ORIGINAL ARTICLE

Histopathological diagnosis and surgical complications following bilateral anal sacculectomy for the treatment of unilateral canine apocrine gland anal sac adenocarcinoma: 35 cases (2019-2023)

A. Franca, P. Stamenova and J. L. Thompson

Department of Small Animal Surgery, The Royal Dick School of Veterinary Studies, Edinburgh, Scotland

[1]Corresponding author email: jamie-leigh.thompson@hotmail.co.uk

Objectives: To report the histopathological diagnosis of both anal sacs in dogs undergoing bilateral anal sacculectomy for the treatment of unilateral apocrine gland anal sac adenocarcinoma and to compare the surgical complication rate associated with this procedure in this population with previously published literature.

Materials and Methods: Records were retrospectively reviewed for dogs that underwent bilateral anal sacculectomy for the treatment of apparently unilateral apocrine gland anal sac adenocarcinoma, at a single institute between 2019 and 2023. Clinical staging, surgical treatment, histological findings, intra- and postoperative complications were evaluated.

Results: Thirty-five dogs were included. Only five of 35 (14%) dogs were found to have histologically normal contralateral anal sacs. Non-neoplastic anal sac disease was found in 23 of 35 (66%) dogs and bilateral apocrine gland anal sac adenocarcinoma was seen in seven of 35 (20%) dogs. None of the dogs diagnosed with bilateral neoplasia had evidence of bilateral neoplasia before surgery despite a thorough work-up. Complications attributable to the primary tumour removal were seen in 9% of dogs intraoperatively and 14% of dogs postoperatively, commonly tumour capsule disruption and surgical site infection, respectively.

Clinical Significance: Bilateral anal sac disease was diagnosed histologically in the majority of presumed normal anal sacs, with 20% of cases being found to have bilateral apocrine gland anal sac adenocarcinoma. The surgical complication rates of this cohort were comparable to those reported for unilateral anal sacculectomy alone. These findings promote and encourage the use of bilateral anal sacculectomy in cases of suspected unilateral anal sac neoplasia.

Journal of Small Animal Practice (2024); **65,** 394–401
DOI: 10.1111/jsap.13731

Accepted: 27 March 2024; Published online: 9 April 2024

INTRODUCTION

Apocrine gland anal sac adenocarcinoma (AGASACA) is a malignant epithelial tumour, arising from the anal sacs and representing around 17% of all perineal neoplasms and 2% of all skin and subcutaneous neoplasms in dogs (Berrocal et al., 1989; Goldschmidt & Zoltowski, 1981). These tumours are reported to be incidentally identified through rectal palpation in 47% of cases but dogs presenting with clinical signs often demonstrate perineal swelling, hematochezia, scooting, pain, weight loss, lethargy, tenesmus, constipation and occasionally, polyuria and polydipsia (Bennett et al., 2002; Mickelson, 2022). AGASACA has a characteristic cytological appearance, allowing presumptive diagnosis to be made with aspiration and cytology in the majority of cases; however, histopathology remains pertinent for definitive diagnosis (Skorupski et al., 2018). Clinical staging following diagnosis comprises a comprehensive haematology and biochemistry profile, ionised calcium, urinalysis with abdominal and thoracic imaging (Dobson & Lascelles, 2011). Computerised tomography is accepted as the gold-standard diagnostic imaging modality as it allows thorough characterisation of the primary lesion, aiding surgical planning, as well as being highly sensitive for identifying metastasis (Palladino et al., 2016). Surgical resection of the primary tumour and the associated anal sac through a para-anal surgical approach is the most effective way of reducing the local disease burden in affected cases, often resulting in palliation of clinical signs (Hobson et al., 2006). Histological analysis of all resected tissue is considered standard of care and is paramount in confirming the diagnosis and allowing clinicians to formulate realistic, evidence-based treatment plans with owners (Wong et al., 2021). Given the close anatomical proximity of the anal sacs to the rectum and other vital structures such as the caudal rectal nerves, surgical margins are seldom achievable and thus, adjunctive therapy following first-line surgical intervention should be recommended in most dogs to prolong overall survival times (Emms, 2005). The prevalence of local and distant metastasis at the time of AGASACA diagnosis has been reported to be as high as 79% (Bennett et al., 2002). More commonly the medial iliac, sacral and internal iliac (locoregional) lymph nodes are implicated, which is presumed to be resultant of local lymphatic drainage (Bennett et al., 2002; Emms, 2005; Goldschmidt & Zoltowski, 1981). The presence of gross metastatic disease at the time of diagnosis has been associated with reduced median survival times, especially if metastasis is identified outwith the iliosacral lymph node centre and is a negative prognostic indicator (Morello et al., 2021). However, the surgical extirpation of those metastatic locoregional lymph nodes has been shown to improve survival times in affected patients (Hobson et al., 2006). Surgical complications associated with AGASACA resection are reported to occur intraoperatively in up to 18% of cases and postoperative in up to 38% of cases, with more severe complications typically being associated with locally aggressive, larger primary masses (Huerta et al., 2022; Tanis et al., 2022). Intraoperative complications may include disruption of the tumour capsule, anorectal perforation, haemorrhage and the creation of a pelvic diaphragm defect resulting in perineal herniation (Griffin et al., 2023; Sterman et al., 2021). Postoperative complications vary in severity and include faecal incontinence, tenesmus, haematochezia, surgical site dehiscence or infection, rectocutaneous fistula formation and perineal fistula (Griffin et al., 2023; Tanis et al., 2022). The intraoperative surgical complication rate increases to roughly 26% when metastatic iliosacral lymphadenectomy is concurrently performed, with haemorrhage being more commonly encountered and the risk of haemorrhage being correlated with size of the node to be extirpated (Huerta et al., 2022). The Clavien-Dindo surgical complication grading system is validated and frequently used to evaluate and compare surgical outcomes among different surgeons, centres and therapies. This system is reliable, reproducible, and logical, and has been used in published studies reviewing the postoperative complications seen following AGASACA surgery (Charlesworth, 2014; Dindo et al., 2004; Sterman et al., 2021). The presence of bilateral AGASACA at initial presentation has been documented in 7–10% of dogs and a single published case series demonstrates temporally separated AGASACA development in four cases (Bowlt et al., 2013; Emms, 2005; Liptak et al., 2020; Ross et al., 1991). Despite this, the current practice and recommendation is to perform a unilateral anal sacculectomy for clinically unilateral anal sac masses in combination with abdominal lymph node extirpation if lymph node enlargement is present, as bilateral anal sacculectomy may increase the postoperative complication rate (Culp et al., 2022; Repasy et al., 2022). Despite this, some institutes are routinely performing bilateral anal sacculectomy in animals that present with clinically unilateral disease with the reasoning that a percentage of affected animals may have undiagnosed bilateral anal sac disease or that bilateral anal sac removal may anecdotally be prophylactic for the development of temporally separated bilateral AGASACA. This is debatable and some surgeons may argue that in the absence of known disease in the contralateral anal sac, performing a bilateral anal sacculectomy may subject the patient to an increased "surgical dose" subsequently increasing the potential complication rate (Repasy et al., 2022). Non-neoplastic anal sac disease (NASD), including anal sacculitis and recurrent impaction, is commonly seen in veterinary practice and is typically a bilateral problem (Lundberg et al., 2022; O'Neill et al., 2021). A recognised treatment option for recurrent or end-stage disease is bilateral anal sacculectomy and evidence suggests that the procedure is well tolerated in these cases with low reported complication rates (Charlesworth, 2014).

