UNIVERSIDADE DE LISBOA

Faculdade de Medicina Veterinária

SURGICAL MANAGEMENT AND OUTCOME FOLLOWING ADRENALECTOMY: A RETROSPECTIVE CASE STUDY IN 16 DOGS (2008-2018)

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Doutora Maria Teresa da Costa Mendes Victor Villa de Brito

Doutor Luís Miguel Alves Carreira

Doutora Lisa Alexandra Pereira Mestrinho

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Dr. David Robinson

CO-ORIENTADOR

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DISSERTAÇÃO DE MESTRADO INTEGRADO EM MEDICINA VETERINÁRIA

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To my grandparents…

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To start with, I would like to thank Dr. David Robinson, my supervisor and mentor, that along with the other clinical directors of KVG, welcomed me into their practice and helped me grow immensely as a veterinary surgeon trainee. Without him this work would not have been feasible, and I sincerely appreciate his kindness in allowing me to use KVG's clinical records to produce this work. I am grateful for all his support and mentorship throughout this period and thank him for inspiring me to be an excellent professional like himself.

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ABSTRACT

SURGICAL MANAGEMENT AND OUTCOME FOLLOWING ADRENALECTOMY: A RETROSPECTIVE CASE STUDY IN 16 DOGS (2008-2018).

Primary neoplasms of the adrenal gland might represent more than 1-2% of all canine tumours and can originate various worrisome clinical presentations; hence why adrenalectomy is generally the treatment of choice. Identification of prognostic factors with occasional uncertainty or contradictions among different authors renders further investigations welcomed. A retrospective study was conducted in 16 dogs undergoing adrenalectomy with the aim to describe the clinical features, surgical management and outcome.

Review of clinical records and interviews with owners and veterinarians involved were performed to register clinical variables, such as, signalment, relevant history, clinical signs, laboratory, imaging and surgical findings, histopathology results, and outcome. The median survival time was calculated through Kaplan-Meier estimate.

Intra- (92%) and postoperative (67%) complications, and perioperative mortality (31%) rates were comparable to recent studies; as was the median survival time (419 days), with 64% of long-term survivors living for more than 1 year, up to 3 years, approximately.

This case series emphasizes that if dogs survive the immediate perioperative period, long-term outcome is generally good with possibility of prolonged survival times, as local or distant tumour recurrence appears to be low. This study also promotes awareness of adrenal *incidentalomas* (25%) and emergency clinical presentations (19%). Outcome predictors such as age of patients with phaeochromocytomas, size of tumour, surgeon's experience in dealing with caval invasion, presence of metastasis at surgery, acute adrenal haemorrhage, major intraoperative haemorrhage, and postoperative disseminated intravascular coagulopathy must be considered in the approach to these cases.

Keywords – dog, adrenal gland tumour, adrenalectomy, incidentaloma, rupture, surgery.

RESUMO

MANEIO CIRÚRGICO E RESULTADO APÓS ADRENALECTOMIA: UM ESTUDO RETROSPETIVO DE CASOS EM 16 CÃES (2008-2018).

Neoplasias primárias das glândulas adrenais poderão representar mais do que 1-2% de todos os tumores caninos e podem originar vários quadros clínicos preocupantes; e por isso é que a adrenalectomia é geralmente o tratamento de escolha. A identificação de fatores de prognóstico com incerteza ou contradições ocasionais entre diversos autores ditam que investigações adicionais sejam bem-vindas.

Um estudo retrospetivo foi conduzido em 16 cães submetidos a adrenalectomia, para descrever o quadro clínico, maneio e resultado cirúrgico.

Foi feita a revisão de historiais clínicos e entrevistas a donos e veterinários envolvidos de forma a registar variáveis clínicas como identificação do animal, historial relevante, sinais clínicos, achados laboratoriais, imagiológicos e cirúrgicos, resultados de histopatologia, e resultado. A mediana dos tempos de sobrevivência foi calculada através da estimativa de Kaplan-Meier.

As taxas de complicações intra- (92%) e pós-cirúrgicas (67%), e de mortalidade (31%) foram comparáveis a estudos recentes; assim como o tempo mediano de sobrevivência (419 dias), com 64% dos sobreviventes a longo prazo a viveram por mais de 1 ano, até 3 anos, aproximadamente.

Esta série de casos enfatiza que se os cães sobreviverem o período peri-cirúrgico imediato, o resultado a longo prazo é geralmente bom com possibilidade de tempos de sobrevivência prolongados, uma vez também que a taxa de recorrência local ou distante aparenta ser baixa. Este estudo promove também a consciencialização de *incidentalomas* das adrenais (25%) e de quadros clínicos de emergência (19%). Fatores de prognóstico tais como idade dos pacientes com feocromocitomas, tamanho do tumor, experiência do cirurgião em lidar com invasão da veia cava, presença de metástases na altura da cirurgia, hemorragia aguda adrenal, hemorragia intra-cirúrgica de maior importância, e coagulopatia intravascular disseminada pós-cirúrgica, devem ser considerados na abordagem a estes casos.

Palavras-chave – cão, tumor da glândula adrenal, adrenalectomia, incidentaloma, rotura, cirurgia.

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LIST OF ABBREVIATIONS

AAH = Acute adrenal haemorrhage
ACTH = Adrenocorticotropic hormone
ACTHST = Adrenocorticotropic hormone stimulation test
ACVIM = American College of Veterinary Internal Medicine
ADH = Adrenal-dependent hyperadrenocorticism
AT = Adrenocortical tumour
BP = Blood pressure
CT = Computed tomography
CVC = Caudal venae cava
DIC = disseminated intravascular coagulopathy
e.g. = *exempli gratia*
eACTH = Endogenous adrenocorticotropic hormone
FMV-UL = Faculty of Veterinary Medicine of the University of Lisbon
HAC = Canine hyperadrenocorticism
HDDST = High dose dexamethasone suppression test
HEV = Hospital Escolar Veterinário/Veterinary Teaching Hospital of the FMV-UL
i.e. = *id est*
KVG = Kingston Veterinary Group
LA = Laparoscopic adrenalectomy
LDDST = Low dose dexamethasone suppression test
MEN = Multiple endocrine neoplasia
MRI = Magnetic resonance imaging
MST = Median survival time
NAD = Non-adrenal disease
NTR = Non-adrenal tumour-related
PDH = Pituitary-dependent hyperadrenocorticism
PT = Portugal
PTE = Pulmonary thromboembolism
PU/PD = Polyuria/polydipsia
TR = Adrenal tumour-related
UCCR = Urinary corticoid:creatinine ratio
UK = United Kingdom
US = Abdominal ultrasound
US-FNA = Ultrasonographic-guided fine-needle aspiration/biopsy

TRAINEESHIP REPORT

As part of the Integrated Master's Degree in Veterinary Medicine from the Faculty of Veterinary Medicine of the University of Lisbon, I fulfilled a 6-month training period between the 4th of September 2017 and the 16th of March 2018, in a total of roughly 1100 hours, at Kingston Veterinary Group, Hull, United Kingdom. Throughout that period, I assisted and participated in numerous procedures carried out in different areas of small animal veterinary medicine. In the Surgery department, led by Dr. David Robinson, who was also my mentor and supervisor, I cooperated by helping in several orthopaedic procedures (e.g. closing-wedge osteotomy, fabello-tibial suture, tibial tuberosity transposition, fracture repairs, pancarpal arthrodesis, placement of transcondylar screw for correction of incomplete ossification of humeral condyle, stabilization of coxofemoral luxation using the toggle pin method), soft tissue surgeries (e.g., exploratory laparotomies, laparoscopies, cystotomies, splenectomies, gastrotomy, enterotomy, perineal hernia repair, anal sacculectomy, incisional/excisional biopsies, brachycephalic obstruction airway syndrome surgery, patent *ductus arteriosus* ligation, bilateral thyroidectomy, cholecystectomy, adrenalectomy, grid keratectomy, temporary eyelid tacking) and postoperative care of the patients. Furthermore, I was also given the opportunity to develop my surgical skills by performing several surgical procedures under the supervision of senior surgeons, such as dog, cat and rabbit castrations, dog and cat ovariohysterectomies, umbilical hernia repair, dewclaw removal, aural haematoma repair, superficial nodule/mass excision, mastectomy, pyometra, cystotomy, and dentistry procedures such as teeth extraction, scaling and polishing. The same applies in terms of Anaesthesia, considering I was able to practice procedures such as induction, intubation and general anaesthetic monitoring. In the Internal Medicine department, I worked on my clinical case solving skills and participated in the care and treatment of the inpatients, practicing procedures such as drugs administration, blood sampling, blood typing, collection and transfusion, venous and urinary catheterization, cystocentesis and running several diagnostic tests. In addition, I accompanied clinicians during consultations and was also able to take the lead and develop my consulting skills. Finally, with regards to the Diagnostic Imaging department, I assisted the surgeons during endoscopy (rhinoscopy, bronchoscopy, gastroscopy) and ultrasound, magnetic resonance imaging and computed tomography scans. Moreover, I was able to practice patient positioning for radiographic examination. During and after these procedures, I was taught by senior vets how to interpret the results and to take conclusions towards diagnostic and treatment planning in specific clinical cases.

I. INTRODUCTION

Primary neoplasms of the adrenal gland were reported to account for 1 to 2% of all canine tumours, though nowadays it is arguable that this fraction might have been undervalued (Lunn & Page, 2013; Myers, 1997). In the past years, both medical and veterinarian practitioners have witnessed an escalation in discovery of incidental adrenal lesions (*incidentalomas*), along with an uncertainty regarding the right manner to address them. The widespread availability of advance diagnostic imaging methods (especially ultrasonography, but also computed tomography and possibly, on a minor role, magnetic resonance imaging) hold the responsibility in this matter (Baum, Boston, & Case, 2016; Cook, Spaulding, & Edwards, 2014; Myers, 1997). The most common types of tumours are, in descending order, cortical adenomas, carcinomas, medullary phaeochromocytomas, and secondary neoplasic lesions (Labelle & De Cock, 2005; Lunn & Page, 2013; Reusch, 2015). Any of these can be associated with a rather vast variety of worrisome clinical scenarios such as endocrine/neuroendocrine derangements (Barthez, Marks, Woo, Feldman, & Matteucci, 1997; Gilson, Withrow, Wheeler, & Twedt, 1994; Reusch & Feldman, 1991; van Sluijs, Sjollema, Voorhout, van den Ingh, & Rijnberk, 1995), local compression or invasion of near-by structures like the ipsilateral kidney and major vessels (e.g., CVC), metastatic disease, and a surgical emergency caused by acute rupture and consequent haemoabdomen or -retroperitoneum (Barrera, Bernard, Ehrhart, Withrow, & Monnet, 2013; Kyles et al., 2003; Lang et al., 2011; Vandenbergh, Voorhout, van Sluijs, Rijnberk, & van den Ingh, 1992; Whittemore, Preston, Kyles, Hardie, & Feldman, 2001).

Generally, adrenalectomy is the treatment of choice, even though it is a technical demanding procedure, associated to considerably high perioperative complications and mortality rates. Yet, more recent studies reported lower mortality, varying from 12 to 26% (Barrera et al., 2013; Kyles et al., 2003; Lang et al., 2011; Massari, Nicoli, Romanelli, Buracco, & Zini, 2011; Schwartz et al., 2008). Furthermore, good long-term outcome with prolonged survival times is possible, provided that dogs survive the perioperative period (Anderson et al., 2001; Barrera et al., 2013; Barthez et al., 1997; Gilson, Withrow, & Orton, 1994; Kyles et al., 2003; Lang et al., 2011; Massari et al., 2011; Schwartz et al., 2008; van Sluijs et al., 1995).

Several authors have appointed a number of variables with or without prognostic significance for dogs with adrenal tumours undergoing adrenalectomy (Anderson et al., 2001; Barrera et al., 2013; Herrera et al., 2008; Kyles et al., 2003; Lang et al., 2011; Massari et al., 2011; Schwartz et al., 2008). Yet, because of the existence of a certain degree of uncertainty or contradictions between studies regarding some of the identified factors, further investigations on the subject are welcomed.

1. NEOPLASMS OF THE ADRENAL GLANDS AND DIAGNOSTIC APPROACH

1.1 Types of neoplasms

1.1.1 Neoplasms of the adrenal cortex

Adrenocortical tumours (ATs), namely, adenomas and carcinomas, are the most frequently seen adrenal gland neoplasms (Barrera et al., 2013; Kyles et al., 2003; Labelle & De Cock, 2005; Lang et al., 2011; Massari et al., 2011; Oblak, Bacon, & Covey, 2016; Schwartz et al., 2008).

Adenomas are classically single, well-demarcated nodules, partially or completely encapsulated by fibrous connective tissue and a compressed border of cortical parenchyma. While small adenomas tend to maintain a yellow colour similar to the normal cortex, larger ones vary from yellow to red, deform the gland's external surface, and may extend into the medulla. Though similar, discrete adenomas differ from nodular hyperplasia predominantly due to the latter inexistence of encapsulation signs along with the typical presence of multiple nodules on both adrenal glands (Rosol & Gröne, 2016). Histologically, adenoma tumour cells are well-differentiated with resemblances of normal zonae fasciculata or reticularis cells. Organised in broad trabeculae or nests divided by small vascular spaces, the cells present abundant lightly eosinophilic cytoplasm, frequently vacuolated and filled with several lipid droplets. Foci of mineralisation, haematopoiesis, and adipose tissue accumulations can be demonstrated, as well as, fibrin thrombi allocated in large dilated blood-filled sinusoids (telangiectasis) (Labelle et al., 2004; Rosol & Gröne, 2016).

Cortical carcinomas arise less commonly in comparison to adenomas (Labelle & De Cock, 2005; Rosol & Gröne, 2016). Carcinomas tend to be larger and are more likely to occur bilaterally. They are constituted by variegated, yellow to red, friable, tissue that incorporates the disturbed adrenal. This malignant AT is commonly locally fixed due to extensive invasion of surrounding structures, namely, the CVC and aorta, resulting in potential large tumour thrombi (Rosol & Gröne, 2016). Histologically, the normal architecture of the gland is often completely destructed by the malignant neoplasm. Tumoural cells are highly pleomorphic – not only typically large and polyhedral with prominent nuclei and densely eosinophilic or vacuolated cytoplasm, but also smaller cells may be present –, form clusters, and are subdivided by fibrovascular stroma. Areas of haemorrhage may be demonstrated as result of rupture of thin-walled sinusoids. The growth pattern varies between tumours and within the same one. Moreover, this feature may be used to distinguish between carcinomas in regard to their type of invasion. Specifically, the existence of a trabecular growth pattern in a minimum of 1/3 of the tumour was significantly more frequent in carcinomas with metastases compared with carcinomas with vascular invasion alone (Labelle et al., 2004). In their study, Labelle et al. (2004) also found that ~50% (14/26) of dogs with carcinomas had metastases, mainly spreading

to the liver and lungs, but also, kidneys, ovary and mesenteric lymph nodes. Other reported locations include thyroid vessels, serosal surfaces of liver and pylorus, and small intestines (Anderson et al., 2001; Barrera et al., 2013). Furthermore, Labelle et al. (2004) noted that metastases may be seen with or without vascular invasion, and *vice versa*. Vascular invasion, specifically caval thrombi, may be formed via direct penetrating entry into the CVC lumen through the adrenal capsule and vascular wall; or via the common trunk (former phrenicoabdominal vein) creating a stalked thrombus (Kyles et al., 2003). In addition to local and distant spread, the clinical presentation may still be complicated by compression of other organs by a large tumour (i.e., mass-effect), or by an haemoabdomen due to non-traumatic rupture of the neoplasm (Rosol & Gröne, 2016; Whittemore et al., 2001).

Whereas differentiation between the adenomas and carcinomas might be challenging, combination of immunohistochemical assessment of the Ki-67 proliferation index with an established group of histologic criteria may simplify the distinction. Features significantly associated with carcinomas included having > 2 cm in diameter, peripheral fibrosis, capsular invasion, trabecular growth pattern, haemorrhage, necrosis, and significantly higher Ki-67 proliferation index; as opposed to extramedullary haematopoiesis, fibrin thrombi, cytoplasmic vacuolation, which were features significantly associated to adenomas (Labelle et al., 2004).

Occasionally, cortical adenomas and carcinomas are endocrinologically active and produce excessive quantities of hormones (glucocorticoids, mineralocorticoids, sex-hormones, steroid precursors) in autonomously and randomly manner. Cortisol-producing tumours are by far the most common in dogs and represent approximately 15% of canine hyperadrenocorticism (Cushing's syndrome). As a consequence of the negative feedback inhibition of pituitary ACTH (adrenocorticotropic hormone) secretion exerted by the hypercortisolaemia (or other intermediates), the contralateral cortex atrophies leaving only the adrenal capsule and the zona glomerulosa. In the remaining zonae (fasciculata and reticularis) only a few secretory cells may be identified. The same atrophy may be demonstrated in the remnants of compressed cortex delimitating producing adenomas (Behrend, 2015; Reusch, 2015; Rosol & Gröne, 2016). In contrast, aldosterone (Johnson et al., 2006; Rijnberk et al., 2001) and sex-hormone (e.g., 17α-hydroxyprogesterone, progesterone, estradiol, androstenedione) (Benitah, Feldman, Kass, & Nelson, 2005; Norman, Thompson, & Mooney, 1999; Ristic, Ramsey, Heath, Evans, & Herrtage, 2002; Syme et al., 2001) secreting-lesions are found very rarely in dogs (Behrend, 2015; Reusch, 2015). Likewise, production of other intermediates (e.g., deoxycorticosterone and corticosterone) is uncommonly reported, as well as, tumours that release multiple types of hormones and with different functions: solely deoxycorticosterone (Gójska-Zygner, Lechowski, & Zygner, 2012; Reine, Hohenhaus, Peterson, & Patnaik, 1999);

deoxycorticosterone and cortisol (Davies et al., 2008); corticosterone and aldosterone (Behrend et al., 2005; Frankot, Behrend, Sebestyen, & Powers, 2012); corticosterone, aldosterone, and cortisol (Machida et al., 2008).

