surgery as a sole therapy (Ross *et al.* 1991; Bennett *et al.* 2002; Emms 2005; Aronson 2012; Wouda *et al.* 2013). Recurrence rates are thought to be higher following marginal resections (Ross *et al.* 1991; Bennett *et al.* 2002; Turek & Withrow 2013).

### **Adjunctive Therapy**

To prevent local recurrence and metastasis, adjunctive therapy is recommended after surgical excision for treatment of ASA (Turek *et al.* 2003; Emms 2005; Polton & Brearley 2007; Wouda *et al.* 2013).

Many different chemotherapeutic agents have been trialled in conjunction with surgery, such as carboplatin, doxorubicin, epirubicin, mitoxantrone and melphalan (Bennett *et al.* 2002; Williams *et al.* 2003; Turek *et al.* 2003; Emms 2005; Polton & Brearley 2007). The lack of standardisation in these studies makes it difficult to compare individual chemotherapy protocols directly, but no specific protocol has been proven to give superior median survival times. It is generally agreed that chemotherapy is of benefit when it follows surgical removal of gross disease (Bennett *et al.* 2002; Williams *et al.* 2003; Emms 2005; Polton & Brearley 2007), with median survival times of surgery and adjunctive chemotherapy exceeding those historical reports of surgery alone (Bennett *et al.* 2002; Emms 2005). Recently, however, a study by Wouda *et al.* (2013) directly compared surgery alone to surgery and adjunct carboplatin and found no statistical difference in time to disease progression or overall survival time between these two groups. It is clear that further studies into adjunct therapy, with adequate cohort numbers, are needed to determine the optimal adjunct therapy to surgery.

The use of chemotherapy would seem to have most potential benefit in those individuals with lymph node involvement (Bennett *et al.* 2002; Polton & Brearley 2007) and chemotherapy is frequently used in individuals who have more advanced or obvious metastatic disease. The presence of metastatic disease, however, substantially reduces median survival time (Ross *et al.* 1991) and this selection bias for adjunctive therapy leads to difficulty in data comparison.

In addition to conventional chemotherapeutics, the new tyrosine kinase inhibitor, toceranib phosphate (Palladia), has also been used to treat anal sac adenocarcinomas, since these tumours express platelet derived growth factor receptor beta (PDGFR-B) which toceranib may target, in addition to c-Kit (Brown *et al.* 2012). In 87.5% of cases, which had already failed other therapies, Palladia demonstrated clinical benefit, used off-licence and at standard doses (London *et al.* 2012). None of the dogs in this study, however, achieved complete remission. The addition of local radiotherapy to surgery and

adjunctive chemotherapy may be beneficial. Turek *et al.* (2003) used curative-intent radiotherapy in combination with mitoxantrone after surgical removal of the primary tumour (Turek *et al.* 2003), a protocol which appeared both well tolerated and successful at extending median survival time. In this study, however, none of the cohort had evidence of distant metastases, which may account for the overall high median survival time.

### **Management of Hypercalcaemia**

If the primary tumour and metastases are removed successfully, paraneoplastic hypercalcaemia should resolve quickly. Whilst waiting for surgery, short-term management of the hypercalcaemia can be achieved with fluid therapy, loop diuretics or prednisolone. If removal of the primary tumour and metastases is not possible and gross disease remains, the hypercalcaemia can be managed more effectively long-term with bisphosphonates such as pamidronate or zoledronate.

### **Palliative Care**

Palliative care is often discussed in animals where aggressive surgery is not possible, due to age, co-morbidities or financial constraints. It centres around managing clinical signs, particular faecal tenesmus, using laxatives, stool softeners and pain relief as necessary. Hypercalcaemia will also need to be managed to prevent renal problems.

### **Prognosis**

Median survival times for patients with ASA differ hugely depending on study date, presenting signs and treatment options, however in most studies they range from six to 22 months (Ross *et al.* 1991; Bennett *et al.* 2002; Turek *et al.* 2003; Emms 2005; Polton & Brearley 2007; Wouda *et al.* 2013). In most cases, euthanasia or death was due to physical tumour progression or related clinical signs, which affected quality of life (Bennett *et al.* 2002; Wouda *et al.* 2013; Potanas *et al.* 2015).

There is little consensus regarding prognostic factors; however, tumour stage appears to be important. The tumour staging system (stages 1-4) used by Polton *et al.* (2007) is useful to predict overall survival time, a higher stage indicative of a shorter median survival.

Primary tumour size may also be significant, with tumours >10cm resulting in decreased survival times (Williams *et al.* 2003; Polton & Brearley 2007). The presence of lymph node metastasis (Polton & Brearley 2007; Potanas *et al.* 2015) is a negative prognostic indicator in some studies, however this was not the case in all (Williams *et al.* 2003; Emms 2005). There is a general consensus that the presence of distant metastases, particularly to the lungs, is a poor prognostic factor and results in shorter median survival times (Williams *et al.* 2003; Emms 2005; Polton & Brearley 2007).

There has also been much debate about the presence of hypercalcaemia as a negative indicator. Early studies (Ross *et al.* 1991; Williams *et al.* 2003; Hobson *et al.* 2006) show that hypercalcaemia was linked to reduced overall median survival times, however this has not been found in more recent studies

(Bennett *et al.* 2002; Emms 2005; Polton & Brearley 2007; Wouda *et al.* 2013).

The other widely accepted poor prognostic factor is lack of treatment, particularly lack of surgery (Williams *et al.* 2003; Polton & Brearley 2007), with longest median survival times being achieved in dogs who receive multimodal therapy (Wouda *et al.* 2013). Interestingly, a study by Bennet *et al.* (2002) shows comparable median survival times in dogs receiving piroxicam as a palliative therapy (8.7 months), to those who had surgery alone (7.9 months), indicating that surgery is not necessarily the answer in every case.

### Conclusion

Anal sac adenocarcinoma is a highly metastatic cancer which can present in a variety of ways; as such, rectal examination should be part of every thorough clinical examination. Early detection, aggressive surgery and adjunctive therapy are recommended as gold standard treatment. Median survival times can vary dramatically but if detected early, good disease control can be achieved for a significant length of time.

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