Anecdotally, the authors perceive that the contralateral (non-cancerous) anal sacs removed in patients with unilateral AGASACA are often found to have histological evidence of disease and that the surgical procedure is associated with a low complication rate, comparable to that published for unilateral AGASACA surgery alone, which could advocate the use of bilateral anal sacculectomy for unilateral AGASACA in canine patients going forward. Therefore, the aims of this study were twofold. Firstly, to report the histological diagnosis of both anal sacs removed from dogs with presumed unilateral AGASACA and secondly, to report the frequency and type of surgical complications encountered in this population undergoing bilateral anal sacculectomy.

MATERIALS AND METHODS

Study design and inclusion criteria

The medical record database (PROVETCloud™) for the Hospital for Small Animals at The Royal (Dick) School of Veterinary Studies was retrospectively reviewed for client-owned dogs undergoing anal sacculectomy for neoplastic anal sac disease between May 1, 2019 and August 1, 2023. Two independent investigators searched the database using the keywords "anal sacculectomy," "anal sac" and "apocrine gland anal sac adenocarcinoma." Additionally, surgeon case logs were reviewed using the same keywords and the results combined.

To be included in the study population, cases must have undergone bilateral anal sacculectomy for presumed unilateral AGASACA and cases needed to possess complete medical records including complete surgical reports, a histological diagnosis of AGASACA in at least one anal sac and veterinary follow-up to a minimum of 3 months. Cases were excluded if there was a preoperative presumptive diagnosis of bilateral AGASACA, incomplete surgical report, absence of a histopathological diagnosis of AGASACA in at least one anal sac or if surgery was performed for recurrent disease only. Data collected included signalment, bodyweight, presenting complaint and clinical signs, physical exam findings including a complete rectal examination, mode of detection of the primary tumour, size of primary tumour, diagnostic investigations performed and clinical stage, surgical details including any additional surgical procedures, histopathological analysis of both anal sacs, details of intra- and postoperative complications, subsequent treatment required and follow-up. This research work received ethical approval from The Royal (Dick) School of Veterinary Studies Institutional Review Board, reference 56.23.

Clinical staging and treatment protocols

All patients presenting with AGASACA were clinically staged using the system described by Polton and Brearley (2007) (Table 1). As part of the staging process, all patients underwent a comprehensive haematology and serum biochemistry analysis, ionised calcium assessment, abdominal (ultrasound or CT) and thoracic imaging (radiography or CT) and cytology of the presenting anal sac mass. All imaging performed of the abdomen included the perineum and anal sacs. In the absence of evident locoregional lymph node enlargement (>0.5 cm diameter) or deformity (altered shape or echogenicity) or distant lesions suggestive of metastatic disease, patients were treated with surgical excision of the anal sacs alone. Surgery involved resection of primary tumour and associated anal sac on one side combined with resection of the contralateral clinically non-cancerous anal sac (bilateral anal sacculectomy); both anal sacs were submitted independently for histopathological analysis. When metastasis to the locoregional lymph nodes was suspected, lymph node extirpation was recommended. When extirpation was performed samples were also submitted for histopathological analysis. All samples were reported by a board-certified clinical pathologist or by a resident in clinical pathology working under the direction of a board-certified pathologist. The primary tumour size was determined from either the physical examination, imaging or histopathology measurements. The imaging measurements were used as the default measurement if there were multiple measurements recorded through different modalities. All CT, abdominal ultrasound and thoracic radiographs images were reviewed by a board-certified radiologist or by a resident under the supervision of a board-certified radiologist.