Lastly, although infrequently seen, myelolipomas are another type of benign adrenocortical neoplasms, endocrinologically inactive, composed of nodular collections of well-differentiated fat and hematopoietic tissue cells with foci of bone formation. Their origin is unclear, however, it is theorised that they result from metaplastic transformation of cortical cells (Rosol & Gröne, 2016; Tursi, Iussich, Prunotto, & Buracco, 2005).

1.1.2 Neoplasms of the adrenal medullary secretory cells

After adrenocortical adenomas and carcinomas, phaeochromocytomas are the most common canine adrenal tumours, and the most frequent neoplasms to arise from the adrenal medulla of animals (Barrera et al., 2013; Kyles et al., 2003; Labelle & De Cock, 2005; Lang et al., 2011; Massari et al., 2011; Oblak et al., 2016; Rosol & Gröne, 2016; Schwartz et al., 2008). Originating from the chromaffin cells of the adrenal medulla, most phaeochromocytomas are unilateral and < 10% are bilateral. Although seldom in veterinary medicine, other chromaffin cells neoplasms sited in other locations of the body may arise. These are designated as paragangliomas or extra-adrenal phaeochromocytomas – for example, the aortic-sympathetic ganglion (organ of Zuckerkandl) near the adrenal gland (Lunn & Page, 2013; Reusch, 2015; Rosol & Gröne, 2016).

Histologically, the neoplastic cells may alternate from small cuboidal or polyhedral to large pleomorphic, with several hyperchromatic nuclei and a lightly eosinophilic and finely granular cytoplasm. They are typically subdivided into small lobules by fine septal tissue and capillaries (Rosol & Gröne, 2016).

Benign phaeochromocytomas are generally small and remain confined to the affected adrenal gland, completely encapsulated by a thin compressed border of cortex (Rosol & Gröne, 2016). In dogs, though, more than 50% are considered malignant due to their capacity to cause compression on or invade local structures (vessels in particular) and/or to spread distantly (Reusch, 2015; Rosol & Gröne, 2016). If the 3 largest case series concerning dogs with phaeochromocytomas are considered (Barthez et al., 1997; Bouayad, Feeney, Caywood, & Hayden, 1987; Gilson, Withrow, Wheeler, et al., 1994), while local invasion occurred in 39% to 62% of dogs, metastases were identified in 13% to 36% of dogs. Local invasion included surrounding organs (e.g., kidney) and/or vessels (e.g., phrenicoabdominal venous trunk, CVC, renal and adrenal vessels, hepatic veins, abdominal aorta). Target-organs for metastatic spread were regional lymph nodes, liver, lungs, spleen, kidneys, bone (e.g., vertebra, ribs), central

nervous system, heart, pancreas, peritoneum, jejunum. Furthermore, local invasion, namely caval thrombi, has been consistently reported to occur more frequently in dogs with phaeochromocytomas (Barrera et al., 2013; Bouayad et al., 1987; Herrera et al., 2008; Kyles et al., 2003; Lang et al., 2011; Twedt & Wheeler, 1984) in comparison to those with ATs (Anderson et al., 2001; Barrera et al., 2013; Kyles et al., 2003; Lang et al., 2011; Scavelli, Peterson, & Matthiesen, 1986).

Phaeochromocytomas may be functional and therefore result in clinical signs associated with an overproduction of catecholamines. Tumoural cells may secrete epinephrine, norepinephrine, or both, and can be distinguished by the morphology of their secretory granules (Rosol & Gröne, 2016).

1.1.3 Neoplasms of cells of the sympathetic nervous system in the adrenal medulla

These are tumours rarely seen in domestic animals: neuroblastomas and ganglioneuromas. Neuroblastomas originate from primitive neuroectodermal cells and give origin to large intraabdominal masses. Histologically, they may be distinguished from phaeochromocytomas by its small and undifferentiated cells with hyperchromatic nuclei and scarce cytoplasm. Not only pseudorosettes may form, but also neurofibrils or unmyelinated nerve fibbers may be seen. They typically occur in young animals (Rosol & Gröne, 2016).

Ganglioneuromas are benign, well-differentiated and generally small neoplasms that can be found in the adrenal medulla. They are composed of multipolar ganglion cells and neurofibrils with a prominent fibrous connective tissue stroma. Sometimes, adjacent phaeochromocytomas and ganglioneuromas may be seen in the same gland due to divergent differentiation of the tumoural cells (Rosol & Gröne, 2016).

1.1.4 Metastatic neoplasms to the adrenal medulla

The adrenal glands are a common location for secondary neoplastic development, namely, the adrenal medulla which represents an early site of metastasis growth as a result of the low-pressure venous blood supply. Due to the adrenal capsule, direct invasion from either primary or secondary tumoural lesions from surrounding tissues is rare. Invasion is usually bilateral and typically results from disseminated malignancies (Rosol & Gröne, 2016). A study showed that metastatic lesions represented 26.7 % of all canine adrenal neoplasms, mainly originating from pulmonary, mammary, prostatic, gastric and pancreatic carcinomas, and melanoma (Labelle & De Cock, 2005). Therefore, it represents an important differential of adrenal masses.

1.1.5 Bilateral tumours, Concurrent PDH (pituitary-dependent hyperadrenocorticism) and Concurrent endocrine neoplasias

Diverse combinations of bilateral ATs have been reported including bilateral adenomas, carcinomas, or a combination of adenoma and carcinoma; combinations which might be causing HAC (Adissu, Hayes, Wood, & Caswell, 2010; Anderson et al., 2001; Ford, Feldman, & Nelson, 1993; Kyles et al., 2003; Lang et al., 2011; Nabeta et al., 2017; Oblak et al., 2016; Stenske, Bemis, Hill, & Krahwinkel, 2005).

Additionally, ATs have also been reported together with phaeochromocytomas as one neoplasm per gland (Hylands, 2005; Oblak et al., 2016; Thuróczy et al., 1998; von Dehn, Nelson, Feldman, & Griffey, 1995), or even, as both on the same gland (Lang et al., 2011; Thuróczy et al., 1998; van Sluijs et al., 1995).

Furthermore, PDH or pituitary tumours may be encountered with ATs (Greco, Peterson, Davidson, Feldman, & Komurek, 1999; Oblak et al., 2016; Thuróczy et al., 1998) or with phaeochromocytomas (Bennett & Norman, 1998; Oblak et al., 2016; von Dehn et al., 1995).

In light of these reports, it is arguable that some of these patients might suffer from a multiple endocrine neoplasia (MEN)-like syndrome, when two or more endocrine tumours and/or hyperplasias that resemble one of the MEN syndromes described in humans are found in the same animal (Beatrice et al., 2018). MEN syndromes are well-known in human medicine and are divided into four major types according to the mutated gene involved and associated group of endocrine glands affected – types 1 to 4 (MEN1 to MEN4 syndromes) (Thakker, 1998, 2014; Thakker et al., 2012):

- MEN1 syndrome combines parathyroid adenoma (90% of cases), entero-pancreatic tumours (30-70% of cases), pituitary adenomas (30-40% of cases), and other associated neoplasms;
- MEN2 (formerly MEN2A) syndrome includes medullary thyroid cancer (90% of cases), phaeochromocytoma (50% of cases), and parathyroid adenoma (20-30% of cases); medullary thyroid cancer may occur alone as a MEN2 syndrome variant;
- MEN3 (formerly MEN2B) syndrome groups medullary thyroid carcinoma (>90%), phaeochromocytoma (40-50%), and other associated abnormalities;
- MEN4 (or MENX) syndrome is the newest reported variant and combines MEN1 syndrome target structures (parathyroid adenoma, pituitary adenoma, pancreatic neuroendocrine tumours) with gonadal, adrenal, renal and thyroid neoplasms.

An equivalent hereditary disorder has not been proven in animals, though several studies report concurrent neoplasms/hyperplasias arising from diverse endocrine tissues, which may be functional or non-functional (Reusch, 2015):

- Medullary thyroid carcinoma, phaeochromocytoma, parathyroid hyperplasia, and bilateral interstitial cell testicular tumours (compares to MEN2 syndrome) (Peterson, Randolph, Zaki, & Heath, 1982);
- Parathyroid tumour and phaeochromocytoma (Wright et al., 1995);
- PDH and phaeochromocytoma; ADH (adrenal-dependent hyperadrenocorticism) and phaeochromocytoma (von Dehn et al., 1995);
- Pituitary adenoma (with PDH) and phaeochromocytoma (Bennett & Norman, 1998);
- Pituitary tumour with malignancy features and ACTH-positive (causing PDH), right adrenal with AT, and left adrenal with 2 ATs and phaeochromocytoma (causing ADH) (Thuróczy et al., 1998);
- Parathyroid adenoma and PDH (compares to MEN1 syndrome) (Walker, Jones, Guildford, Burbidge, & Alley, 2000);
- Insulinoma, bilateral adrenocortical carcinomas, and aortic paraganglioma (Kiupel, Mueller, Ramos Vara, Irizarry, & Lin, 2000);
- Pancreatic islet cell somatostatinoma, and gastrinoma in the mesenteric lymph nodes and liver (Hoenerhoff & Kiupel, 2004);
- Thyroid carcinoma, adrenocortical carcinoma, and bilateral interstitial cell testicular adenomas (Proverbio et al., 2012);
- Medullary thyroid carcinoma, bilateral phaeochromocytomas, and parathyroid adenoma (compares to MEN2 syndrome) (Arias, Castillo, Trigo, & Caneda Aristarain, 2016);
- Parathyroid chief cell adenoma and bilateral phaeochromocytomas (Arias, Castillo, & Trigo, 2017).

A recent study suggests that the prevalence of concurrent endocrine neoplasias in animals might be higher than previously thought (Beatrice et al., 2018). The reported prevalence of concurrent endocrine neoplasias was 2.1% in dogs and 1.3% in cats, with the adrenal glands being the most common organ to be affected in dogs. In this species, the most frequent combination of endocrine tumours and/or hyperplasias involved multiple concurrent adrenal gland lesions with ACTH-positive pituitary adenomas. However, the notion of MEN-like syndromes, as described in human medicine, were found extremely rare in dogs and cats.

In sum, concurrent endocrine neoplasias has been proven to be more common than previously believed and it is only likely to be increasingly reported in light of an ageing patient population, advancement of veterinary medical care, and augmented clinician awareness (Galac & Grinwis, 2018). Therefore, it might be important to undertake comprehensive assessments in face of an endocrine tumour diagnose, in order to be able to make adjustments to the treatment plan and to provide in-depth expectations to the owners (Galac & Grinwis, 2018; Reush, 2015).

1.2 Signalment

1.2.1 Adrenocortical tumours

Canine ADH affects middle-aged and older individuals (Anderson et al., 2001; Barrera et al., 2013; Behrend, 2015; Kyles et al., 2003; Reusch & Feldman, 1991; van Sluijs et al., 1995). In an earlier study, the age of dogs with adrenocortical tumours varied between 6 to 16 years old (mean 11.3 ± 2.3 years) and, despite inexistence of significant difference in comparison with the group of PDH dogs (mean 10.4 ± 3.2 years), it seemed that animals with ADH tended to be older than those with PDH. This is, a larger proportion of dogs with ATs (92.5%, 37/41) were 9 years of age or older, in contrast to dogs with PDH (77%, 34/44) (Reusch & Feldman, 1991). Both cortical adenomas and carcinomas are more frequently seen in old dogs (8 years and older) (Rosol & Gröne, 2016). Accordingly, Reusch & Feldman (1991) reported a mean age of 11.4 ± 2.1 years old for the adenoma group and 11.1 ± 2.3 years old for the carcinoma group. Later on, Barrera et al. (2013) described similar results.

No gender predisposition has been established (Behrend, 2015); in spite of diverse studies (concerning ATs and PDH) contributing to an apparent overrepresentation of females (Anderson et al., 2001; Gallelli, Cabrera Blatter, & Castillo, 2010; Kyles et al., 2003; Reusch & Feldman, 1991; van Sluijs et al., 1995). For instance, in the study by Reusch & Feldman (1991), 63% and 57% of individuals with ATs or PDH, respectively, were females. Yet, others found no significant difference between the sex distribution of dogs with HAC and the general population (Ling, Stabenfeldt, Comer, Gribble, & Schechter, 1979 cited by Behrend, 2015); and, in another study, females were not even the majority (Hess, Kass, & Ward, 1998 cited by Behrend, 2015).

Virtually every breed has been reported with PDH and ATs, with frequent association of German Shepherd, Labrador Retriever, and Terriers to functioning adrenocortical adenomas or carcinomas (Behrend, 2015). However, for HAC overall, a breed predilection has only been proven for Poodles, Dachshunds, and Boxers (Ling et al., 1979), and no difference was found in expression of the disorder between purebred and mixed-breed dogs (Bellumori, Famula, Bannasch, Belanger, & Oberbauer, 2013).

Weight-wise, PDH may seem more common in smaller dogs (77% weighted < 20 kg) in comparison to ATs (46% weighted > 20 kg) (Reusch & Feldman, 1991). With regard to ATs in particular, Anderson et al. (2001) described a weight range from 4 to 51 kg (median 20 kg). Moreover, Barrera et al. (2013) reported a mean weight of 22.8 kg (16.1 to 29.5 kg) and 25.5 kg (21.8 to 29.2 kg) for dogs with cortical adenomas and carcinomas, respectively.

1.2.2 Phaeochromocytomas

Wide age ranges have been reported in the 2 largest case series of dogs with phaeochromocytomas: 3 to 15 years old (mean and median 10.5 years) (Gilson, Withrow, Wheeler, et al., 1994); 1.6 to 18 years old (mean 12 ± 2.8 years) (Barthez et al., 1997). Despite having been reported at practically every age, middle-aged to older animals are more commonly affected (Barrera et al., 2013; Barthez et al., 1997; Gilson, Withrow, Wheeler, et al., 1994; Herrera et al., 2008; Kyles et al., 2003; Reusch, 2015).

No gender predisposition exists, neither between male and female, nor between entire and neutered dogs (Barthez et al., 1997; Gilson, Withrow, Wheeler, et al., 1994; Reusch, 2015).

Likewise, and despite apparent overrepresentation of certain breeds (namely, Golden and Labrador Retriever, Boxer, Doberman, German Shepherd, Poodle, and Terriers) which might well result from their popularity, there is no clear breed predilection and more than 40 breeds have been reported (Barthez et al., 1997; Gilson, Withrow, Wheeler, et al., 1994; Reusch, 2015).

Finally, in terms of weight, Barthez et al. (1997) observed a mean weight of 22.3 ± 11.6 kg. In posterior investigations, Herrera et al. (2008) described a weight range from 9 to 62 kg (median 22.5 kg), while Barrera et al. (2013) observed a mean weight of 29.3 kg (24.5 to 34.1 kg).

1.3 History, Clinical signs and Physical examination

The clinical presentation generated by an adrenal neoplasm may be diverse, depending primarily on the tumour functionality. Inherently, producing tumours result in clinical manifestations caused by the pathophysiologic effects of the released substances. Accordingly, non-functional neoplasms are typical incidental discoveries (*incidentaloma*). However, in the later course of the disease, these endocrine-inactive tumours may similarly result in clinical signs caused by space-occupying effects, invasive nature of the tumour, rupture, and/or metastases (Arenas, Pérez-Alenza, & Melián, 2013).

1.3.1 Adrenocortical tumours

With regard to ADH, expected duration and type of clinical signs are similar to those observed with PDH (Behrend, 2015). The ACVIM (American College of Veterinary Internal Medicine) Consensus Statement for the Diagnosis of Spontaneous Canine Hyperadrenocorticism (Behrend, Kooistra, Nelson, Reusch, & Scott-Moncrieff, 2013) sums up the associated clinical manifestations, categorising them by frequency (**Table 1**). Additionally, the Panel points out that, in the present days, the signs reported are subtler and fewer as a result of increased awareness and consequential earlier detection of the disease. Also, care should be taken to avoid over diagnose HAC, pursuing it only if one or more of the common clinical signs and physical examination features are consistently identified (Behrend et al., 2013). On the contrary, the

likelihood of HAC decreases in the presence of unrelated manifestations, such as, vomiting, diarrhoea, coughing, sneezing, pain, or bleeding (Behrend, 2015).

Whereas clinical signs may vary between patients, and from subtler to dramatical, the clinical presentation typically progress slowly, with the uncommon possibility of entering intermittent phases of remission (Behrend, 2015; Peterson, Gilbertson, & Drucker, 1982). Acute, life-threatening presentations attributed to ADH typically result from either pulmonary thromboembolism (PTE) or, rarely, tumour rupture (addressed in the following subsection – **1.3.2**) (Behrend, 2015).

Table 1. Clinical manifestations of HAC and respective frequency at initial presentation. (Adapted from: Behrend, E.N., Kooistra, H.S, Nelson, R., Reusch, C.E., & Scott-Moncrieff, J.C. (2013). Diagnosis of Spontaneous Canine Hyperadrenocorticism: 2012 ACVIM Consensus Statement (Small Animal). J Vet Intern Med, 27: 1293.)

Common	Less Common	Uncommon
Polydipsia	Lethargy	Thromboembolism
Polyuria	Hyperpigmentation	Ligament rupture
Polyphagia	Comedones	Facial nerve palsy
Panting	Thin skin	Pseudomyotonia
Abdominal distension	Poor hair regrowth	Testicular atrophy
Endocrine alopecia	Urine leakage	Persistent anoestrus
Hepatomegaly	Insulin-resistant diabetes mellitus	
Muscle weakness		
Systemic hypertension		

In dogs, ADH typically results from cortisol-producing ATs – the most common functional type of ATs (Reusch, 2015). Yet, as previously mentioned, other hormones (aldosterone, sex steroids, precursors) can be secreted ever so rarely[1]: in singularity (Gójska-Zygner et al., 2012; Johnson et al., 2006; Reine et al., 1999; Rijnberk et al., 2001; Syme et al., 2001) or along with other cortical steroids which, evidently, may create confusing clinical presentations due to the mixture of clinical signs (Behrend et al., 2005; Davies et al., 2008; Frankot et al., 2012; Machida et al., 2008). Likewise, puzzling presentations may arise from the coexistence of an AT with a phaeochromocytoma (Hylands, 2005; von Dehn et al., 1995).