Table 1. Clinical stage scheme recommendation for canine anal sac gland carcinoma (Polton & Brearley, 2007)

Clinical stage	Tumour (T)	Nodes (N)	Metastasis (M)
Stage I	≤2.5 cm max diameter (T0)	None (N0)	None (M0)
Stage II	>2.5 cm max diameter (T1)	None (N0)	None (M0)
Stage IIIa	Any T	Present ≤4.5 cm max diameter (N1)	None (M0)
Stage IIIb	Any T	Present >4.5 cm max diameter (N2)	None (M0)
Stage IV	Any T	Any N	Present (M1)

Surgical technique

Routine closed or open bilateral anal sacculectomy was performed at the operating surgeon's discretion (Tobias & Johnston, 2018). All the patients were placed in sternal recumbency, with the tail reflected cranially over the dorsum and secured. Faeces were manually evacuated from the rectum and gauze sponges were placed into the rectum as part of the hospital's standard surgical preparation protocol, to reduce potential contamination during surgery. The perineal area was routinely clipped and prepared before surgery using a 2% chlorhexidine gluconate and 70% isopropyl alcohol combination. During surgery, the anal sacs were probed with a Spruells needle or filled with suture material to allow identification of anal sac position before a curvilinear paraanal skin incision was made over the base of each anal sac. The non-cancerous anal sac was firstly carefully dissected away from surrounding external anal sphincter musculature, ligated and transected at the level of the duct and removed and the surgical site was closed routinely. In AGASACA cases, the anal sac and mass were then carefully dissected from the external anal sphincter muscle and any surrounding adhesions through the second para-anal skin incision before being ligated and transected at the level of the duct and being closed routinely. All masses were able to be freed from associated musculature, without the need for significant muscular reconstruction. Incisions were routinely closed with polydioxanone (PDS™) in the muscle layers using a continuous pattern, poliglecaprone 25 (Monocryl™) in the subcutaneous layer using a continuous pattern, and poliglecaprone 25 (Monocryl™) in the skin using an intradermal pattern or nylon (Ethilon™) in a simple interrupted pattern or a combination of both at the operating surgeon's discretion. Skin sealant was applied at the surgeon's discretion.

For cases in which abdominal lymph node extirpation was performed, the abdomen was also clipped and aseptically prepared. Dogs were firstly positioned in dorsal recumbency, and lymph node extirpation performed through a midline celiotomy

before routine abdominal closure and repositioning for anal sacculectomy as described above.

Outcome and follow-up

The presence and details of any intraoperative complications were documented, and postoperative complications were classified retrospectively using the Clavien-Dindo 5-grade system as detailed in Table 2, whereby any deviation from the normal postoperative course was classed as a complication. Sequela, defined as an "after effect(s)" that are inherent to the procedure being performed were also reported (Sterman et al., 2021). Routine follow-up clinical assessments were performed at 10 to 14 days postoperatively, either at the operating institute or at the referring veterinary clinic. Details on any additional follow-ups required were obtained from medical records. The presence and duration of postoperative alterations such as tenesmus, faecal incontinence or dyschezia and required medical treatment were reported. If appropriate, adjunct treatment and longer-term ongoing staging were discussed with the owners on receipt of the histopathology results and were undertaken as necessary but the detail of further treatment is outside the scope of this paper. Current General Data Protection Regulations (GDPR) were fully complied with.

Statistical analysis

Continuous data was assessed for normality using the Shapiro–Wilk test using commercially available software (SPSS Statistics, IBM, New York, USA). Normally distributed data sets were reported as mean ±standard deviation (sd). Non-normally distributed data sets were reported as median and range (minimum and maximum). Categorical data were reported as number (n) and/or percentage (%). Descriptive statistics were performed using the same software. Further statistical analysis was not performed due to low case numbers.

RESULTS

One hundred and twenty-nine dogs were presented to the Hospital for Small Animals at The Royal (Dick) School of Veterinary Studies for suspected AGASACA during the study period. Of these, 70 were excluded due to owners declining surgical treatment following identification of any metastatic disease at the time of presentation. Of the remaining cases, a further 24 cases were excluded for the following reasons: unilateral anal sacculectomy performed (n=7), lack of histopathology report (n=5), histopathological diagnosis of a perineal hepatoid gland carcinoma (n=3), histopathological diagnosis of bilateral sacculitis only (n=3), incomplete surgical report (n=2), resection of recurrent disease (n=2) and preoperative diagnosis of bilateral AGASACA (n=2). A cohort of 35 dogs that satisfied the inclusion criteria was selected for use in this study.

Table 2. The Clavien-Dindo grading system for surgical complications (Dindo et al., 2004)

Grade	Description
1	Any deviation from the normal postoperative course without the need for pharmacological treatment (other than analgesics, antipyretics, antiemetics and antidiarrheals) or surgical, endoscopic or radiological intervention
2	Requiring pharmacological treatment with drugs other than those allowed for grade 1 complications
3	Requiring surgical, endoscopic or radiological intervention: 3a. Intervention not performed under general anaesthesia 3b. Intervention requiring general anaesthesia
4	Life-threatening complication requiring ICU management: 3a. Single organ dysfunction 3b. Multi-organ dysfunction
5	Death of a patient

Signalment

Breeds distribution included Labrador retriever (n=10), English cocker spaniel (n=7), cross bred (n=5), springer spaniel (n=4), Staffordshire bull terrier (n=2) and one of each of Rhodesian Ridgeback, Spanish Water Dog, German shepherd dog, golden retriever, boxer, Border Collie and Border terrier. Twenty-one of the included dogs were male (19 of which were neutered) and 14 were female (12 of which were neutered) and the mean age at the time of the first surgery was 9 years and 3 months (±1 year 8 months). Mean weight of the study population was 25.8 kg (±10.7 kg).

Presenting signs and clinical staging

Presenting complaints were incidental palpation of anal sac mass during clinical exam for other presenting disease (n=14), scooting (n=5), tenesmus (n=3), polyuria and polydipsia (n=3), haematochezia (n=3), incidental finding on abdominal imaging (n=2), anal gland infection (n=1), epistaxis (n=1), cough (n=1), weight loss (n=1) and lethargy (n=1). A primary (unilateral) mass lesion was palpable through rectal examination in 35 cases but was first incidentally detected with CT in three of these cases undergoing investigations for other disease processes. The contralateral anal sac was normal on palpation in all cases. The median size of the primary tumour was 2.1 cm (range 0.4 to 6.5 cm). Clinical staging was achieved with CT of the thorax and abdomen in 27 dogs and a combination of thoracic radiography and abdominal ultrasonography in eight dogs. Clinical stage was assigned to all cases; 10 cases were assigned to stage I disease, eight cases to stage II, 16 cases to stage IIIa and one case to stage IIIb. No cases included in this study had evidence of distant metastases. Investigations did not reveal evidence of contralateral anal sac disease in any dog. Additionally, at the time of presentation for surgery, six cases had paraneoplastic hypercalcaemia (defined for the study as ionised calcium >1.4 mmol/L) and these cases were categorised as clinical stage II or IIIa and the remaining 29 cases were normocalcaemic before surgery.

Surgery and histological diagnosis

Removal of all presumed neoplastic anal sacs was achieved using a closed sacculectomy technique. The presumed normal anal sacs were removed with an open sacculectomy technique in three dogs and a closed technique in 31 dogs and the technique was not clearly specified in one dog. Bilateral anal sacculectomy alone was performed in 20 dogs, bilateral sacculectomy plus abdominal lymphadenectomy *via* a celiotomy was performed in 12 dogs,

and a secondary procedure unrelated to the primary disease was performed alongside bilateral anal sacculectomy in three dogs. One dog underwent three surgical procedures which included bilateral anal sacculectomy, abdominal lymphadenectomy and a procedure unrelated to the primary disease (liver biopsy). An average of three (range one to five) abdominal lymph nodes were removed from animals undergoing concurrent abdominal lymph node extirpation. All samples were submitted for histopathology. Four dogs with suspected metastatic disease did not undergo abdominal lymph node extirpation at the owner's discretion despite recommendations. All cases which did not undergo extirpation had a single lymph node enlarged and in all cases the lymph node was between 7 and 8 mm. The clinical records elude to the fact that three of these cases declined extirpation due to financial limitations.

Unilateral AGASACA was confirmed histologically in 28 cases (80%) and bilateral AGASACA in seven cases (20%). There was no evidence of bilateral AGASACA preoperatively in any of the cases diagnosed histologically with bilateral AGASACA. Of the cases diagnosed with unilateral AGASACA, the contralateral anal sacs were histologically normal in five cases (14%) and abnormal in 23 cases (66%). Of the abnormal anal sacs, anal sacculitis was found in 22 dogs and anal sac adenoma was found in one dog.

Complications and follow-up

Intraoperative complications in this study were seen relating to both abdominal and perineal surgery. The overall intraoperative complication rate was 14% (n=5); two of five dogs had mild intraoperative haemorrhage during abdominal lymph node dissection and three of five dogs had disruption of primary tumour capsule intraoperatively. Importantly, only 9% (n=3) of intraoperative complications were attributable to removal of the primary tumour with anal sacculectomy. Two intraoperative complications were seen concomitantly in one dog; disruption of primary tumour capsule and haemorrhage on abdominal lymph node dissection.