1.3.2 Phaeochromocytomas

Phaeochromocytomas may generate highly diverse clinical manifestations depending on the causal nature of the clinical signs (**Table 2**). Functionally-active medullary tumours secrete catecholamines in an intermittent episodic manner, which means physical examination findings will be in accordance with the secretory activity of tumour at the time of presentation and

[1] In consideration of their rarity, these will not be explored in-depth here. Readers are directed to the citations.

explains why these findings are often unremarkable. The causes behind the triggering of catecholamine release are generally undetermined. The episodes may fluctuate in: clinical presentation (certain signs may be continuously present, others may be added transiently, and unremarkable presentations may be noted between episodes); frequency (multiple times per day/week or spaced by numerous weeks/months – the longer the interval, the harder is to perceive the inherent connection between the episodes); severity (mild to potentially lethal; similar to previous episodes or, usually, exhibiting gradual progression); time period until first presentation to the veterinarian (from hours to years). Further difficulties may be encountered due to concurrence of other more common and worrisome illnesses, which are expected in patients of advanced age and stand out more than the phaeochromocytoma itself. Moreover, the wide variability and non-specific nature of clinical signs would be cause for raising suspicion of a phaeochromocytoma very often, virtually every day. Even though encountering a phaeochromocytoma is a rare event, it should be kept in mind that it is still missed quite frequently as a result of poor awareness. Phaeochromocytomas may also produce acute, life-threatening situations generated by either a massive catecholamine surge that leads to collapse and sudden death, or by tumour rupture (Reusch, 2015).

Table 2. Clinical signs in dogs with phaeochromocytomas divided by cause-related categories. (Adapted from: Reusch, C. E. (2015). Pheochromocytoma and Multiple Endocrine Neoplasia. In E. C., Feldman, R.W., Nelson, C. E., Reusch & J. C. R., Scott-Montcrieff (Eds.): *Canine and Feline Endocrinology*, (4th ed.), (p. 528). Missouri: Saunders, Elsevier.)

Cause	Clinical signs
Catecholamine excess	
Nonspecific	Anorexia[b], weight loss[b], lethargy[a]
Related to cardiorespiratory system and/or hypertension	Tachypnoea[a], dyspnoea, panting[a], tachycardia[b], arrhythmias[b] (mostly tachyarrhythmias), collapse[a], pale mucus membranes, nasal/ocular/gingival haemorrhages, acute blindness
Related to neuromuscular system	Weakness[a], anxiety, pacing, disorientation, muscle tremor, seizures
Miscellaneous	PU/PD[b], vomiting[b], diarrhoea, abdominal enlargement, abdominal pain[b]
Large, invasive tumour	Abdominal enlargement, ascites, abdominal pain, hind limb oedema
Ruptured tumour	Acute severe lethargy, painful abdomen, tachypnoea, weakness, collapse, tachycardia, pale mucus membranes, prolonged CRT
Metastases	To brain: seizures and other CNS signs; To vertebral canal or bone: tetraparesis, paraparesis, lameness, swelling, local pain

Caption: a=the most common; b=others frequently encountered; PU/PD=polyuria/polydipsia; CRT=capillary refill time; CNS=central nervous system.

Note that the signs described in **Table 2** caused by a large mass, local invasion, tumour rupture, or metastases, may be compatible with any type of malignant adrenal tumour (cortical or medullar; functional or non-functional), though benign neoplasms may also grow substantially resulting in mass-occupying effects and/or rupture (Behrend, 2015; Lang et al., 2011; Tursi, Iussich, Prunotto, & Buracco, 2005). Metastases-related clinical signs will naturally depend on the organs/structures affected. Traumatic and non-traumatic rupture of adrenal tumours resulting in intraabdominal or retroperitoneal bleeding is rather rare, accounting for 20 reported cases, and represent both medical and surgical emergencies (Barrera et al., 2013; Evans, Hosgood, Boon, & Kowalewich, 1991; Lang et al., 2011; Santamarina et al., 2003; Vandenbergh et al., 1992; Whittemore et al., 2001; Williams & Hackner, 2001).

1.4 Diagnostic testing

1.4.1 Basic bloodwork, Urinalysis and Blood pressure measurement

Routine diagnostic workup includes complete blood count, serum biochemistry, urinalysis, urine protein : creatinine ratio, and blood pressure (BP) measurement.

1.4.1.1 Adrenocortical tumours

Together with hypertension, the laboratory abnormalities enumerated in **Table 3** are consistent with HAC and reinforce the diagnosis, provided that common clinical features (reviewed in **Table 1**) are identified as well from history and physical examination. However, HAC cannot be excluded solely on the basis of results within the reference ranges obtained on these profiles (Behrend et al., 2013).

Table 3. Common abnormal laboratory findings associated with HAC. (Adapted from: Behrend, E.N., Kooistra, H.S, Nelson, R., Reusch, C.E., & Scott-Moncrieff, J.C. (2013). Diagnosis of Spontaneous Canine Hyperadrenocorticism: 2012 ACVIM Consensus Statement (Small Animal). J Vet Intern Med, 27: 1293.)

CBC	Serum biochemistry	Urinalysis
Neutrophilic leucocytosis	Increased ALKP	Specific gravity ≤1.018-1.020
Lymphopenia	Increased ALT	Proteinuria
Eosinopenia	Hypercholesterolemia	Indicators of UTI
Thrombocytosis	Hypertriglyceridemia	
Mild erythrocytosis	Hyperglycaemia	

Caption: CBC=complete blood count; ALKP=alkaline phosphatase; ALT=alanine transaminase; UTI=urinary tract infection.

1.4.1.2 Phaeochromocytomas

No consistent alterations are found in the basic screenings with capability to support the presumptive diagnosis of a phaeochromocytoma (Reusch, 2015). Reusch (2015) combines the laboratory abnormalities reported in the literature with their own findings on their canine population presenting with phaeochromocytomas, excluding animals with coexisting endocrine neoplasias – the irregularities encountered are listed in **Table 4**. Note that normal laboratory results have also been reported in these dogs.

Likewise, hypertension is not a consistent finding, probably due to its cyclic nature. Besides, its presence is not specific for phaeochromocytomas – it is also often seen with HAC. Yet, the higher the systolic blood pressure, the higher the chance of dealing with a phaeochromocytoma (e.g., so far, a systolic BP over 300 mm Hg has solely been registered in dogs with phaeochromocytomas) (Reusch, 2015).

Table 4. Reported laboratory abnormalities in dogs with phaeochromocytomas (Reusch, 2015).

CBC	Serum biochemistry	Urinalysis
Mild to moderate anaemia (usually non-regenerative)	Increased ALKP	Specific gravity: 1.006-1.044, (50% hyposthenuric or isosthenuric)
Leucocytosis or stress leucogram	Increased ALT	Proteinuria
Thrombocytopenia	Increased AST	
Thrombocytosis	Increased BUN	
Polycythaemia	Increased creatinine	
	Hypercholesterolemia	
	Hypoalbuminemia	
	Hyperglycaemia	
	Hyperphosphatemia	
	Hypokalaemia	
	Hyponatraemia	

Caption: CBC=complete blood count; ALKP=alkaline phosphatase; ALT=alanine transaminase; AST=aspartate transaminase; BUN=blood urea nitrogen.

1.4.2 Functional testing

Because the findings gathered from history, physical examination, imaging, and routine laboratory profiles might be similar between dogs with phaeochromocytomas and those with ADH (e.g., weakness, tachypnoea, panting, PU/PD, hypertension, identification of an adrenal mass, raised alkaline phosphatase, alanine transaminase, and cholesterol, hyposthenuric or isosthenuric urine), it makes sense to test for ADH first in respect of their higher frequency relatively to phaeochromocytomas (Reusch, 2015).

Note that even more puzzling scenarios can arise from concurrence of HAC (PDH or ADH) with phaeochromocytomas, which have been reported (Bennett & Norman, 1998; Hylands, 2005; Lang et al., 2011; Oblak et al., 2016; Thuróczy et al., 1998; van Sluijs et al., 1995; von Dehn et al., 1995).

1.4.2.1 Adrenocortical tumours

For a suspected producing-AT, a variety of individual or combinations of tests are routinely used to diagnose HAC and differentiate PDH from ADH: UCCR (urinary corticoid : creatinine ratio), ACTHST (ACTH stimulation test), LDDST/HDDST (low/high dose dexamethasone suppression test), eACTH (endogenous ACTH) measurement. As no assay is 100% accurate, a combination of tests is sometimes required to get to the bottom of the matter. Furthermore, interpretation of differentiating tests is only viable if the HAC diagnosis has been already confirmed on a screening test (Behrend, 2015).

UCCR is a sensitive test to detect cortisol hypersecretion and therefore useful to rule out HAC (Behrend, 2015; Behrend et al., 2013). For instance, it might be particularly handy when an adrenal *incidentaloma* is encountered and clinical examination suggests a non-functional lesion. The contrary, i.e., rule in HAC, is unattainable due to the low specificity of the assay. Reported sensitivity and specificity for the diagnosis of HAC ranges from 75-100% and 20-25%, respectively, when a single, random urine sample is collected in veterinary hospitals (Behrend, 2015; Behrend et al., 2013). To minimise false-positive results, it is advisable to collect a urine sample at home with a minimal interval of 2 days after a visit to the veterinary practice (Behrend et al., 2013). Apart from the low specificity, other drawback of UCCR is its inability to differentiate between PDH and AT on its own (Behrend, 2015).

The ACTHST is a specific test for the diagnosis of HAC, thus useful to rule it in. While the reported sensitivity for dogs with HAC caused by and AT in particular ranges from 57-63%, overall specificity varies from 59-93% (Behrend et al., 2013). Shortcomings include: primarily a lower sensitivity than the LDDST, especially for dogs with an AT; inconclusive results when post-ACTH values fall within a grey range zone; and not being able to discriminate between PDH and AT on its own (Behrend, 2015). Moreover, results should be interpreted carefully. For instance, while the detection of an adrenal mass by means of imaging techniques along with an ACTHST consistent with HAC would point towards ADH, case reports of concurrent PDH/pituitary tumours and ATs have been described (Greco et al., 1999; Oblak et al., 2016; Thuróczy et al., 1998). Interestingly, in one study dogs with carcinomas had higher responses to the test than those with adenomas (Peterson, Gilbertson, et al., 1982), however, no consistent differences were noted in another (Feldman, 1983 cited by Behrend, 2015).

Because cortisol-secreting neoplasms are the most frequent hormonally-active ATs, the typical ACTHST measures cortisol response. Yet, normal or subnormal ACTHST results accompanied by clinical manifestations strongly suggestive of HAC can be uncommonly encountered. In these situations, it is possible that other hormones are being secreted which can be measured instead of cortisol: sex steroids (e.g. progestins) (Norman et al., 1999; Ristic et al., 2002; Syme

et al., 2001) or cortisol intermediates (e.g. corticosterone) (Behrend et al., 2005; Frankot et al., 2012). Progestins and cortisol intermediates may interact with glucocorticoid receptors, thus resulting in HAC-associated clinical signs, inhibition of the pituitary gland to release ACTH, atrophy of the normal adrenal cortical parenchyma, and in the drop of endogenous cortisol concentrations (Behrend, 2015). Furthermore, in the presence of clinical evidence of mineralocorticoid excess other hormones may equally be measured through an ACTHST, such as, aldosterone (Frankot et al., 2012; Johnson et al., 2006; Machida et al., 2008) or steroid precursors (e.g. deoxycorticosterone) (Davies et al., 2008; Reine et al., 1999).

The LDDST stands out for its high sensitivity, being the screening test of choice for spontaneous HAC, and for its ability to potentially discriminate between PDH and AT. Reported sensitivity and specificity varied from 85-100% and 44-73%, respectively (Behrend et al., 2013). Remarkably, the overall sensitivity was roughly 95%, when numerous previous reports are combined (Behrend & Kemppainen, 2001). Demerits include a lower specificity (affected by non-adrenal disorders and possibly stress) and being a lengthy assay (needs 8h to be concluded) (Behrend et al., 2013; Kaplan, Peterson, & Kemppainen, 1995; May, Frank, Hnilica, & Lane, 2004). In addition, occurrence of an "inverse pattern" (i.e., cortisol concentration increased at 4h and suppressed at 8h post-dexamethasone) is non-diagnostic but highly suspicious of HAC – warrants further testing (Behrend et al., 2013).

LDDST and HDDST share many of advantages and disadvantages, namely their role as differentiation tests (Behrend, 2015). However, none can be considered 100% absolute. While the lack of suppression at 8h post-dexamethasone (i.e., increased cortisol concentration above the laboratory reference cut-off) supports a HAC diagnosis, the 4h value holds the key for differentiation: suppression likely confirms PDH – pattern seen in ~75% of dogs with PDH; little to no suppressive effect renders the test inconclusive – pattern seen in all dogs with ATs independently of dexamethasone dosage and in ~25% of dogs with PDH. If no suppression is seen on a LDDST, an HDDST will only offer differentiation in about 12% additional cases of PDH. For this reason, it is preferable to opt for an assessment of eACTH or abdominal ultrasound (Behrend et al., 2013).

Measurement of eACTH is the most accurate standalone biochemical test with ability to definitively differentiate PDH from AT. Whereas dogs with PDH would be expected to have normal to elevated eACTH concentrations (secreted by a pituitary tumour), those with ADH would present below normal values (as a result of the negative feedback exerted by the autonomous AT secretion of cortisol) (Behrend, 2015). Yet, it should be noted that this is not an appropriate assay for the screening of HAC, considering that healthy dogs and those with PDH have similar concentrations of eACTH (Hanson, Kooistra, Mol, Teske, & Meij, 2006).

The assay's accuracy for differentiation depends on the analytical sensitivity (poor sensitivity is the most common concern with some assays) and working range (namely, poorly at the lower end) of the analyser/technique. Some dogs with PDH have eACTH concentrations at or below the sensitivity of the test, i.e., what the assay can measure accurately. The chance of obtaining falsely low value results in dogs with PDH increases with intra- and inter-assay variability (especially at lower eACTH concentrations), episodic ACTH release, and with inadequate sample handling in consideration of inherent eACTH lability (Behrend et al., 2013).
A combination of tests can be useful in allowing both screening and differentiation, for instance, UCCR and HDDST; ACTHST and HDDST (Behrend et al., 2013).

1.4.2.2 Phaeochromocytoma

Biochemical testing for the diagnosis of phaeochromocytomas in dogs has only recently started its evolution process in veterinary medicine as result of poor medical awareness, limited availability of assays, absence of species-specific reference ranges, and impracticality associated with 24-hour urine collections in client-owned dogs (difficult task on its one; demanding sampling and conditioning for shipment requirements; implicates postponing medical therapy with phenoxybenzamine, which is known from humans to be a possible cause of false-positive results) (Reusch, 2015).
Taking into account the already mentioned inconveniences, the urine assays began to be studied on the basis of single-voided samples with results expressed as ratios to the urinary creatinine in the same sample, and timing and setting of collection were investigated as possible influencing aspects to consider (namely, in regard of the stress associated with veterinary care and hospital environment) (Kook, Boretti, Hersberger, Glaus, & Reusch, 2007). Significant higher epinephrine-, norepinephrine-, and metanephrine-to-creatinine ratios were found in samples taken in the hospital compared to those taken 7 days after discharge, from healthy client-owned dogs; however, these differences were relatively small and normetanephrine ratios did not differ. Furthermore, a similar evaluation made in another study did not find difference in any of the parameters (Quante et al., 2010). Hence, collection of urine samples in the hospital has been reported as a standard approach (Reusch, 2015).
Dogs with phaeochromocytomas have been reported to have significantly higher urinary catecholamines, and normetanephrine ratios compared to healthy dogs (Kook, Grest, Quante, Boretti, & Reusch, 2010; Quante et al., 2010; Salesov et al., 2015).
Along with the already expose similarities between dogs with phaeochromocytomas or HAC, Quante et al. (2010) reported that approximately 50% of dogs with HAC also had statistical significant higher urinary catecholamines and normetanephrine ratios compared to healthy

dogs. These results serve as another reminder to bear HAC in mind as a differential diagnosis and to highlight the importance of identifying discriminative parameters/assays.

Likewise, differentiation from non-adrenal diseases (NAD) is fundamental. It is possible that the greater the severity of illness, the higher the values obtained for urinary catecholamines and their metabolites (Cameron, Monroe, Panciera, & Magnin-Bissel, 2010). Therefore, it might be more difficult to interpret results in dogs with concurrent illnesses.

In sum, several studies have demonstrated the superior performance of urinary normetanephrine over urinary catecholamines and metanephrine, namely for being the most sensitive and allowing the best differentiation between dogs with phaeochromocytoma, HAC, NAD, and healthy dogs, with the least overlap (Kook et al., 2007, 2010; Quante et al., 2010; Salesov et al., 2015). No overlap has been consistently detected between healthy dogs and those with phaeochromocytoma (Kook et al., 2010; Quante et al., 2010; Salesov et al., 2015). Yet, the same cannot be said between dogs with phaeochromocytoma and HAC. While in one study there was an overlap of results (Quante et al., 2010), in another there was not (neither between dogs with phaeochromocytoma and HAC, nor between those with NAD) (Salesov et al., 2015). Taking into consideration the results of the former, the authors of the latter study recognized that their results were most likely coincidental and possibly affected by sample size.

To work around this adversity, cut-off values were defined. For instance, a cut-off urinary normetanephrine ratio of 4 times the upper limit of "normal" (measured in healthy dogs) permitted discrimination without overlap of values between dogs with phaeochromocytoma and those with HAC (Quante et al., 2010; Salesov et al., 2015). While this meant the test specificity was perfect, sensitivity would not as some phaeochromocytoma cases would have been overlooked. Sensitivity could benefit from lower cut-off values; however, specificity would be hurt. A *gold standard* method to determine the true function of the adrenal gland (e.g., cut-off of 4 times the urinary normetanephrine ratio of healthy dogs) remains to be defined (Salesov et al., 2015).