Postoperative sequelae were reported in 54% (n=19) of the animals and comprised of mild swelling at the perineal surgical site (n=5), self-limiting loose stools (n=5), mild erythema around the perineum (n=4), self-limiting haematochezia (n=2), persistent hypercalcaemia (n=1), self-limiting tenesmus (n=1) and transient faecal incontinence (n=1). Of these 19 cases, one case had an open anal sacculectomy performed and developed self-limiting loose stools postoperatively. The postoperative complication rate was 14% (n=5) and included surgical site infection in four of five dogs, and rectocutaneous fistula formation in one of five dogs. All postoperative complications occurred on the same side as the primary tumour. Surgical site infections were classified as such when an antibiotic course was prescribed by the attending surgeon and cases were subsequently classified as grade 2 using the Clavien-Dindo grading system. The case of persistent hypercalcaemia demonstrated a reduction in the ionised calcium postoperatively, while hospitalised and had normal calcium levels at reassessment 10 days later.

DISCUSSION

Based on a review of the relevant literature, the authors believe this is the first study to report the histological diagnosis of both anal sacs in dogs undergoing bilateral anal sacculectomy following the diagnosis of unilateral AGASACA. The objective was to report the incidence of contralateral anal sac disease in this cohort and to report the associated surgical complications and to compare these to the previous literature. Thirty-five cases met the criteria to be included in this study, with spaniel breeds (English and Springer) and the Labrador retriever being overrepresented in this cohort, in line with previous studies (Repasy et al., 2022; Sterman et al., 2021). Male dogs appeared to be overrepresented in this population, with 21 males and 14 females being included but this likely reflects the small study size and has not previously been reported in the literature. Again, congruous with previous studies the incidental identification of an anal sac mass was the most common means of tumour detection in the above cases, followed by patients presenting for scooting and tenesmus; the latter likely due to local irritation and the compressive mass-effect of the tumour on the rectal wall (Bennett et al., 2002; Goldschmidt & Zoltowski, 1981; Griffin et al., 2023; Tanis et al., 2022; Wong et al., 2021).

All dogs included in the present study had a comprehensive work-up performed which yielded no evidence of bilateral anal sac disease and despite this, histopathology identified bilateral neoplasia in 20% of these cases. Interestingly, Rossi et al. (2013) published on a small cohort of dogs with metastatic disease without the identification of a primary tumour. Among those cases was a dog presenting with iliac lymphadenopathy and hypercalcaemia, presumed to have AGASACA without an identifiable mass lesion despite comprehensive work up. After surgical removal of the enlarged lymph nodes and both anal sacs, the hypercalcaemia resolved, and the dog was believed to be in complete remission (Rossi et al., 2013). Although AGASACA was only presumed in this case, the inability to identify a primary anal sac tumour despite advanced imaging and physical assessment was alike these presented cases.

The diagnosis of bilateral AGASACA at the time of initial presentation has previously been historically described in up to 10% of the cases and one report presents four cases of temporally separated AGASACA (Bennett et al., 2002; Bowlt et al., 2013; Williams et al., 2003). A Veterinary Society of Surgical Oncology (VSSO) collaboration has enabled one of the largest dataset-focused canine AGASACA to be published online. The retrospective report refers to an 8.4% incidence of bilateral AGASACA with around half of those patients presenting with the contralateral anal sac tumour at a later stage, *i.e.* after initial treatment with a unilateral anal sacculectomy (Liptak et al., 2016). Previous suggestions that bilateral neoplasia may represent two independent tumours or may present as metastasis of a unilateral tumour have been sounded, but neither hypothesis has been confirmed. Although the current study did not aim elucidate the cause of bilateral anal sac neoplasia, it did reveal an alarming prevalence of incidental bilateral AGASACA.

Conventional unilateral surgical treatment would have left the contralateral neoplasm in the affected 20% of cases in situ, undiagnosed and that tumour may have become misdiagnosed as second tumour development at a later stage. These findings put previous reports of delayed bilateral tumour development under scrutiny and instead queries if early histological evidence of bilateral adenocarcinoma would have identified at initial presentation in the described cases, despite the lack of palpable or identifiable mass lesions.

Up to 32% of dogs with AGASACA are reported to demonstrate paraneoplastic hypercalcaemia on presentation (Bennett et al., 2002; Huerta et al., 2022; Williams et al., 2003). This is a more frequent finding than the above population whereby only a 17% incidence was found. Study size will inevitably impact this finding; however, it could also be influenced by the exclusion of many cases with metastatic disease for which owners declined surgery or with known bilateral disease which did not fit the inclusion criteria for this study. It is possible that the overall incidence of paraneoplastic hypercalcaemia would have been higher and more in line with previous literature when combining all cases presented during the study time. Very few reports describe persistent hypercalcaemia following conventional surgical treatment with primary tumour removal *via* a unilateral anal sacculectomy with or without metastatic lymph node extirpation. This is interesting, as the present results suggest that up to 20% of dogs may have contralateral neoplasia left in situ after undergoing this surgical treatment. The authors question whether the size of the primary tumour or metastatic lymph node may correlate with the presence of paraneoplastic hypercalcaemia given the tumour itself is responsible for the release of parathyroid-related protein (PTHrP) consequently increasing serum calcium. This theory may explain why dogs without a palpable contralateral mass but with histological bilateral neoplastic disease may be less likely to demonstrate a persistent hypercalcaemia of malignancy. Additionally, dogs included in this cohort with hypercalcaemia were all clinical stage II or above. A large proportion of cases with metastatic disease were excluded in line with the inclusion criteria and this could have also artificially lowered the incidence of hypercalcaemia in the usable cohort or consequently the complication rate.