Whereas in urine only total normetanephrine and metanephrine (free and sulfoconjugated) are measured, in plasma total and free can be measured. Alike the urine assay, plasma-total and plasma-free normetanephrine have also proven to be diagnostically superior over plasma catecholamines and metanephrine, allowing discrimination of dogs with phaeochromocytoma from those with ATs/HAC, NAD, and healthy dogs, with nearly no overlap (Gostelow, Bridger, & Syme, 2013; Salesov et al., 2015).

Although in one study the inexistence of overlap of values for the urinary normetanephrine assay seemed to merit superiority to the test in comparison to the corresponding plasma assay (Salesov et al., 2015), as previously argued, the authors themselves viewed it just to be a matter

of coincidence, as an overlap in the urinary assay had been previously found in another study (Quante et al., 2010). Therefore, currently, both urine and plasma assays have similar acceptable performances, leaving the choice between one of the two dependent upon availability of technical facilities, as well as, of dog-specific reference ranges (values are much higher than in humans) (Gostelow et al., 2013; Salesov et al., 2015). The diagnosis of phaeochromocytoma should be based on the separated measurement of metanephrines (normetanephrine and metanephrine). The major difficulty with these tests will be patients with smaller tumours because of their likely lower levels. Special consideration of sampling and conditioning for shipment requirements is imperative as they might represent key influencing factors (Reusch, 2015).

1.4.3 Imaging

1.4.3.1 Radiography

Radiography may contribute to back-up the suspicion of HAC. However, because all thoracic and abdominal findings are non-specific and rather rare, it cannot be solely used to confirm the diagnosis of HAC or to differentiate between PDH, ADH, other endocrine conditions (e. g., diabetes and hypothyroidism), and obesity (Behrend, 2015; Schwartz, Störk, Mellor, & Sullivan, 2000). Radiographic alterations consistent with HAC include abdominal distension/pendulous abdomen, good contrast as result of abdominal fat deposition (primarily omental), hepatomegaly, bladder distension, osteopenia, mineralisation of the perihilar bronchi and pulmonary interstitium, as well as, of dermal and subcutaneous tissues in areas prone to calcinosis cutis (Behrend, 2015; Behrend et al., 2013; Berry, Hawkins, Hurley, & Monce, 2000; Schwartz et al., 2000). Furthermore, in the event of PTE, plain thoracic radiographs will most commonly demonstrate an alveolar or alveolar interstitial pattern in one or multiple areas (Flückiger & Gomez, 1984; Goggs, Benigni, Fuentes, & Chan, 2009).

ATs can be visualised either due to mass-effect or calcification within the neoplasm (Behrend et al., 2013; Penninck, Feldman, & Nyland, 1988; Reusch & Feldman, 1991), although mineralisation is not tumour-specific and may also occur with PDH-induced hyperplastic glands less commonly (Grooters, Biller, Theisen, & Miyabayashi, 1996; Penninck et al., 1988). Still, many ATs can be missed, and that is why radiography does not allow exclusion of the diagnosis. In one study, only 56% of 23 dogs with functioning ATs had radiological evidence of adrenomegaly with or without calcification; besides, mineralisation of the adrenal did not permit to discriminate between adenoma and carcinoma (Penninck et al., 1988). Similar results were reported by Reusch & Feldman (1991), who also observed inferior radiographic detection of right-sided carcinomas. Bilateral tumours may also be overlooked (Ford et al., 1993; Reusch

& Feldman, 1991). Ultimately, tumours measuring ≤ 20 mm in diameter are unlikely to be visualised (Voorhout, Rijnberk, Sjollema, & van den Ingh, 1990 cited by Behrend, 2015).

In dogs with phaeochromocytomas, abdominal radiographs add limited value and, similarly to ATs, difficulties may be encountered (e.g., sufficient size of the mass to be detectable, rarity of mineralisation in medullary masses). Yet, identifiable neoplasms may show as soft tissue opacities in close relation to the kidney, with or without displacement/distortion/obscuration of the ipsilateral kidney or near-by structures. Other radiographic findings observed in dogs with phaeochromocytomas included loss of serosal detail as result of abdominal effusion or diffuse retroperitoneal soft tissue radiopacity due to haemorrhage from a ruptured tumour, enlarged CVC, hepatomegaly, generalised cardiomegaly, ventricular enlargement, and pulmonary oedema (Barthez et al., 1997; Gilson, Withrow, Wheeler, et al., 1994; Reusch, 2015).

Finally, radiography plays an important role as a part of the preoperative investigations prior to removal of any adrenal tumour. Three-view thoracic radiographs constitute a suitable method of searching for lung metastases, which appear as soft tissue nodules (Barthez et al., 1997; Behrend, 2015; Gilson, Withrow, Wheeler, et al., 1994; Reusch & Feldman, 1991). However, this finding has not been commonly encountered at diagnosis/preoperative assessment in several studies (Anderson et al., 2001; Arenas et al., 2013; Barrera et al., 2013; Jiménez-Peláez, Bouvy, & Dupré, 2008; Kyles et al., 2003; Lang et al., 2011; Massari et al., 2011; Oblak et al., 2016; Schwartz et al., 2008). For ruling out abdominal metastases radiography is not ideal, thought it may raise suspicion of rather evident lesions such as, for instance, hepatic masses (Reusch, 2015; Reusch & Feldman, 1991).

1.4.3.2 Ultrasonography

Abdominal ultrasound (US) allows identification of both adrenal glands by experienced practitioners, recognition of smaller and non-mineralised adrenal tumours, retroperitoneal effusion, tumour invasion into vessels and adjacent structures, as well as, of intraabdominal metastases – all of the above are verified with higher resolution and precision. Nonetheless, ultrasonographic examination may be difficulted by presence of gas in the gastrointestinal tract, large body size, obesity, abdominal lymphadenopathy or masses, renal mineralization, or liver disease (Behrend, 2015; Reusch, 2015).

Size-wise, the measurements obtained by this imaging technique underestimates the actual size of the adrenal glands (Behrend, 2015; Pagani et al., 2016). Depending on the alignment of the adrenal glands' long axis, cross-sectional oblique views can result in miscalculated dimensions. The US cut-off value of 7.4 mm for the normal maximum diameter of the larger of the cranial or caudal pole, in sagittal or transverse planes, independently of body weight, has been

frequently used and is the most widely accepted (Behrend, 2015). A recent study has also reported that the caudal pole thickness of both left and right adrenals is the best parameter for ultrasonographic evaluation of normal and pathological adrenal glands size in dogs (Pagani et al., 2016).

On US images, features consistent with an adrenal tumour include moderate asymmetry within and/or between glands, distortion of normal parenchymal architecture, and contralateral gland cortical atrophy (in case of a secreting-AT) (Behrend et al., 2013). Other neoplastic characteristics have great variability: shape (focal, minimal-disrupting nodules or diffuse masses obviously altering the gland's figure) and echogenicity (hypo-, iso-, or hyperechoic relatively to the renal cortex; and homo- or heterogenous). Mineralisation (hyperechoic areas with acoustic shadowing), necrosis or haemorrhage (an-, hypo- or isoechoic areas) can be present as foci (Besso, Penninck, & Gliatto, 1997; Hoerauf & Reusch, 1999).

Ambiguity arises when mild asymmetry between glands is encountered, as it may also be deceptively found in dogs with PDH. Yet, ADH (main form of ACTH-independent HAC) can be appropriately diagnosed with US when the maximal dorsoventral thickness of the smaller gland (SDV) is ≤ 5.0 mm, with 82-100% sensitivity and 82-99% specificity (95% confidence interval) for that same cut-off value. Hence, secreting-ATs and equivocal asymmetric hyperplasia, occasionally observed with ACTH-dependent HAC (mainly PDH), can be differentiated (Benchekroun et al., 2010).

For detection of a tumour thrombus within the CVC, US has been reported to be 100% sensitive and 96% specific. However, if all forms of vascular invasion were to be considered (i.e., including vascular wall invasion without coexistent thrombus), sensitivity and specificity would be altered to 76% and 96%, respectively (Davis, Schochet, & Wrigley, 2012). Accordingly, another study reported a sensitivity of 80% and a specificity of 90% (Kyles et al., 2003). This can be explained by the difficulty in discriminating mural compression from actual vascular invasion (into the vessel wall or as a tumor thrombus) and a blood clot ("true" thrombus), when using this imaging method. Furthermore, identification of thrombi confined to the phrenicoabdominal vein might be challenging due to the small caliber nature of the vessel (Reusch, 2015).

US is also a suitable screening test for recognition of intraabdominal metastatic lesions, namely in the liver (Reusch & Feldman, 1991). Confirmation can be obtained through ultrasonographic-guided aspiration/biopsy (Behrend, 2015).

Shortcomings of this imaging method include: occasional undetectability of contralateral adrenal atrophy to a functional AT (Hoerauf & Reusch, 1999); inability to discern between macronodular hyperplasia from an AT; and possible misleading presentations such as

identification of bilateral tumours which may deceptively point towards a PDH diagnosis (Behrend, 2015).

Additionally, being able to infer on tumour origin or behaviour with US is improbable, especially in earlier stages, unless obvious features attributed to malignancy (local or distant invasion) are perceived. No pattern of echogenicity or architecture is specific, and even mineralization (which occurs more frequently within cortical masses rather than medullar) cannot be used as a differentiating factor in an individual patient (Besso et al., 1997).

Ultimately, size can provide helpful guidance. An adrenal gland with a maximum diameter superior to 40 mm is highly correlated with malignancy (Behrend et al., 2013; Besso et al., 1997). Moreover, any mass measuring ≥ 20 mm in maximum diameter or presenting signs of vascular invasion, deserves serious ponderation of malignancy (Cook et al., 2014; Labelle et al., 2004) and growth potential (Arenas et al., 2013).

Interestingly, by means of contrast-enhanced ultrasonography (a modality of ultrasonography), it might be feasible to take conclusions towards tumour type and behaviour, for instance, using vascular patterns and contrast-enhancement features (Bargellini et al., 2016; Pey et al., 2014).

1.4.3.3 Computed tomography and Magnetic resonance imaging

In comparison to US, computed tomography (CT) provides a facilitated and superior assessment of tumour size, shape, architecture, and margination (Reusch, 2015). What is more, contrast-enhanced CT has been shown to accurately execute crucial preoperative determinations regarding canine adrenal masses, with 92% sensitivity and 100% specificity for detection of vascular invasion (into the phrenicoabdominal vein, venae cava, and renal vein). It was possible to correctly differentiate between mural compression and actual vascular invasion, as well as, to identify invasion into the local musculature (Schultz, Wisner, Johnson, & MacLeod, 2009). Likewise, a tumour thrombus and a blood clot may be reliably distinguished (Reusch, 2015).

CT also improves the search for distant metastatic lesions (Behrend, 2015). Indeed, it was proven to be a more sensitive method for detection of pulmonary metastases than thoracic radiography (Armbrust et al., 2012).

On CT images, adrenal tumours features may vary: attenuation (homo- or heterogeneous with cystic or mineral components); margins (smooth, lobular, irregular); contrast enhancement (heterogeneous, peripheral, mild) (Rosenstein, 2000; Schultz et al., 2009). Notably, this imaging method may reveal mineralization, masses with diameters ≤ 20 mm, and atrophy of an adrenal contralateral to a functional AT, that might have been missed by radiography or ultrasonography (Hoerauf & Reusch, 1999; Voorhout, Stolp, Rijnberk, & van Waes, 1990).

Still, even with its advantages, it might be tricky to distinguish unilateral nodular hyperplasia from an AT (Voorhout, Stolp, Lubberink, & van Waes, 1988).

Interestingly, distinction of dogs with ACTH-independent HAC from those with ACTH-dependent HAC can be conjectured on the basis of an adrenal gland diameter ratio > 2.08 on reformatted images, with 100% sensitivity and 98% specificity (95% confidence interval) for that same threshold value (Rodríguez Piñeiro et al., 2011).

The level of accuracy and detail of CT findings provides valuable guidance when constructing a surgical plan, namely when opting for a particular surgical approach (e.g. midline or retroperitoneal) (Bailey, 1986; Emms, Wortman, Johnston, & Goldschmidt, 1986).

Relatively to CT, magnetic resonance imaging (MRI) may be more accurate in establishing the exact cranial extension of the CVC thrombosis, like has been showed in human medicine (Goldfarb et al., 1990). However, use of MRI is still limited, primarily due to significant inferior availability. Other drawbacks include being more expensive and taking longer time to complete a scan (Reusch, 2015).

In fact, in veterinary medicine, studies describing the systematic use of MRI as a method of assessment of adrenal lesions in dogs and cats are scarce. Yet, the appearance of supposed normal canine adrenal glands in MRI scans was reported (Llabres-Diaz & Dennis, 2003). MRI may prove useful as method of identification of metastases, namely when distant spread of a phaeochromocytoma to the central nervous system is present (Spall et al., 2011). Its modalities may also have the potential to infer on tumour behaviour (benign, malignant) and detect vascular invasion, in similarity to protocols used in human medicine (Larson et al., 2013).

A variety of imaging techniques, including modalities of CT and MRI, have been use in human medicine to distinguish between types of adrenal tumours (cortical, medullar, metastatic) and to infer on malignancy (Blake, Cronin, & Boland, 2010; Fitzgerald, 2018; Leung, Stamm, Raja, & Low, 2013). In dogs, however, these investigations are taking its first steps. In one study, it was not possible to discriminate between tumour types as a result of the overlap of CT-identified characteristics, though intratumoural localisation and transition of contrast enhancement was not evaluated (Gregori, Mantis, Benigni, Priestnall, & Lamb, 2015). Later on, another study has proven the worth of triple-phase helical CT, where specific characteristics were significant in differentiating between adrenocortical adenoma and carcinoma, and phaeochromocytoma (Yoshida et al., 2016).

1.4.4 Incidental discovered adrenal mass

The National Institutes of Health State-of-the-Science Statement (2002, p.4) National Institutes defines the term *incidentaloma* for human medicine:

> Clinically inapparent adrenal masses are discovered inadvertently in the course of diagnostic testing for other clinical conditions that are not related to suspicion of adrenal disease and, thus, are commonly known as incidentalomas. The definition of incidentaloma excludes patients who undergo imaging procedures as part of staging and work-up for cancer.

Over the past years, the use of US routinely has proven its key-role in the discovery of adrenal *incidentalomas* as predicted by Myers (1997), with a prevalence estimated at 4% and >80% of affected dogs being at least 9 years old (study period: 2007-2010) (Cook et al., 2014). An even higher prevalence (9.3%) was reported in a similar study using abdominal CT (study period: 2013-2014) (Baum et al., 2016). While these findings may indeed represent early stages of a worrisome adrenocortical carcinoma or phaeochromocytoma, it is imperative that they are interpreted critically considering that these animals tend to be older, thus their likelihood of having age-related minor alterations in their adrenal glands (non-functional and -neoplastic, with less than 15 mm in diameter, affecting one pole of a gland with a normal contralateral), as well as, other concomitant diseases (inclusively, other neoplastic diseases) (Behrend, 2015).
Upon this discovery, careful investigation of the nodule/masse endocrinological activity, behaviour (benign, malignant), and origin (cortical, medullar, metastatic) is warranted (Reusch, 2015) (**Table 5**). Aggressiveness of the diagnostic and therapeutic approach depends on diverse aspects: age of the patient; concurrent medical issues and respective severity; original motive that led to the US or CT scan; probability of the nodule/mass being or becoming hormonally active, grow considerably, and/or invade local or distant structures; and finally, the client's wishes and willingness to take action (Behrent, 2015).

Table 5. Major differential diagnoses of an incidentally discovered adrenal gland mass. (Adapted from: Reusch, C. E. (2015). Pheochromocytoma and Multiple Endocrine Neoplasia. In E. C., Feldman, R.W., Nelson, C. E., Reusch & J. C. R., Scott-Montcrieff (Eds.): *Canine and Feline Endocrinology*, (4th ed.), (p. 533). Missouri: Saunders, Elsevier.)

Major differentials of an incidentally discovered adrenal mass
Hormonally active adrenal nodule/mass
> Aldosterone-producing adenoma, carcinoma, or hyperplasia
> Glucocorticoid-producing adenoma or carcinoma
> Adrenocortical hyperplasia
> Sex-hormone producing adenoma or carcinoma
> Phaeochromocytoma
Hormonally inactive adrenal nodule/mass
> Hormonally silent adenoma, carcinoma, or hyperplasia
> Metastasis
> Miscellaneous: myelolipoma, lipoma, cyst, abscess, hematoma, or granuloma

Although some of the differentials in **Table 5** are no cause for concern, being able to identify those cases is highly difficult without histopathological examination. Even in the presence of small, non-functional nodules/masses (< 15-20 mm), it should be beared in mind that they might become functionally active with time and there might be a ~14-30% chance of an *incidentaloma* being malignant (Cook et al., 2014). Moreover, for any mass measuring ≥ 20 mm in maximum diameter, the likelihood of malignancy (Cook et al., 2014; Labelle et al., 2004) and growth potential (Arenas et al., 2013) might also be high.

As such, it would be prudent to closely monitor these cases for growth and evolution, which can be easily accomplished with US. Behrend (2015) suggests starting intervals between scans of 2 to 3 months, which later can be extended to 4 to 6 months. If size increases considerably, pursuing surgical excision should be recommended.

1.4.5 Fine-needle aspiration

Cytological evaluation of specimens acquired by ultrasonographic-guided fine-needle aspiration/biopsy (US-FNA) of an adrenal nodule/mass may reveal or point towards its origin and malignancy potential. Particularly, it may have a valuable role in the investigation of adrenal *incidentalomas* of uncertain clinical significance, avoiding lengthy postponements in pursuing the ultimate definite treatment (i.e., adrenalectomy) (Sumner, Lacorcia, Rose, Woodward, & Carter, 2018). Furthermore, these findings allow an accordingly adjustment of preoperative planning, therefore minimising perioperative mortality (Behrend, 2015; Herrera et al., 2008).

Indeed, a recent study showed that cytology may be as accurate as in 90 to 100% of cases in distinguishing cortical from medullary tumours in companion animals (Bertazzolo et al., 2014). Unfortunately, it was not reliable enough to judge tumour biological behaviour.

In veterinary medicine, this diagnostic tool has been infrequently reported (Bertazzolo et al., 2014; Besso et al., 1997; Rosenstein, 2000; Spall et al., 2011). Inherently, little is known regarding potential risks and complications associated with percutaneous US-FNA of adrenal lesions, though there is no reason not to extrapolate possibilities from human medicine literature (e.g., increased difficulty in surgical resection of the mass as a result of inflammation and retroperitoneal fixation, haematoma, error or inadequate biopsy, severe pain, severe hypertension due to triggering of a catecholamine surge, delay in pursuing the surgical procedure) (Besso et al., 1997; McCorkell & Niles, 1985; Reusch, 2015; Vanderveen et al., 2009). Even so, in the previously cited veterinary case studies, no detrimental effects were encountered.

Very recently, in an attempt to provide clinical safety information regarding percutaneous US-FNA of adrenal lesions, a study reported a complication rate of 5%, where only in 1 of 20 separate uni- or bilateral sampling events, a dog develop a subsequent adverse reaction (ventricular tachycardia) – its cytological sample was consistent with a phaeochromocytoma (Sumner et al., 2018). Although this diagnostic instrument seemed to be relatively safe in this small study, further supportive investigations are required.

2. TREATMENT OF ADRENAL GLAND NEOPLASMS

2.1 Conservative management

2.2.1 Adrenocortical tumours

Medical therapy is generally reserved for patients to whom the risk of undertaking adrenalectomy does not outweigh the benefits to their welfare – those of very old age, debilitated, with deemed unresectable masses, metastases or concerning comorbidities – and when pursuing surgery is against owners wishes (Kintzer & Peterson, 1997; Lunn & Page, 2013; Reusch, 2015).

The primary choices for medical management are mitotane and trilostane. Mitotane is an adrenocorticolytic agent, causing selective necrosis of the zonae fasciculata and reticularis (Behrend, 2015). Treatment with mitotane serves as a medical adrenalectomy by using it as a proper chemotherapeutic agent, aiming to obliterate all tumour tissue and even to cause hypoadrenocorticism (Kintzer & Peterson, 1997). Its effectiveness and relative safety was shown (Kintzer & Peterson, 1994). For this purpose, doses required are typically higher than those for PDH and still, relapses are common. Unfortunately, its effectiveness might be limited by adverse reactions to direct mitotane toxicity (e.g., anorexia, lethargy, weakness, diarrhoea), which prevent completeness of treatment (Kintzer & Peterson, 1997).

Trilostane acts as an inhibitor of the adrenal enzyme 3β-hydroxysteroid dehydrogenase, thereby suppressing production of progesterone and its end-products (e.g., cortisol and aldosterone). While, theoretically, these effects should be fully reversible, adrenal necrosis can occur with consequential extended or perpetual cortisol deficiency with or without aldosterone deficiency. In terms of doses, the protocol is identical whether one is dealing with PDH or an AT (Behrend, 2015). Even without adrenocortical cytotoxicity, trilostane has been associated with successful outcomes of patients with ADH (Eastwood, Elwood, & Hurley, 2003; Feldman, 2011; Vaughan, Feldman, Hoar, & Nelson, 2008), including dogs with metastases (Benchekroun et al., 2008).

Two studies have compared trilostane and mitotane in dogs with ADH and reported median survival times of 353 and 102 days (Helm et al., 2011), respectively; and of 14.0 and 15.6 months (Arenas, Melián, & Pérez-Alenza, 2014), respectively. In both studies, no significant

differences were detected between survival times. However, because the trilostane has milder and less frequent adverse effects, i.e., is less toxic, it is advisable to use trilostane primarily (Arenas et al., 2014). Evidence of metastases (Helm et al., 2011), old age, weakness, and high post-ACTH cortisol concentrations (Arenas et al., 2014) were found to be negative prognostic indicators with statistical significance.

Ketoconazole can also be used as palliative therapy in light of its action as an inhibitor of adrenal and gonadal steroidogenesis through enzymatic blockade. Basically, it blocks cortisol production and rapidly decreases circulating concentrations. Therefore, ketoconazole may allow control of clinical signs (Feldman, Bruyette, Nelson, & Farver, 1990; Kintzer & Peterson, 1997). Nevertheless, in contrast to mitotane, this alternative drug lacks adrenocortical cytotoxicity and would not be expected to act on tumour growth; rendering it to be a second-line option (Kintzer & Peterson, 1997).

Recently, a study evaluated the feasibility and efficacy of a modality of radiotherapy in treating canine adrenocortical tumours with vascular invasion (Dolera et al., 2016). Though promising, further investigations regarding treatment safety and efficacy are due.

2.2.2 Phaeochromocytomas

No successful chemotherapy or radiotherapy protocol has been reported in detriment of the surgical route (Lunn & Page, 2013; Reusch, 2015). Conservative management can solely manage clinical signs (namely, excessive circulating catecholamine-related), with no effect on other neoplastic evolutive behaviours (growth, local invasion, distant spread). Even though the majority of dogs succumb to disease rather quickly, considering the vast tumour-generated complications which can lead to death (triggering of catecholamine surges resulting in fulminant cardiac arrest, tumour thrombosis, rupture, and spread to local and distant sites), according to Reusch (2015), patients handled exclusively medically with phenoxybenzamine may still live for more than a year after the diagnosis.

Interestingly, a case report documents the conservative management of a dog with a malignant phaeochromocytoma, by means of radiotherapy using iodine-131 metaiodobenzylguanidine (Bommarito et al., 2011). The treatment was clinically well tolerated with a notable improvement in clinical signs after the first session. To determine clinical utility of this therapeutic route, further prospective investigations are required.

2.2 Surgical management

2.2.1 Indications

In spite of being a technically challenging surgical procedure, commonly associated to intra- and postoperative complications resulting in high mortality rates, adrenalectomy is still widely recognised as the treatment of choice in dogs in the following circumstances: with functional adrenocortical tumours, phaeochromocytomas, large masses, and in presence of malignancy characteristics. Accordingly, in case of benign, small, non-invasive, and non-producing neoplasms, there might be no indication for surgery. Sadly, this assessment is quite difficult to predetermine without excision and histopathological examination. Even with non-functional tumours, there is still a risk for local and distant spread, thus, rendering virtually impossible to predict tumour evolution (Behrend, 2015; Myers, 1997; Reusch, 2015).

Size may be a helpful feature in guiding the decision process. As previously mentioned, any mass measuring ≥ 20 mm in maximum diameter or presenting signs of vascular invasion, warrants suspicion of malignancy (Cook et al., 2014; Labelle et al., 2004) and growth potential (Arenas et al., 2013); thus, adrenalectomy ought to be recommended in these cases.

Interestingly, occurrence of metastases and/or tumour thrombi may not constitute outright contraindications for adrenalectomy (Anderson et al., 2001; Frankot, Behrend, Sebestyen, & Powers, 2012; Reusch, 2015). While it is unknown whether surgery will or not extend survival in patients with metastases, resections of tumours and their respective thrombus have been described with subsequently successful outcomes (Barrera et al., 2013; Kyles et al., 2003; Lang et al., 2011; Reusch, 2015).

2.2.2 Perioperative management

In the preoperative period, ideally as close as possible of the surgical intervention, key tumour-related features, that may alter the surgical plan or the expected risk for intra- or postoperative complications, should be reassessed. Thoracic radiography to rule out pulmonary metastases and abdominal ultrasonography to obtain an updated dimension of the mass, evaluate local invasion (specifically, vascular invasion and tumour thrombus characteristics), identify eventual haemorrhage within the tumour or retroperitoneal space, and also search for metastatic lesions on other abdominal structures (with or without US-FNA to attain confirmation) (Behrend, 2015). These imaging verifications can be superiorly fulfilled with CT or MRI (Armbrust et al., 2012; Goldfarb et al., 1990; Schultz et al., 2009).

When vascular invasion is identified in pre-surgical evaluations, blood typing and cross-matching should be part of preoperative measures in consideration of the risk of significant blood loss that might result from venotomy or tumour dissection (e.g., iatrogenic laceration of

the CVC or aorta) and consequent necessity of intraoperative blood transfusion (Barrera et al., 2013; Behrend, 2015; Kyles et al., 2003; Oblak et al., 2016; Schwartz et al., 2008). Also, preparations can be made to systematically induce intraoperative hypothermia (oesophageal temperature of 32°C), before vascular occlusion, as a protective measure against tissue ischemia (Kyles et al., 2003).

These procedures are advocated irrespectively of type of adrenal tumour.

2.2.2.1 Adrenocortical tumours

As a result of functional ATs, several worrisome complications may arise, namely, cortisol-induced immunosuppression, compromised wound healing, systemic hypertension, hypercoagulability and consequent thromboembolism, local invasion (namely, major-caliber vessels), hypoadrenocorticism, and pancreatitis (Behrend, 2015). Therefore, perioperative medical therapy may be key in preventing or reducing many of these adversities.

Short-term treatment targeting to reduce or reverse HAC and its respective metabolic consequences may be accomplished with trilostane for 3-4 weeks prior to surgery. The aim is to improve clinical presentation and reduce post-ACTH serum cortisol levels, so that adrenalectomy can be pursued as soon as hypercortisolemia is tamed. However, irrespectively of the state of control, surgery should not be booked for later than 30 days after beginning the medication. Serum electrolytes should be monitor at the same time for alterations consistent with hypoaldosteronism (Behrend, 2015; Vaughan, Feldman, Hoar, & Nelson, 2008).

As a part of the preoperative assessment, BP should be measured and addressed fittingly, along with routine preanesthetic bloodwork and urinalysis. Even though it might be possible to normalise HAC-related hypertension once the HAC itself is under control, severely elevated systolic BP (> 180 mm Hg) may warrant initiation of antihypertensive therapy (Behrent, 2015).

PTE is a major complication caused by HAC which can result in death and it is typically noted within the first 72h after surgery (Adin & Nelson, 2012; Behrend, 2015). Despite inexistence of a proven protective effect, anticoagulant therapy may still be routinely used to combat thromboembolic events (Barrera et al., 2013; Kyles et al., 2003). A protocol suggested by Adin & Nelson (2012) includes intraoperative intravenous administration of heparinised plasma to supply antithrombin III, to be continued postoperatively with subcutaneous heparin administration during 2-3 days at gradually reducing doses. In addition, adequate anesthetic and pain relief therapy to attain quick return to ambulatory condition (within 4h of surgery) works in favour of circulation and, consequently, minimizes clot formation.

Recognition of PTE in the perioperative period may be tricky in consideration of highly variable, inconsistent, and nonspecific clinical signs, as a result of equally variable degrees of

physiological impairment. Dyspnoea, tachypnoea and depression are the most common signs; coughing, haemoptysis, cyanosis, syncope, collapse, and sudden death may also occur. Physical examination may reveal harsh respiratory sounds or crackles upon auscultation, as well as, tachycardia with a louder or split 2nd heart sound. Conversely, auscultation may be muffled (due to pleural effusion) and other indications of congestive right-sided heart failure (e.g. jugular pulse, ascites) or deficient forward heart function (pale mucous membranes, prolonged capillary refill time, weak pulse) may occur. Basic bloodwork abnormalities are of limited added value, routine coagulation profiles are typically normal, and blood gas analysis are nonspecific – results may contribute to escalate the suspicion (hypoxaemia, hypocapnia, raised alveolar-arterial gradient) or may be normal; thus, without power to confirm or exclude the diagnosis. Plain thoracic radiographs most commonly reveal an alveolar or alveolar interstitial pattern in one or multiple areas, though, selective pulmonary angiography is the appointed diagnostic *gold standard* (until CT angiography becomes promptly available). However, most of these patients are unstable, representing a high anaesthetic risk, and therefore, this and other useful diagnostic tools (such as, CT and MRI) are rendered unviable. Ultimately, PTE is frequently a diagnosis of exclusion. Anticoagulant, and/or platelet antiaggregant medication should be instituted accordingly with individual patient necessity (Goggs et al., 2009).

Acute hypoadrenocorticism is also expected after removal of an endocrinologically active AT. The return of this physiologic function is dependent on the degree of atrophy of the contralateral adrenal secreting-cells. To prevent hypoadrenocorticism, intravenous fluids should be used (at a surgical maintenance rate) and, after intraoperative excision of the tumour, dexamethasone can be administrated intravenously. Glucocorticoid supplementation prior to surgery is contraindicated on the basis that it might increase the risk of facing perioperative complications, specifically, hypertension, overhydration, and thromboembolism. In the postoperative period, dexamethasone should be continued at inferior doses (Anderson et al., 2001; Andrade et al., 2014; Behrend, 2015; Kyles et al., 2003; Lang et al., 2011; Massari et al., 2011). Afterwards, upon full regain of autonomous eating and drinking, prednisone may start to be progressively reduced over an extended time period (up to 3-6 months) while keeping a close eye on appetite, lethargy, and vomiting. This process can be monitored with ACTHSTs: a normal test result renders glucocorticoid supplementation unnecessary; a low test result proves glucocorticoid insufficiency and the need to elevate the prednisone dosage if matching clinical signs are also reported during tapering. The ACTHST may also be used to evaluate surgery success and, at the same time, to assert the real necessity for glucocorticoid supportive therapy. This is, when performed 6-8h postoperatively, reduced pre-ACTH and post-ACTH serum cortisol concentrations support the successful complete removal of the neoplasm and the demand for

supportive drug therapy; yet, non-functional metastases cannot be ruled out. Conversely, if values obtained were similar to the previous preoperative results, it could be argued that functional tumour cells are still present and supplementation with glucocorticoids is uncalled-for (Behrend, 2015).

Besides postoperative hypocortisolism, hypoaldosteronism may also occur since aldosterone-secreting cells can also suffer from a certain level of atrophy. Hence, development of hyponatremia and hyperkalaemia should be closely monitored, especially in the first 72h following surgery. Nevertheless, this electrolyte imbalance is commonly transient, lasting about 24-48h and normalising once substitution glucocorticoid therapy is tapered and the animal resumes normal feeding routines. However, it is impossible to predict and distinguish the patients that will have a self-limiting electrolyte derangement from those who will seriously need mineralocorticoids supplementation. Therefore, and because short-term therapy is rather benign, it is advisable to start supplementation if the imbalance lasts longer than 72h or when serum sodium is < 135 mEq/L or serum potassium is > 6.5 mEq/L (Behrend, 2015). Mineralocorticoid substitution may be accomplished with injectable desoxycorticosterone pivalate (Lynn, Feldman, & Nelson, 1993); or oral fludrocortisone acetate to be reduced and eventually discontinued within 1-2 weeks. Measurement of serum electrolytes is used to guide the process and adopt accordingly dose adjustments (Behrend, 2015).

When bilateral adrenalectomy is pursued (Anderson et al., 2001; Behrend, 2015; Kyles et al., 2003; Lang et al., 2011; Oblak et al., 2016; van Sluijs et al., 1995), life-long substitution therapy with gluco- and/or mineralocorticoids will be required.

2.2.2.2 Phaeochromocytomas

Depending upon the exact perioperative moment, a different set of complications is expected to arise from the effects of excessive catecholamine release. While anaesthetic induction and surgical handling of the tumour may spike circulating catecholamine levels with subsequent severe events of hypertension, tachycardia, cardiac arrhythmias, and even cardiac arrest; after excision of the tumour, the inverse (hypotension) may occur due to a brisk drop of blood catecholamines resulting in equally rapid descent of vascular tone and resistance (Adin & Nelson, 2012; Herrera et al., 2008; Reusch, 2015).

Neither hormonal nor anticoagulant treatments are indicated in the peri- or postoperative periods in dogs with phaeochromocytomas alone (Adin & Nelson, 2012). However, if the tumour origin is uncertain (cortical or medullar) or if there is a suspicion of a concurrent functional AT, the recommendation is to proceed with the administration of dexamethasone and evaluate the need for further supplementation in the postoperative period (Reusch, 2015).

In dogs with phaeochromocytomas, preoperative treatment with phenoxybenzamine (a non-competitive α-adrenergic receptor antagonist) can be useful. The intention is to reverse vasoconstriction and hypovolaemia prior to surgery, to control/stabilise fluctuations of BP, heart rate, and rhythm before and during anaesthesia, and ultimately, to influence surgical outcome (i.e., survival). In fact, Herrera et al. (2008) reported a significantly lower mortality rate in a group of dogs pre-treated with phenoxybenzamine (13%) in comparison to the untreated group (48%), with the former being 6 times more likely to survive surgery than the latter. However, the etiologic mechanism behind these results was unclear taking into account that no significant differences were found in regard to theoretically influencing factors: intra- and postoperative frequency and severity of hypertensive and hypotensive episodes, and intra- and postoperative BP variability. Moreover, in another study, phenoxybenzamine did not have a significant protective effect as previously reported (Barrera et al., 2013). Still, the results obtained by Herrera et al. (2008) do strongly support pre-adrenalectomy therapy with phenoxybenzamine in dogs with phaeochromocytomas; and its use has been frequently stated (Andrade et al., 2014; Barrera et al., 2013; Gilson, Withrow, & Orton, 1994; Kyles et al., 2003; Massari et al., 2011; Oblak et al., 2016; Schwartz et al., 2008).