NASD, most commonly anal sacculitis, was diagnosed in 66% of contralateral anal sacs in this cohort. NASD can be a difficult and expensive condition to manage in practice, with frequent veterinary visits, rectal examinations, manual expressions and anal sac irrigations being commonplace in the conservative treatment protocol (O'Neill et al., 2021). Failure of medical management is not uncommon and curative-intent surgery is consequently sought by means of bilateral anal sacculectomy without lasting impact on the patient. It is difficult to determine if the presenting clinical signs (*e.g.* scooting and tenesmus) in some animals were primarily related to undiagnosed NASD or primary AGASACA. However, the authors believe that with two thirds of contralateral anal sacs having histological evidence of NASD, further justification is provided to perform bilateral anal sacculectomy as a first-line surgical treatment for AGASACA. Researchers have previously attempted to link inflammatory anal sac disease to the neoplastic transformation of cells in AGASACA, due to cyclo-oxygenase 2 being found to be expressed in both disease processes' and although this is not proven and remains disputed, the concept provides greater support of bilateral sacculectomy in these cases (Knudsen et al., 2013).

An overall intraoperative complication rate of 14% was seen in the above cases, with a 9% rate for complications solely related to primary tumour resection. Griffin et al. (2023) recently published similar findings whereby an overall intraoperative complication rate of 18% was found with 14% being related to the primary tumour site. Despite similar findings, direct comparison between previous and present studies poses difficulty given a lack of standardisation of the term "complication" within the literature and varying complication classification systems being utilised (Follette et al., 2019). A more direct comparison can be made with the Sterman et al. (2021) paper which found an overall intraoperative complication rate of 9% with 7% being related to anal sac surgery site with rectal wall perforation being the most frequently encountered. Interestingly, despite similar primary tumour sizes, no cases of anorectal perforation were reported in this study which may be a result of a much smaller sample size or influenced by the retrospective nature of this study. The Clavien-Dindo classification scheme was used by this group to define postoperative complications and they reported sequela and complications separately, on the basis that sequela are expected and self-limiting known after effects of a surgery. They found a postoperative sequela and complication rate of 14% and 17%, respectively. To promote standardisation in surgical outcome reporting, the same definitions were adopted in the present retrospective review, hopefully allowing comparability between similar studies going forward. Although the postoperative complication rate was similar, postoperative sequela were far more commonly encountered in the above cohort. This is likely influenced by smaller sample sizes described in combination with a lack of standardisation in previous clinical notes given the retrospective design of both studies. It is possible that accepted sequale or anticipated "after effects" of a surgery could be underreported in previous studies given their anticipated and benign nature. The aforementioned study by Griffin et al. used the Accordion grading scheme to report postoperative complication and found a significantly higher overall postoperative complication rate of 36% in their population, mostly relating to the anal sacculectomy site. Similarly, the Charlesworth (2014) study reviewing the postoperative complication rates following bilateral anal sacculectomy for NASD found that 32% of cases had postoperative complications. Postoperative sequela, or "after effects," were not reviewed in either of these papers and instead have been incorporated into the complication rates. Subsequently, both reports are believed to demonstrate an artificially increased overall postoperative complication rate compared to the present study and the use of postoperative sequela. Postoperative sequela accounted for 54% in our cases which is higher than previous reports and although the juxtaposition of this data to other studies remains challenging and results may also be influenced by the inherent subjectivity of reporting signs such as "swelling" and "erythema" in gradations such as "mild" and "moderate" between clinicians. Surgical site infection was the most common postoperative complication in the

above cases which is comparable with previous literature (Sterman et al., 2021). Iatrogenic anal sac and duct penetration during dissection and open anal sacculectomy techniques are suggested to result in an increased incidence of postoperative complications and surgical site infection (Hill & Smeak, 2002). An open technique was performed for removal of the apparently normal anal sac in three of 35 cases here, at the operating surgeon's discretion, and none of these dogs, nor the dogs that had iatrogenic disruption of the tumour capsule developed a postoperative surgical site infection or tumour recurrence within the 3-month follow-up window. This is interesting to note but the small numbers utilised fundamentally increase the risk of type 1 errors, limiting the conclusions that can be made from this.

The overall intra- and postoperative surgical complication rates reported in this study are in line with previous literature, refuting the theory that bilateral sacculectomy for unilateral AGASACA would be associated with increased patient morbidity compared to the unilateral procedure (Liptak et al., 2016; Sterman et al., 2021). Moreover, the incidence of bilateral disease, especially neoplasia, supports the use of bilateral sacculectomy for unilateral AGASACA. AGASACA is accepted as a surgical condition with adjuvant therapy and repeat staging commonly being recommended in the months following surgery (Chambers et al., 2020). Despite this, one group found that only 21% of owners were adherent to staging recommendations and 34% of owners were adherent with further treatment recommendations following initial surgery. Several factors can have an impact on pet owners' decisions to pursue ongoing treatment such as cost, other disease morbidity and travel to referral hospitals but the authors speculate that bilateral anal sacculectomy may serve to reduce or remove any unidentified cancer burden and may even act as prophylaxis in cases with failed follow up. This could ultimately impact the patient's survival, although further investigations would be warranted to support this suggestion.