Currently, is still uncertain which dose and duration of drug therapy are the best effect-wise. The protocol used by Reusch (2015) involves the administration of phenoxybenzamine in progressively augmented doses up to a maximal dose or until the patient exhibits signs of hypotension (e.g., lethargy, weakness, syncope) or other adverse side effects (e.g., tachycardia, vomiting). Monitoring throughout the treatment period and dose adjustments are generally based on owner feedback, although regular examination of BP, heart rate, and heart rhythm would be preferable. The surgery may be planned for ~2 weeks after the start of phenoxybenzamine, with the last dose being given in the evening before the intervention. This protocol is standardly used in dogs undergoing adrenalectomy for their phaeochromocytomas, in spite of being hyper- or normotensive when examined. Additionally, if persistent tachycardia or tachyarrhythmias are recognised, preoperative therapy may be complemented with a β-adrenergic receptor antagonist (preferably a selective β_1-blocker – e.g., atenolol), but never before or soon after initiation of α-adrenergic blockade medication, in consideration of the risk of severe hypertension.

Hospitalisation prior to adrenalectomy is recommended sooner rather than later (24h before), in order to assert and monitor BP, heart rate and rhythm, as well as, to regularise circulating volume through institution of fluid therapy (at maintenance rate). It is also imperative to maintain a close monitorisation of these parameters during the subsequent high-risk periods for the development of hypertension and arrhythmias (anaesthetic induction and surgery), as well

as, after the intervention (Adin & Nelson, 2012; Reusch, 2015). Various anaesthetic drugs can be used, although one might want to steer clear of those that are arrhythmogenic, anticholinergic, act on α-receptors, or amplify the effects of catecholamines (Adin & Nelson, 2012); thus, avoiding increasing the risk of complications.

Taking into account the already described implications of manipulating the tumour, it is vital that the surgeon and the anaesthesiologist work in an intimate relationship. Whereas the former should give fair warning before carefully approaching the area of the tumour, the latter should be readily prepared drugs-wise to face inherent complications (Reusch, 2015). Persistent tachycardia and tachyarrhythmias can be handled with esmolol (an ultra-short-acting β1 blocker) (Kyles et al., 2003; Lang et al., 2011), while lidocaine or procainamide are adequate for more serious ventricular arrhythmias (Lang et al., 2011; Whittemore et al., 2001). With regard to hypertension, management methods include deepening of the anaesthesia and/or administration of phentolamine (a short-acting α-adrenergic blocker) and/or nitroprusside (a direct vasodilator) (Kyles et al., 2003; Lang et al., 2011; Reusch, 2015). To deal with hypotension, other BP dropping treatments should be primarily reduced or interrupted, and thereafter, crystalloid (or colloid) fluids can be used to replace intravascular volume (Gilson, Withrow, & Orton, 1994; Kyles et al., 2003; Lang et al., 2011; Massari et al., 2011). In more serious cases, other drugs may be added to increase contractility (e.g., dobutamine) or vascular tone (e.g., phenylephrine, norepinephrine, vasopressin) (Gilson, Withrow, & Orton, 1994; Kyles et al., 2003; Reusch, 2015). Furthermore, an effort to keep surgical time to minimum might be crucial according to Herrera et al. (2008). In their study, for every hour increase in surgical time, the likelihood of 10-day survival dropped by 75%.

After the procedure, equally thorough monitorisation should be continued for at least 48h, as episodes of arrhythmias, and BP derangements may still occur. Hypotension may be attributed to the resection of the tumour and consequential abrupt fall in blood catecholamines or may suggest haemorrhage. Accordingly, in theory, hypertension would not be expected and may indicate remnant functional neoplastic tissue (primary or metastatic) (Reusch, 2015).

As anteriorly mentioned, bilateral adrenalectomy implicates subsequent gluco- and/or mineralocorticoid replacement for life. Fortunately, in the event of bilateral medullary tumours, there might be a chance of avoiding this setback if adrenal cortex-sparing surgery is attempted – so far only reported in human medicine (Esen et al., 2012). Yet, interestingly, a unilateral complete followed by a contralateral partial adrenalectomies were reported in a canine patient, which permitted the maintenance of adequate adrenal function with no need of supplementation therapy (Larson et al., 2013).

2.2.3 Surgical approaches

2.2.3.1 Ventral midline celiotomy with or without a paracostal extension

A ventral midline celiotomy is the most frequently used approach to surgical manage the adrenal glands in dogs (Anderson et al., 2001; Gilson, Withrow, & Orton, 1994; Herrera et al., 2008; Kyles et al., 2003; Massari et al., 2011; Oblak et al., 2016), probably because of familiarity with the technique and associated anatomic perspective. Besides, it is the only method to enable full abdominal exploration and bilateral procedures through a single wound, and may prevent postoperative discomfort associated with muscular transection by entering the abdomen through the *linea alba* instead. In case of large adherent masses and when temporary occlusion of circulation is required during resection, a ventral midline incision provides better exposure, namely, of the vessels like the CVC. On the other hand, accessing the dorsal retroperitoneal space may be difficult, especially, in large and deep-chested patients. Extending the cranial aspect of the midline incision into a paracostal one may prove helpful in these cases, though it is rarely needed (Adin & Nelson, 2012; Anderson et al., 2001; Fossum & Caplan, 2013; Massari et al., 2011). In certain cases, visualisation may also be improved through mobilisation of the falciform ligament, either by releasing it from one or both sides of the incision, or by its excision after respective ligation at its base (Tillson & Tobias, 2012). To expose the left adrenal and kidney, the colon should be retracted medially; the right adrenal gland is more challenging, hence, the hepatorenal ligament can be broken/cut followed by cranial retraction of the right lateral and caudate liver lobes to simplify the task ahead. Regardless the side which will be addressed, self-retaining abdominal retractors (e.g. Balfour) should be placed primarily. Nonabsorbable monofilament suture material has been advised to close the *linea alba* in consideration of the delayed wound healing expected in patients with HAC (Adin & Nelson, 2012). Because the degree of this compromise is hard to judge, stitches should stay put until regrowth of hair in the area of the incision is perceived, irrespectively of the surgical approach used (Behrend, 2015). When a paracostal extension is made, closure should start by approaching the abdominal wall at the connection point between both incisions, followed by closure of the *linea alba*, and lastly, closure of the paracostal wound (each muscle layer individually) (Fossum & Caplan, 2013).

2.2.3.2 Flank/Paracostal/Paralumbar/Retroperitoneal approach

Referred by different nominations, this approach is less invasive/traumatic, provides better access to the dorsal abdomen (especially in right-sided adrenalectomies), and the risk of pancreatic injury and wound breaking with subsequent herniation is considerably inferior in comparison to the midline celiotomy. Nonetheless, it is only appropriated for unilateral procedures and more straightforward tumour resections. Hence, proper presurgical abdominal

imaging should take place to ensure no other structures need handling or further exploration (Adin & Nelson, 2012; Emms, Wortman, Johnston, & Goldschmidt, 1986; Fossum & Caplan, 2013; van Sluijs et al., 1995).

The animal is positioned in lateral recumbency and an elevating object may be placed (e.g. rolled towel or sandbag) between the abdomen and the surgical table. The skin incision is made just caudally to the last rib, with roughly 10-14 cm in length, starting from the lateral vertebral processes and finishing 3-4 cm before the ventral midline (Fossum & Caplan, 2013). Thereafter, the muscles layers are incised separately and following each respective fibber orientation. To expose the adrenal gland, the ipsilateral kidney should be retracted ventrally with care throughout in order to avoid traumatising and consequent rupturing of near-by vascular structures. If required, the last ribs may be sectioned and retracted cranially. In patients with HAC, it is still advisable to use nonabsorbable monofilament suture material when closing the muscle wall layers individually, despite the unlikelihood of wound breaking down occurring in comparison to an approach through the *linea alba* (Adin & Nelson, 2012).

More recently, a 12th intercostal space approach for right adrenalectomy specifically, with or without involvement of the CVC, has been described by Andrade et al. (2014) as a superior method of exposure of the right adrenal and associated vasculature in detriment of the paracostal, midline or a combination of both approaches. Obtaining suitable access is a persistent challenge common to the paracostal and midline approaches because of the positioning of the right adrenal gland: far cranial, under the ribs, dorsal to the CVC. Excellent access with acceptable complication rates and clinical outcomes were reported with this innovative intercostal approach (Andrade et al., 2014).

2.2.3.3 Laparoscopy approach

Laparoscopic adrenalectomy (LA) combines the best of both previously described techniques by permitting a thorough abdominal exploration while being a minimal invasive procedure with enhanced visualisation and exposure (Adin & Nelson, 2012; Jiménez-Peláez et al., 2008; Mayhew, 2009). In comparison to open procedures, LA studies have described faster recoveries, shorter hospitalisation periods, fewer and only minor wound complications, and shorter operative times (Jiménez-Peláez et al., 2008; Mayhew et al., 2014; Naan, Kirpensteijn, Dupré, Galac, & Radlinsky, 2013; Pitt et al., 2016). Moreover, dogs with known cortisol-secreting ATs submitted to LA might benefit from a superior prevention of thromboembolism considering that they will recover to ambulatory condition faster, thus enabling frequent short walks and, ultimately, promoting blood flow and minimizing clot formation (Behrend, 2015). Additionally, the use of LA might be of particular interest in the event of incidentally found adrenal masses of uncertain clinical significance (Ko et al., 2018; Mayhew, 2009). Indeed,

because surgical removal and histopathological examination are the only way to attain a definite diagnosis and prognosis, the minimal traumatic nature of this method works in favour of opting for surgery sooner rather than later.

Careful patient selection is imperative. LA is conditioned by large masses (> 6 cm) or vascular invasion, for which open adrenalectomy is indicated; thus, the importance of preoperative diagnostic imaging. Other contraindications include animals with systemic instability, uncontrolled metabolic or acid-base disturbances and coagulopathies, untreated severe arrhythmias, hypertension, and conditions that determine poor tolerance to pneumoperitoneum (e.g., severe cardiorespiratory disease, diaphragmatic herniation) (Mayhew, 2009).

An important downside of LA is the compromised ability to tackle intraoperative complications such as haemorrhage. Occasionally, if significant haemorrhage occurs, the procedure has to be immediately converted to an open approach (Mayhew et al., 2014; Pitt et al., 2016). Furthermore, despite its clinical consequences remaining unclear, capsule disruption and masses removed in fragments might raise concern for abdominal tumour seeding and should be avoid as much as possible (Jiménez-Peláez et al., 2008; Mayhew, 2009; Mayhew et al., 2014; Naan et al., 2013).

Very recently, a pilot study evaluated the feasibility of a new modality of LA in dogs with an interesting promise of providing better outcomes with minimal complications, postoperative pain, or damage to the adrenal gland – single-port retroperitoneoscopic adrenalectomy (SPRA) (Ko et al., 2018). In detriment of other transabdominal LA techniques, SPRA provided direct access to and a clear view of the adrenal gland without necessity of retracting other organs. Anticipated advantages include: shorter operative time, less blood loss, less pain, better patient comfort, faster recovery, superior cosmetic results, reduced risk of postoperative adhesions and of tumor cells seeding to the abdominal organs. On the other hand, the small working space may prove challenging to work with, the ability to explore other organs is rather compromised, and tumour size might limit applicability of this technique to benign tumours (e.g., adenomas) and small *incidentalomas*, up to 3 cm (based on the 3 cm incision used in the study).

2.2.4 Surgical technique

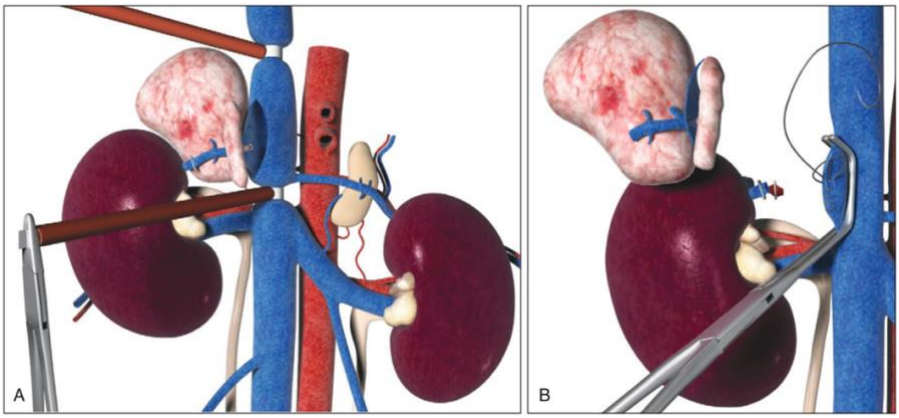
Irrespective of the chosen surgical approach, obtaining a perfectly adequate exposure is an adversity shared by all techniques, thus having a surgical assistance may be vital to achieve suitable retraction. Dissection of the gland is often started at the lateral aspect, distantly from the large calibre vasculature, with ligation and transection of the formerly-denominated phrenicoabdominal vein at the lateral border of the gland. This free-end is manipulated medially, aided by a stay suture or an atraumatic instrument, revealing dorsal vascular branches to be addressed. Thereafter, dissection progresses on the caudal border of the gland, with

occlusion of renal arterial branches. At this stage, if the kidney or its correspondent irrigation appears to have been invaded, concurrent ipsilateral nephrectomy may be warranted. Finally, prior to complete tumour excision, the medial plane is bluntly dissected and the common trunk (for the caudal phrenic and cranial abdominal veins) has to be ligated close to its entry point on the CVC (Adin & Nelson, 2012). Due to the intimate relation between the CVC and the right adrenal capsule (Hullinger, 2013), the utmost care while separating the two structures is vital to prevent iatrogenic rupture of the venae cava (Adin & Nelson, 2012; Oblak et al., 2016).
Availability of vascular clips, mono- or bipolar electrocoagulation, or a vessel-sealing device can ease haemostasis throughout the dissection process (Andrade et al., 2014; Jiménez-Peláez et al., 2008; Ko et al., 2018; Lang et al., 2011; Massari et al., 2011; Mayhew et al., 2014; Naan et al., 2013; Oblak et al., 2016; Pitt et al., 2016).

2.2.4.1 CVC Venotomy and Thrombectomy

Caval thrombi has been reported to occur in 33 to 55% of dogs with phaeochromocytomas (Barrera et al., 2013; Bouayad et al., 1987; Kyles et al., 2003; Lang et al., 2011; Twedt & Wheeler, 1984) and as high as 71% (Herrera et al., 2008). Lower rates of caval thrombi, from 2 to 21%, have been reported in dogs with ATs (Anderson et al., 2001; Barrera et al., 2013; Kyles et al., 2003; Lang et al., 2011; Scavelli et al., 1986). While this difference was found significant in two studies (Barrera et al., 2013; Kyles et al., 2003), no significant difference was found between right- and left-sided adrenal tumours invading the CVC in those same reports, though it seemed more common with right- (35%) than with left-sided (20%) neoplasms (Kyles et al., 2003).
When addressing CVC invasion, Rumel tourniquets should be loosely applied primarily, even before any attempt of dissecting the neoplastic adrenal. They are positioned just caudal to the liver and just cranial to the renal veins; if the caudal tourniquet is placed caudally to the right renal vein, a third tourniquet is required around the referred vessel; if the thrombus extends into the intrahepatic CVC, the cranial tourniquet is tightened only after thrombectomy (Adin & Nelson, 2012; Fossum & Caplan, 2013; Kyles et al., 2003). Afterwards, the adrenal may be freed from its surrounding connections, leaving for last the entry point of the tumour thrombus in the CVC – right adjacently is the target area to perform a longitudinal incision in the vessel, but not before tightening the tourniquets (**Figure 1**). A suction device may help conserve a clear view by preventing blood pooling. Following thrombus excision, a minor quantity of blood may be permitted into the delimitated area (to prevent air embolism), the venotomy is isolated with a partial occlusion clamp and the tourniquets released. Either 4-0 or 5-0 suture material are appropriated to close the venotomy in a continuous pattern (Adin & Nelson, 2012).

Figure 1. Resection of a right-sided adrenal gland tumour invading the CVC (From: Adin, C. A., & Nelson, R.W. (2012). Adrenal Glands. In K. M., Tobias & S. A., Johnston (Eds.): *Veterinary surgery: Small animal*, (volume two), (p. 2041). Missouri: Saunders, Elsevier.).



Caption: (A) Rumel tourniquets are applied to provide adequate temporary blood-flow occlusion of the CVC to allow tumour thrombus resection. (B) Blood-flow is restored while suturing the venotomy incision aided by a partial occlusion clamp.

Blood-flow occlusion should be attempted to last as briefly as possible. MacPail (2013), in respect of inflow occlusion – a technique which entails interruption of all venous flow to the heart –, stipulates an ideal time between 2 and 4 minutes for circulatory arrest in normothermic animals. This period can be prolonged up to 8 minutes provided mild, whole-body induced-hypothermia is attained to protect tissues from ischemia. To do so, oesophageal temperatures have to be maintain below 34°C, yet, above 32°C to prevent spontaneous ventricular fibrillation (Herrera et al., 2008; Kyles et al., 2003; MacPhail, 2013; Moon & Ilkiw, 1993).

An experimental study has demonstrated that acute complete CVC occlusion can be safely performed in dogs for periods up to 8 minutes, with subsequent full haemodynamic recovery within 5 minutes (Hunt, Malik, Bellenger, & Pearson, 1992). The explanation behind was hypothesised by Horvath & Bender (1961), who argued that collateral circulation developed rapidly thus preventing major physiologic consequences. Likewise, another experimental study has shown the formation and growth of collateral vessels in cases of chronic gradual CVC occlusion (Peacock, Fossum, Bahr, Miller, & Edwards, 2003).

A recent case report confirms previous published findings by supporting the ability of canine patients to survive prolonged acute CVC occlusions (Halwagi, Crawford, Hoddinott, & Oblak, 2017). It describes a successful outcome with minimal postoperative complications (namely, mild pelvic limb oedema) following an 18-minute-long complete obstruction of the CVC, which resulted from iatrogenic transection and consequent repair of the CVC during right liver lobectomy to remove a hepatocellular carcinoma. In a follow-up CT scan 9 months later, extensive venous collateral neovascularisation and caval stricture were identified without any

associated clinical consequences. The dog remained alive and asymptomatic for more than 1 year after surgery.