Main limitations of the study relate to its retrospective nature, small sample size and lack of long-term follow-up. Few cases were excluded due to incomplete clinical records subsequently, reducing the usable population and some usable cases had different treatments performed (*i.e.* different imaging modalities or surgical approaches) impacting overall case standardisation. Selection bias must also be considered as all cases included in the study presented to a referral academic institution to pursue treatment after initial diagnosis and some cases may have been filtered at first-opinion level. Seventy cases were excluded due to the presence of metastatic disease and the owners consequently declining surgery. This was inclusive of cases with locoregional and/or distant metastasis. These numbers appear to be in keeping with previous literature showing 50% to 80% of cases having metastasis at the time of presentation but was not further defined as part of this study (Bennett et al., 2002; Liptak et al., 2016). Few institutes are routinely performing bilateral anal sacculectomy for the treatment of unilateral AGASACA; however, a large multicentre prospective study would be beneficial in investigating the true incidence of incidental bilateral AGASACA and determining the consequences of this phenomenon.

Author contributions

Adriana Franca: Data curation (equal); investigation (equal); writing – original draft (lead); writing – review and editing (equal). **Polina Stamenova:** Data curation (supporting); investigation (equal). **Jamie Leigh Thompson:** Conceptualization (lead); data curation (lead); formal analysis (lead); investigation (equal); methodology (lead); project administration (lead); supervision (lead); writing – original draft (equal); writing – review and editing (equal).

Conflict of interest

None of the authors of this article has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

Bennett, P.F., DeNicola, D., Bonney, P., Glickman, N.W. & Knapp, D.W. (2002) Canine anal sac adenocarcinomas: clinical presentation and response to therapy. *Journal of Veterinary Internal Medicine*, **16**, 100–104.

Berrocal, A., Van Den Ingh, T.S.G.A.M., Molenbeek, R.F. & van Sluijs, F.J. (1989) Canine perineal Tumours. *Journal of Veterinary Medicine Series A*, **36**, 739–749.

Bowlt, K.L., Friend, E.J., Delisser, P., Murphy, S. & Polton, G. (2013) Temporally separated bilateral anal sac gland carcinomas in four dogs. *Journal of Small Animal Practice*, **54**, 432–436.

Chambers, A.R., Skinner, O.T., Mickelson, M.A., Schlag, A.N., Butler, J.R., Wallace, M.L. et al. (2020) Adherence to follow-up recommendations for dogs with apocrine gland anal sac adenocarcinoma: a multicentre retrospective study. *Veterinary and Comparative Oncology*, **18**, 683–688.

Charlesworth, T.M. (2014) Risk factors for postoperative complications following bilateral closed anal sacculectomy in the dog. *Journal of Small Animal Practice*, **55**, 350–354.

Culp, W.T.B., Cavanaugh, R.P., Calfee, E.F., III, Buracco, P. & Banks, T.A. (2022) Alimentary tract. In: Kudning, S.T. & Seguin, B. (Eds.) Veterinary surgical oncology, 2nd edition. Chichester: Wiley Blackwell, pp. 265–392.

Dindo, D., Demartines, N. & Clavien, P.A. (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Annals of Surgery*, **240**, 205–213.

Dobson, J.M. & Lascelles, B.D. (2011) BSAVA manual of canine and feline oncology, 3rd edition. Cheltenham: British Small Animal Veterinary Association, pp. 223–228.

Emms, S.G. (2005) Anal sac tumours of the dog and their response to cytoreductive surgery and chemotherapy. *Australian Veterinary Journal*, **83**, 340–343.

Follette, C.M., Giuffrida, M.A., Balsa, I.M., Culp, W.T.N., Mayhew, P.D., Oblak, M.L. et al. (2019) A systematic review of criteria used to report complications in soft tissue and oncologic surgical clinical research studies in dogs and cats. *Veterinary Surgery*, **49**, 61–69.

Goldschmidt, M.H. & Zoltowski, C. (1981) Anal sac gland adenocarcinoma in the dog: 14 cases. *Journal of Small Animal Practice*, **22**, 119–128.

Griffin, M.A., Mayhew, P.D., Culp, W.T.N., Giuffrida, M.A., Telek, S., Singh, A. et al. (2023) Short- and long-term outcomes associated with anal sacculectomy in dogs with massive apocrine gland anal sac adenocarcinoma. *Journal of the American Veterinary Medical Association*, **261**, 1–8.

Hill, L.N. & Smeak, D.D. (2002) Open versus closed bilateral anal sacculectomy for treatment of non-neoplastic anal sac disease in dogs: 95 cases (1969–1994). *Journal of the American Veterinary Medical Association*, **221**, 662–665.

Hobson, H.P., Brown, M.R. & Rogers, K.S. (2006) Surgery of metastatic anal sac adenocarcinoma in five dogs. *Veterinary Surgery*, **35**, 267–270.

Huerta, Y., Selmic, L.E., MacGrath, A., Skinner, O.T., Dark, K.V., Traverson, M. et al. (2022) Complications associated with iliosacral lymphadenectomy in dogs with metastatic apocrine gland anal sac adenocarcinoma. *The Canadian Veterinary Journal*, **63**, 929–934.

Knudsen, C.S., Williams, A., Brearley, M.J. & Demetriou, J.L. (2013) Cox-2 expression in canine anal sac adenocarcinomas and in non-neoplastic canine anal sacs. *The Veterinary Journal*, **197**, 782–787.

Liptak, J., Selmic, L., Amdellem, P., Annoni, M., Bacon, N., Berg, J. et al. (2016) Apocrine Gland Anal Sac Adenocarcinoma and Submlumbar Lymph Node Metastasis: A VSSO Retrospective Study. Available at: http://www.vssoc.com/wp-content/uploads/2019/06/ACVS-AAGASAC-lecture-PP-Updated.pdf [Accessed 5th September 2023]

Liptak, J.M., Thamm, D.H. & Vail, D.M. (2020) Cancer of the gastrointestinal tract. In: Withrow & Macewen's small animal clinical oncology, 6th edition. Edinburgh: Elsevier, pp. 432–491.

Lundberg, A., Koch, S.N. & Torres, S.M.F. (2022) Local treatment for canine anal sacculitis: a retrospective study of 33 dogs. *Veterinary Dermatology*, **33**, 426–434.

Mickelson, M.A. (2022) Updated concepts in oncologic surgery: apocrine gland anal sac adenocarcinoma and mast cell tumors. *Veterinary Clinics of North America. Small Animal Practice*, **52**, 549–580.

Morello, E.M., Cino, M., Glacobino, D., Nicoletti, A., Iussich, S., Buracco, P. et al. (2021) Prognostic value of ki67 and other clinical and histopathological factors in canine apocrine gland anal sac adenocarcinoma. *Animals*, **11**, 1649.

O'Neill, D.G., Hendricks, A., Phillips, J.A., Brodbelt, D.C., Church, D.B. & Loeffler, A. (2021) Non-neoplastic anal sac disorders in UK dogs: epidemiology and management aspects of a research-neglected syndrome. *Veterinary Record*, **189**, e203.

Palladino, S., Keyerleber, M.A., King, R.G. & Burgess, K.E. (2016) Utility of computed tomography versus abdominal ultrasound examination to identify iliosacral lymphadenomegaly in dogs with apocrine gland adenocarcinoma of the anal sac. *Journal of Veterinary Internal Medicine*, **30**, 1858–1863.

Polton, G.A. & Brearley, M.J. (2007) Clinical stage, therapy, and prognosis in canine anal sac gland carcinoma. *Journal of Veterinary Internal Medicine*, **21**, 274–280.

Repasy, A.B., Selmic, L.E. & Kisseberth, W.C. (2022) Canine apocrine gland anal sac adenocarcinoma: A Review. *Topics in Companion Animal Medicine*, **50**, 100682.

Ross, J.T., Scavelli, T.D., Matthiesen, D.T. & Patnaik, A.K. (1991) Adenocarcinoma of the apocrine glands of the anal sac in dogs: a review of 32 cases. *Journal of the American Animal Hospital Association*, **27**, 349–355.

Rossi, F., Aresu, L., Vignoli, M., Buracco, P., Bettini, G., Ferro, S. et al. (2013) Metastatic cancer of unknown primary in 21 dogs. *Veterinary and Comparative Oncology*, **13**, 11–19.

Skorupski, K.A., Alarcón, C.N., de Lorimier, L.P., LaDouceur, E.E.B., Rodriguez, C.O. & Rebhun, R.B. (2018) Outcome and clinical, pathological, and immunohistochemical factors associated with prognosis for dogs with early-stage anal sac adenocarcinoma treated with surgery alone: 34 cases (2002–2013). *Journal of the American Veterinary Medical Association*, **253**, 84–91.

Sterman, A., Butler, J.R., Chambers, A., Dickson, R., Dornbusch, J., Mickelson, M. et al. (2021) Post-operative complications following apocrine gland anal sac adenocarcinoma resection in dogs. *Veterinary and Comparative Oncology*, **19**, 743–749.

Tanis, J.B., Simlett-Moss, A.B., Ossowksa, M., Maddox, T.W., Guillem, J., Lopez-Jimenez, C. et al. (2022) Canine anal sac gland carcinoma with regional lymph node metastases treated with sacculectomy and lymphadenectomy: outcome and possible prognostic factors. *Veterinary and Comparative Oncology*, **20**, 276–292.

Tobias, K.M. & Johnston, S.A. (2018) Veterinary surgery: small animal, 2nd edition. St. Louis, MO: Elsevier, pp. 1303–1339.

Williams, L.E., Gliatto, J.M., Dodge, E.K., Johnson, J.L., Gamblin, R.M., Thamm, D.H. et al. (2003) Carcinoma of the apocrine glands of the anal sac in dogs: 113 cases (1985–1995). *Journal of the American Veterinary Medical Association*, **223**, 825–831.

Wong, H., Byrne, S., Rasotto, R., Drees, R., Taylor, A., Priestnall, S.L. et al. (2021) A retrospective study of clinical and histopathological features of 81 cases of canine apocrine gland adenocarcinoma of the anal sac: independent clinical and histopathological risk factors associated with outcome. *Animals*, **11**, 3327.