Occasionally, due to extensive local invasiveness, tumour thrombi are deemed unresectable through venotomy. In such situations, segmental resections of the afflicted portion of the CVC (venectomies) have been described in two case reports of dogs with phaeochromocytomas: the suprarenal, infrahepatic CVC was excised *en bloc* with (Louvet, Lazard, & Denis, 2005) or without (Guillaumot et al., 2012) concurrent ipsilateral nephrectomy. In both cases, dogs were successfully managed and presented good long-term outcomes. This might be explained by the previously discussed logic, i.e., collateral circulation forms in simultaneous with the development of the tumour thrombus. Having this option might simplify the surgery itself and would also allow wider margins for tumour excision.

3. OUTCOME FOLLOWING ADRENALECTOMY

3.1 Complications

A series of complications can be expected to derive from the hypercortisolism caused by an AT, specifically, because of concomitant immunosuppression, compromised wound healing, systemic hypertension, existence of a hypercoagulative state, and atrophy of the contralateral gland (Behrend, 2015). In dogs with phaeochromocytomas, complications are generally linked to the peaks and drops in catecholamine release, producing variations in blood pressure, hyper- and hypotensive episodes, and cardiac arrhythmias with potential to lead to cardiac arrest (Herrera et al., 2008). Additionally, the chosen surgical approach may also influence the existence of complications as poor exposure raises concern for intraoperative adversities such as the surgeon's ability to prevent or address haemorrhage, as well as, iatrogenic injuries to the liver, pancreas, vena cava, and kidney (van Sluijs et al., 1995).

When adrenal tumours in general are surgical managed, intraoperative complications are common and have been reported at different rates: 15% (Kyles et al., 2003), 43% (Lang et al., 2011), 83% (Barrera et al., 2013). Main complications include haemorrhage, hypotension, hypertension, cardiac arrhythmias, which can result in death (Barrera et al., 2013; Kyles et al., 2003; Lang et al., 2011; Schwartz et al., 2008). Acute haemorrhage may be secondary to a ruptured adrenal tumour (Lang et al., 2011; Whittemore et al., 2001) or to inadvertent injury of abdominal viscera and vascular structures while dissecting or struggling for adequate exposure (Kyles et al., 2003; van Sluijs et al., 1995).

Likewise, postoperative complications are reported at high rates, ranging from 30 to 51%, and include hypotension, pancreatitis, renal insufficiency/failure, peritonitis, PTE, cardiac arrhythmias, cardiac arrest, disseminated intravascular coagulopathy (DIC),

hypoadrenocorticism, wound dehiscence, haemoperitoneum, vomiting, diarrhoea, tachypnoea, dyspnoea, and hypoxaemia (Barrera et al., 2013; Kyles et al., 2003; Lang et al., 2011; Schwartz et al., 2008). Furthermore, it is not uncommon for dogs to develop more than one of these complications (5/13, 38%) (Schwartz et al., 2008). Also, postoperative complications were found to occur with no significant different between dogs with ATs and those with phaeochromocytomas (Barrera et al., 2013; Kyles et al., 2003).

3.2 Mortality

In earlier case series, overall mortality rates of dogs undergoing surgical excision of an AT were reported to be as high as 28% (10/36) (van Sluijs et al., 1995) and 60% (15/25) (Scavelli et al., 1986). Dogs were euthanised at time of surgery for a variety of reasons (e.g., deemed unresectable masses, visible metastases, vascular invasion) or died from serious complications in the postoperative period (up to 2 weeks). Similarly, high rates have been reported in dogs with phaeochromocytomas: 33% (2/6) (Gilson, Withrow, & Orton, 1994) and 47% (8/17) (Barthez et al., 1997). What is more, in the study by Barthez et al. (1997) 29% (5/17) of dogs died from cardiac arrest or were euthanised (because of widespread metastatic disease or a tumour judged unresectable) during the surgical intervention.

Interestingly, subsequent reports have demonstrated an improvement in the overall perioperative mortality rates for dogs with adrenal tumours in general: 22% (9/40) (Kyles et al., 2003), 22% (9/41) (Schwartz et al., 2008), 15% (8/52) (Massari et al., 2011), 12% (7/60) (Lang et al, 2011), 26% (22/86) (Barrera et al., 2013). Possible explanations include improved case selection as a result of increased availability of advance imaging methods, precluding surgery in patients with irremediable disease (e.g., already spread to distant sites, irresectable masses) (Armbrust et al., 2012; Schultz et al., 2009); altered preconceptions regarding the impact of caval thrombi on perioperative morbidity and mortality rates, which have been shown not to suffer significant increases provided that the surgeon is familiarised with appropriate techniques (Kyles et al., 2003) and the tumour thrombus does not extend into or beyond the hepatic portion of the CVC (Barrera et al., 2013); and also, the developments in perioperative management and anaesthetic techniques might have positively influenced outcomes – a theory supported by the results of Herrera et al. (2008), where mortality associated with adrenalectomy was observed to be significantly decreased (from 48% to 13%) by using phenoxybenzamine preoperatively.

Yet, for those dogs undergoing emergency adrenalectomy due to acute adrenal haemorrhage (AAH), mortality rates might be higher. In their study, Lang et al. (2011) observed that 4 of 8 dogs (50%) died in the perioperative period as result of euthanasia (suspected PTE, refractory

seizures, progressive lung oedema) or cardiopulmonary arrest, surviving between 1 to 4 days. In another case series involving 4 dogs with AAH, for 1 dog (25%) euthanasia was elected during surgery due to failure to accomplish resection and attain adequate haemostasis (Whittemore et al., 2001).

In regard of bilateral procedures, a recent case series reported the outcome of bilateral adrenalectomy in 9 dogs (7 concurrent, 2 staged) with a perioperative mortality of 11% – a rate comparable to those of elective unilateral adrenalectomies (Oblak et al., 2016).

3.3 Survival

Reported median survival times (MST) for dogs undergoing adrenalectomy for adrenocortical carcinomas was 778 days or, if those who did not survive the immediate 14 days post-surgery were to be excluded, MST would be 992 days with long-term survival extending up to 1593 days (Anderson et al., 2001). Other studies reported MST of 48 months, 360 days, and 230 days for dogs with carcinomas (Barrera et al., 2013; Massari et al., 2011; Schwartz et al., 2008), compared to 688 for dogs with adenomas (Schwartz et al., 2008).

In regard of phaeochromocytomas, Schwartz et al. (2008) reported a MST of 374 days, and some dogs may survive for as long as 2 to 3 years (Barthez et al., 1997; Gilson, Withrow, & Orton, 1994).

What is more, Barrera et al. (2013) observed 1-, 2-, and 3-year survival rates of 88% for adrenocortical carcinomas, and 83%, 60%, and 60%, respectively, for phaeochromocytomas.

When all adrenal gland tumours are considered, overall MST reported has varied from 375 to 953 days (Lang et al., 2011; Massari et al., 2011; Schwartz et al., 2008), and in one study 65% survived more than 1 year, up to 1941 days (~5 years) (Massari et al., 2011).

Even for those patients presented as surgical emergencies with AAH, to whom a high mortality rate (50%) is associated, MST was 208 days (overall) and 844 days for the 4 dogs that survived the designated perioperative period which had extended survival times of up to 1020 days, and none was reported to have died or been euthanised due to recurrence of clinical signs or metastases (Lang et al., 2011).

Moreover, interesting case reports describe notably extended long-term survival times allied to somewhat unexpected circumstances: the resection of phaeochromocytomas, which also implicated an *en bloc* excision of a suprarenal part of the CVC, as the concomitant tumour thrombi were deemed unresectable through venotomy. While one dog was clinical well, with no significant vascular or renal dysfunction, at a follow-up 20 months after surgery (Louvet et al., 2005), another survived for 49 months postoperatively and was healthy until then – it died of unknown causes after a hyperacute onset of vomiting and diarrhoea (Guillaumot et al., 2012).

3.4 Prognosis

A number of investigators have evaluated prognostic factors, namely predictors for short-term survival, for dogs with different types of adrenal gland neoplasms undergoing adrenalectomy. Preoperative variables significantly associated with shorter survival times included adrenal gland tumour size (particularly, when the major axis length was ≥ 5cm), vein thrombosis, extensive invasion of the CVC (into or beyond the hepatic hilus), weakness, lethargy, increased blood urea nitrogen concentration, thrombocytopenia, increased partial thromboplastin time, increased aspartate transaminase, hypokalaemia, presence of metastases, and presence of AAH (Barrera et al., 2013; Lang et al., 2011; Massari et al., 2011; Schwartz et al., 2008). Intraoperative variables significantly associated with shorter survival times included blood loss requiring transfusion, and concurrent nephrectomy (Barrera et al., 2013; Schwartz et al., 2008). Postoperative variables significantly associated with shorter survival times were development of pancreatitis, acute renal failure, DIC, hypotension, and hypoxemia (for which PTE is a possible cause, although it could not be confirmed due to the retrospective nature of the studies) (Barrera et al., 2013; Schwartz et al., 2008).

These results, however, should be interpreted critically in terms of their clinical relevance as some of these findings lacked in specificity and/or were found in a small number of patients (Schwartz et al., 2008). Besides, reports can be conflictive about which factors are in fact of prognostic significance or not.

To start with, the presence of tumor thrombus was not predictive of outcome, with no significant differences in perioperative morbidity and mortality, or in survival duration in several studies (Herrera et al., 2008; Kyles et al., 2003; Lang et al., 2011; Schwartz et al., 2008). Conversely, Massari et al. (2011) found that vein thrombosis was associated with a poorer prognosis and also with "larger" neoplasms (major axis length ≥ 5cm). In a more recent study (Barrera et al., 2013), both invasion of the CVC and extent of the tumour thrombus were risk factors for death in the short-term. Yet, when invasion of the CVC was adjusted for the extent of the tumor, invasion of the CVC was no longer a risk factor, which is in agreement with the results of Kyles et al. (2003). Thus, it appeared that extensive caval invasion was the most important risk factor for poor short-term survival. Still, long-term survival was possible regardless of invasion status or any other risk factor evaluated for that matter.

Secondly, the histological type of tumour was also not related with survival time in various case series (Anderson et al., 2001; Kyles et al., 2003; Lang et al., 2011; Schwartz et al., 2008). However, while in univariate analysis models, adrenocortical carcinomas (Massari et al., 2011) or phaeochromocytomas (Barrera et al., 2013) were significantly associated with a worse prognosis in detriment of other tumour types, they were not predictive of outcome in their

respective multivariate analysis. This is likely explained by the suggestive results of carcinomas being more likely to yield metastases, namely based on the highest rates of metastatic lesions registered for carcinomas in one study (Schwartz et al., 2008) and the significant association between the presence of metastases with carcinomas found by another (Massari et al., 2011). Similarly, the fact that caval invasion has been shown to occur at higher rates with phaeochromocytomas (Barrera et al., 2013; Bouayad et al., 1987; Herrera et al., 2008; Kyles et al., 2003; Lang et al., 2011; Twedt & Wheeler, 1984) and the high proportion (7/14) of extensively invasive CVC tumours found in the population studied by Barrera et al. (2013), clarifies the obtained results. Therefore, although the tumour type on its own is not predictive of outcome, its potentialities identified as negative prognostic factors make it a possible indirect risk factor to consider.

Size-wise, while this variable was not associated with survival in some studies (Anderson et al., 2001; Herrera et al., 2008; Schwartz et al., 2008), it is possible that this finding was due to the great majority of tumours being relatively small, with a major axis length < 5 cm. In fact, Massari et al. (2011) observed that an adrenal gland tumour with major axis length ≥ 5 cm was associated with 85% shorter survival time. Moreover, Lang et al. (2011) found that each 1 mm increase in tumour size was associated with a 7.9% increase in odds of perioperative mortality and with a 6% increase in odds of AAH. From a subjective point of view, Lang et al. (2011) suggested that, because "smaller" tumours apparently had less local invasion, less intraoperative blood loss, shorter anaesthetic and operative periods, and fewer postoperative complications; early detection and surgical intervention might be associated with greater postoperative survival.

In regard of detection of metastases at time of surgery, their prognostic implications are somewhat uncertain, with some reporting it as predictive for shorter survival (Massari et al., 2011), whereas others discovered no significant differences in survival (Kyles et al., 2003; Schwartz et al., 2008). Furthermore, Schwartz et al. (2008) detected a high number of gross lesions in other organs during surgery; yet, the histologic evidence of metastases was low. Hence, euthanasia should not be advised exclusively on the basis of gross lesions identified during surgery. Likewise, it remains to be determined if partial tumour resection would provide a therapeutic benefit in comparison to no surgery at all. In one study, completeness of tumour excision was not prognostic for survival time (Schwartz et al. 2008). Reported successful outcomes in cases of residual disease at surgery include: 1 was alive at 18 months after resection with violation of tumour margins (Gilson, Withrow, & Orton, 1994); 1 had recurrence of clinical signs after 5 months since partial resection which resolved with medical treatment until being euthanised at 13 months after surgery (van Sluijs et al., 1995); 1 was alive after ~1 year

and 1 died of disease ~3 years later, after partial resections (Anderson et al., 2001); 1 was still alive and healthy at 9 months after emergency partial excision (Whittemore et al., 2001); 1 had recurrence of clinical signs after 2 years since incomplete surgical excision – hepatic metastases were detected at that point and were treated with lobectomies – and was reported doing well and clinically stable at ~3.5 years after initial presentation (Frankot et al., 2012).

Even the survivors of emergency adrenalectomy due to AAH, might not be at increased risk for local or distant recurrence, as none were reported to have died or been euthanised due to relapse of clinical signs or metastatic disease (Lang et al., 2011).

Therefore, incomplete excision of primary tumours, evidence of metastases, or ruptured adrenal tumours may not necessarily be indications for euthanasia. Still, it is assumed that there is a high probability for these dogs to eventually have relapses (Kyles et al., 2003).

Finally, whereas age was not considered to significantly affect survival in dogs with ATs (Anderson et al., 2001) or adrenal tumours in general (Massari et al., 2011; Schwartz et al., 2008), one study in dogs with phaeochromocytomas found that younger age was a significant prognostic factor for improved survival, as well as, preoperative medical treatment with phenoxybenzamine, lack of intraoperative arrhythmias, and decreased surgical time (Herrera et al., 2008).

The bottom line is that there might be risk factors which are more significant than others, and indirect risks still have to be taken into consideration when pondering on prognosis. Uncertainty or contradictions regarding some variables identified as predictors of outcome dictate that, ultimately, clinical sense and experience prevails. In general, dogs with "large" tumours, infiltrated kidney or body wall, extensive CVC invasion, metastatic lesions, low anti-thrombin III concentrations, who are old, debilitated, or have serious endocrine manifestations originating from the tumour or concurrent concerning illnesses, are at high risk of developing serious perioperative complications and of having a poor outcome. A good prognosis benefits from earlier detection and intervention, an experienced surgeon-anesthesiologist team, and in-depth understanding of adrenal gland physiology and perioperative care (Behrend, 2015; Lunn & Page, 2013; Reusch,2015).

Overall, it has been consistently observed that if dogs survive the immediate perioperative period, long-term outcome is generally good with possibility of prolonged survival times, as local or distant tumour recurrence appears to be low. Adrenalectomy offers at least as good a prognosis as chronic medical management (Anderson et al., 2001; Barrera et al., 2013; Barthez et al., 1997; Gilson, Withrow, & Orton, 1994; Kyles et al., 2003; Lang et al., 2011; Massari et al., 2011; Schwartz et al., 2008; van Sluijs et al., 1995).

II. OBJECTIVES

The purposes of this study were to describe the clinical features, surgical management and outcome following adrenalectomy in a case series of 16 dogs with adrenal gland lesions.

III. MATERIAL AND METHODS

1. Case selection criteria

Medical records of 16 dogs that underwent surgical management of adrenal gland lesions, at Kingston Veterinary Group (KVG, Hull, United Kingdom) and the Veterinary Teaching Hospital of the Faculty of Veterinary Medicine of the University of Lisbon (HEV, FMV-UL, Portugal), between the year of 2008 and June 2018, were reviewed. Inclusion criteria were dogs where adrenalectomy was performed.

2. Medical records review

Data was collected after review of medical records and occasionally through interview with owners and/or veterinarians involved with the cases. Clinical variables included: signalment, relevant history, clinical signs, physical examination findings, results of functional testing, imaging exams (radiography, US, CT), abdominocentesis, and US-FNA, pre- and postoperative drug therapy, surgical findings and procedures, intra- and postoperative complications, duration of hospitalisation, histopathology and necropsy examinations, follow-up, and outcome.

3. Procedures

3.1 Imaging assessment

Evaluation of the suspected adrenal tumours, in terms of size, shape, appearance, and relationship with immediate structures (i.e., compression or invasion) was executed beforehand for every electice unilateral adrenalectomy.

Presence of tumour thrombi, namely in the CVC, was systematically verified. This assessment was made either through US or abdominal CT (**Figures 2** and **3**). Both of these methods were also utilised in the inspection of distant spread in the abdominal cavity. For verification of pulmonary metastases, the preferred methods were thoracic radiography or CT.

Regarding the clinical cases presented as emergencies, US and abdominal radiography assisted exclusively the diagnosis of abdominal effusion; comprehensive US scans were not pursued in these patients. Subsequent abdominocentesis confirmed the presence of a haemoabdomen of unknown origin.

Figure 2. Ultrasonographic pictures demonstrating the measurement of an adrenocortical myelolipoma (A) and verification of vascular invasion using Doppler (B) (Kindly dispensed by Dr. David Robinson, KVG).

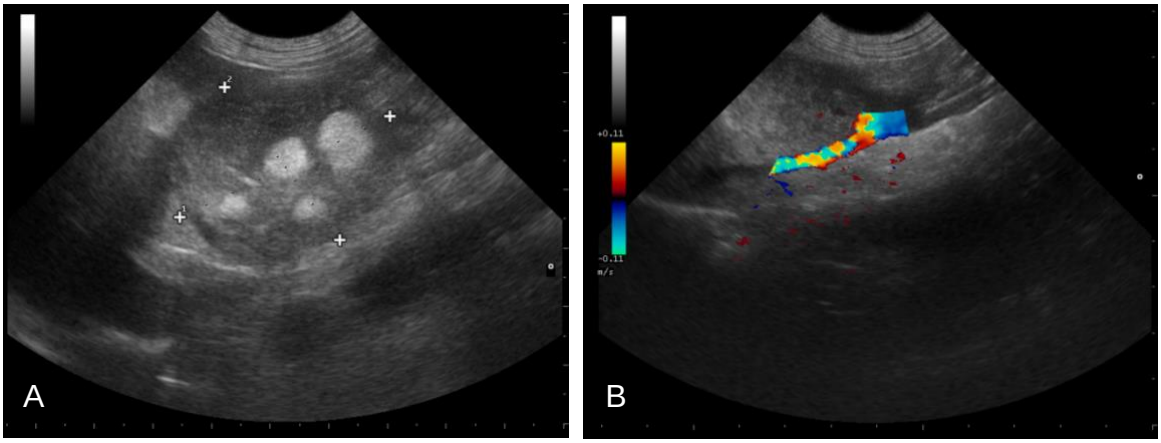
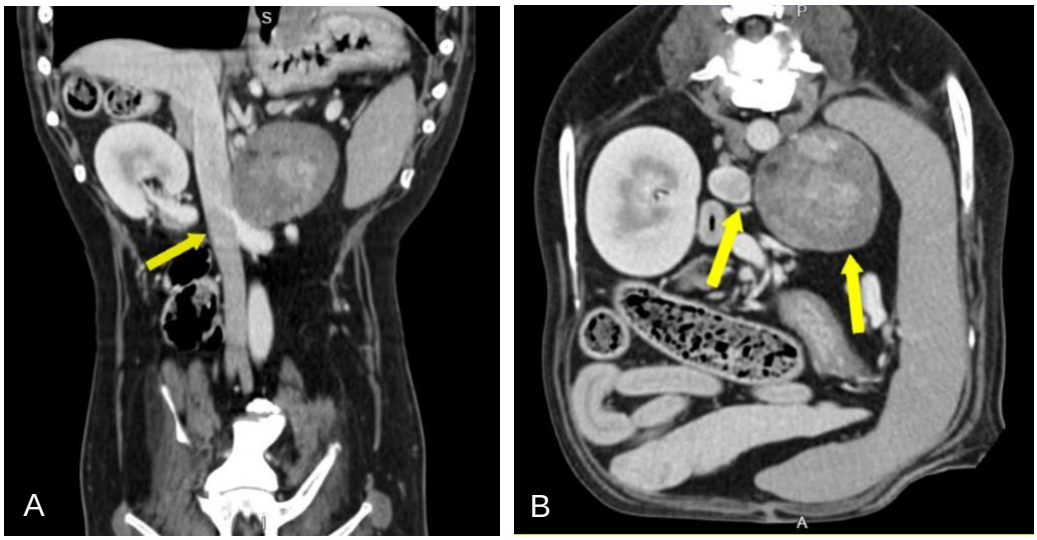


Figure 3. Computed-tomography pictures after administration of intravenous contrast representing a left-sided adrenocortical adenoma with a concurrent caval "true" thrombus (Kindly dispensed by Prof. Dr. Sandra Jesus, HEV).



Caption: (A) Arrow=filling-defect in CVC, suspected of being caused by a thrombus. (B) Left arrow= filling-defect in the CVC; Right arrow=altered left adrenal gland.

3.2 Perioperative management

Dogs suspected of having endocrinologically active ATs, based on clinical manifestations, basic bloodwork and results of functional tests (ACTHST, LDDST, UCCR), were treated with injectable dexamethasone postoperatively, which was continued with oral prednisolone in the postoperative period according to need. Mineralocorticoid supplementation (e.g., oral fludrocortisone or injectable desoxycorticosterone pivalate) was performed after surgery, when needed, based on clinical signs and measurement of electrolytes. Heparin was occasionally

administrated postoperatively according to the suspicion of HAC and practitioner criteria, as a preventive measure of PTE. Furthermore, dogs would stay hospitalised for at least 24h after surgery to monitor for signs of PTE, among other aspects.

Diagnostic work-up of phaeochromocytomas included measurement of blood pressure and functional testing. Because the plasma assay was performed by laboratories of human medicine, i.e., without species-specific reference ranges, the results were interpreted through comparison with the findings of relevant studies on the subject (Gostelow et al., 2013; Salesov et al., 2015). Those suspected of having phaeochromocytomas were preoperatively treated with phenoxybenzamine.

3.3 Surgical technique

The surgical intervention was performed in 11 dogs at KVG by 3 different veterinary surgeons and in 5 dogs at HEV by 4 different veterinary surgeons. Anaesthetic time was defined as the time period between induction and extubation. Surgical time was defined as the time period between skin incision and skin closure.

A ventral midline approach was used in all dogs. When deemed appropriate, the falciform ligament was excised and one or two abdominal retractors were placed in in order to improve access. An exploration of the abdomen viscera in search of suspected metastatic alterations was performed systematically. Conversely, biopsies (e.g., of the liver) were not obtained in all cases.

A surgical assistant helped with retraction of the abdominal viscera to enable approach of the adrenal gland. Local vasculature (CVC, aorta, renal artery and vein) was examined to identify vascular invasion and thrombi. The ipsilateral kidneys were also inspected for invasion and nephrectomy was executed if reckoned necessary.

Regarding the 3 cases of haemoabdomen of unknown origin, firstly, the source of haemorrhage was procured and dealt with, prior to any attempt of dissection of the tumours.

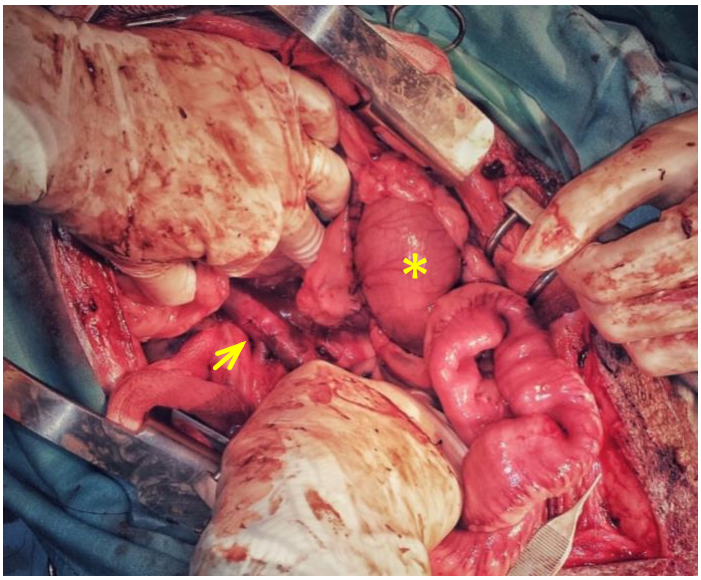
A combination of blunt and sharp dissection along with ligation and transection of relevant vessels (generally leaving the medial plane, including the phrenicoabdominal trunk, for last) were used to free the altered adrenals from their surrounding connections, before completing resection.

In one case, tumoural invasion of the aorta wall without concurrent thrombus determined its partial resection and subsequent reconstruction. In another, the presence of a “true” thrombus in the CVC without any other signs of neoplastic invasion from the concurrent adrenal tumour, a 10 to 20-mm longitudinal incision in the vessel, posteriorly sutured in a continuous pattern, was sufficient to perform thrombectomy (**Figure 4**). In both scenarios, Rumel tourniquets were

placed primarily to occlude local circulation temporarily (aiming to last less than 4 minutes) in order to enable surgical handling of the vascular structures.

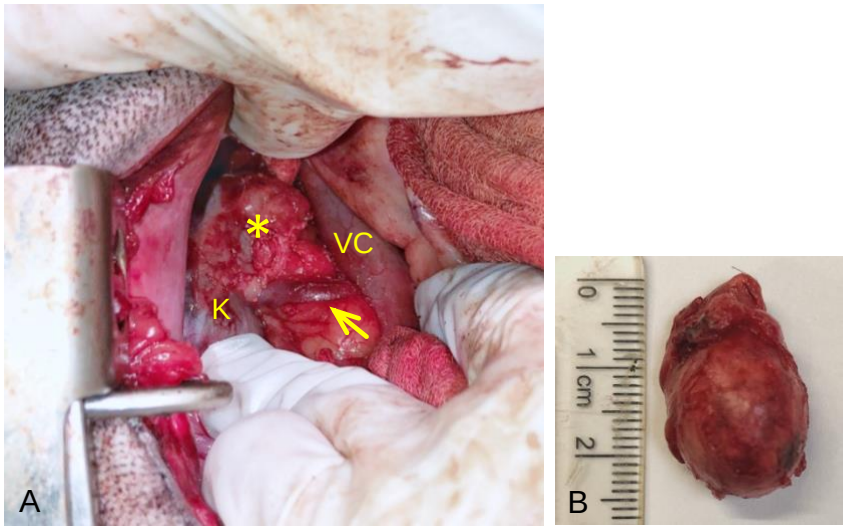
Prior to closure, lavage of abdominal cavity was executed with a warmed saline solution and occasionally a splash of bupivacaine was applied into the surgical field. Routine layered wound closure was performed. The excised tissue was submitted to histopathological examination (**Figure 5**).

Figure 4. Intraoperative view after removal of a "true" CVC thrombus in a patient with a left-sided adrenocortical adenoma (Original photography).



Caption: Arrow=sutured venotomy; Asterisk=adrenal tumour. Note the use of two sets of retractors to improve access and visualisation.

Figure 5. Intraoperative view of the surgical field after removal of a right-sided adrenal gland phaeochromocytoma (A) and the tumour itself following excision (B) (Original photography).



Caption: Arrow=right renal vein; Asterisk=surgical field after removal of the tumour; VC=venae cava; K=right kidney.

4. Outcome

All complications that occurred intra- and postoperatively were recorded, as well as, hospitalisation times, the need for substitution therapy, and palliative treatments pursued. Major and minor haemorrhage was defined according to the necessity or not of a transfusion, respectively. Cardiac arrhythmias were identified on the basis of electrocardiography. Bradycardia and tachycardia were defined as a heart rate < 60 and > 140 beats/min, respectively. Hypotension and hypertension were defined as systolic blood pressure < 80 and > 180 mm Hg, respectively. A diagnosis of pancreatitis was mainly based on clinical signs and response to symptomatic treatment and occasionally supported by US and specific pancreatic lipase assay. Hypoadrenocorticism was diagnosed on basis of clinical signs and measurement of electrolytes. Dogs were followed until death or, if still alive, until the most recent contact before the end of the study. Those lost to follow up were duly noted. Cause of death was classified as adrenal-tumour related (directly, or indirectly from consequences of the intervention) or non-related. This distinction was mainly based on clinical signs, physical examination, laboratory, and imaging findings. Necropsy was not routinely performed.

Survival time was defined as the interval between surgery and death. The postoperative (short-term) period was defined as the 14 days following surgery. The long-term period started from this point, inclusively, forward.

5. Statistical analysis

Data was analysed using Microsoft® Excel for Mac 2016 (version 16.14.1). General descriptive statistics was used for both quantitative and qualitative variables. Categorical variables were presented as proportions or percentages. Numerical variables were expressed using mean, median, and range (minimum to maximum value).

Survival analysis was achieved using R© for Mac OS X (version 3.5.0) – a free software environment for statistical computing and graphics, available at http://www.r-project.org. An overall median survival time was determined by use of the Kaplan-Meier life-table analysis. Dogs were censored if they were still alive at the end of the study period or if they have died from causes non-attributed to the adrenal lesion or the surgical procedure itself.

IV. RESULTS

1. Signalment

During the 10-year study period, 16 dogs were identified that met the inclusion criteria. Nine were females (56.3%), 2 intact (12.5%) and 7 neutered (43.8%); and 7 were males (43.8%), 5 intact (31.3%) and 2 neutered (12.5%). The mean age at time of surgery was 9.8 years (range 0.8-15 years) and the mean body weight was 25.1 kg (range 7.6-46.6 kg). Breeds included were 2 Golden Retrievers (12.5%), 2 Labrador Retrievers (12.5%), 2 Scottish Terriers (12.5%), and 1 each (6.3%) of the following: Boxer, Brittany Spaniel, German Shepherd, Rhodesian Ridgeback, Tibetan Mastiff. The remaining 5 dogs were mixed breeds (31.3%).

2. Preoperative evaluation

2.1 Relevant history

Twelve dogs (75%) had history of concomitant diseases or other neoplasms: degenerative joint disease (n=4), atopy (n=2), intervertebral disk disease (n=1), urolithiasis (n=1), epilepsy (n=1), mast cell tumour (n=2), anal gland adenoma (n=1), anal gland carcinoma (n=1), benign mixed mammary tumour (n=1), mammary carcinoma (n=2), and lingual plasma cell tumour (n=1).

2.2 Clinical presentation

Adrenal lesions presented as *incidentalomas* in 4 dogs (25%) through the use of US (n=3) or CT (n=1) in the control of metastases from other neoplasms (n=2), as a part of pre-anaesthetic geriatric procedures (n=1), or while investigating clinical signs non-related to the adrenal abnormality (n=1).

Three dogs (19%) had ruptured adrenal tumours and presented with acute clinical signs, including collapse (n=2), lethargy (n=3), vomiting (n=3), anorexia (n=2), tachypnoea (n=1), tachycardia (n=1), ascites on abdominal palpation (n=3). Abdominocentesis confirmed the diagnosis of haemoabdomen in all 3 animals.

In the remaining 9 dogs (56%) the most commonly observed clinical sign was PU/PD (n=6). Other registered clinical manifestations included: dermatological changes (n=2), abdominal enlargement (n=1), recurrent urinary tract infections (n=1), persistent haematuria (n=1), hypertension (n=1), panting (n=1), signs of anxiety (n=1), anorexia (n=2), lethargy (n=1), nonspecific cervical pain (n=1), palpation of a firm mass in the cranial mid-abdomen associated with pain (n=1).

2.3 Functional testing

Only dogs undergoing elective (n=13) adrenalectomy had functional tests performed. Assessment of adrenocortical functionality was performed in 9 of those (69%) and included ACTHST and LDDST (n=4), ACTHST only (n=2), LDDST only (n=2), or UCCR only (n=1). Evaluation of adrenal medullary neuroendocrine activity was performed in 4 of those (31%) and included measurement of urinary catecholamines and metanephrines (n=2), or measurement of plasma free (n=1) or total (n=1) metanephrines.

Results of dogs that had both an ACTHST and a LDDST performed (n=4) were within reference limits in two dogs, inconsistent in another (ACTHST within reference limits and LDDST supportive of PDH), and consistent with HAC and PDH in a fourth dog; for this latter patient, results of plasma free metanephrines were not supportive of a productive phaeochromocytoma. In regard of the two dogs that only had an ACTHST performed, results were consistent with HAC, and in one of them, the urinary catecholamines and metanephrines assay was also supportive of a productive phaeochromocytoma. The two patients that only had a LDDST done, results were within reference limits. Lastly, one dog had UCCR results within reference limits, thus ruling out HAC; and plasma total metanephrines values were not supportive of a productive phaeochromocytoma.

Two of the 4 dogs with adrenal *incidentalomas* were submitted to functional testing. In both cases, tests were consistent with non-productive lesions: both ACTHST and LDDST within reference limits in one; UCCR within reference ranges and plasma total metanephrines values not supportive of a phaeochromocytoma in another.

2.4 Imaging assessment

All dogs undergoing elective (n=13) adrenalectomy had their adrenal lesions preoperatively identified and assessed through US (n=7), CT (n=1), or US followed by CT (n=5).

The presence of ‘true’ thrombus in CVC (n=1) was missed by US, but not by CT post-contrast administration scans. In the remaining 7 cases evaluated through US, the inexistence of actual intravascular invasion compared to extrinsic compression causing luminal narrowing was correctly recognised. Unfortunately, the 2 dogs in this study with CVC tumour thrombus did not undergo comprehensive imaging examinations because for all the cases undergoing emergency (n=3) adrenalectomy, imaging methods were purely used to assist the diagnosis of abdominal effusion – namely, US (n=2) and radiography (n=1).

Verification of abdominal metastases was systematically performed along with evaluation of adrenal masses in the 13 dogs undergoing elective procedures. Intrathoracic distant spread was evaluated in 12 of 16 dogs either by using radiography (n=10) or CT (n=2). No evidence of

abdominal or pulmonary metastases was found. Yet, other major abnormalities were detected and included a 10-cm hepatic mass (US-FNA yielded the differentials of nodular hyperplasia or hepatoma), a 2.5-cm splenic mass alongside with irregular aspect of the spleen head, an ~8-cm splenic mass in the body of the organ, both a 1.5-cm bladder calculi and a 1.65-cm renal pelvic calculi, a 'true' thrombus in the CVC, and dilatation of renal pelvis and respective ureter on its proximal third due to extrinsic involvement and compression by the tumoural mass (US-FNA yielded a diagnosis of malignant neoplasia, without cytological differentiation).

3. Surgical procedures and findings

Thirteen dogs underwent elective unilateral adrenalectomy and 3 required an emergency adrenalectomy to stop potentially fatal blood depletion from ruptured adrenal masses. Affected adrenals were right-side in 12 dogs (75%) and left-sided in 4 (25%). The aspect of the masses varied from well encapsulated, to very friable and haemorrhagic. They also varied in size (**Table 6**) and presented different degrees of local invasiveness (addressed in detail in the following section). Tumour invasion of the CVC was detected intraoperatively in two dogs.

Concurrent surgical procedures were performed in 12 dogs (75%) and included: CVC venotomy to remove a "true" thrombus (n=1), repair of a caval iatrogenic rupture while dissecting (n=1), partial resection and reconstruction of the aorta wall (1) due to an area of greater tumour adhesion to the vessel wall, ipsilateral nephrectomy (n=3) when a large adherence between the tumour and the kidney and/or invasion of the respective vasculature was noted, liver biopsy (n=6), liver lobectomy (n=1) to remove a 10-cm hepatic mass, splenectomy (n=2) due to the presence of multiple abnormalities in one case and a single ~8-cm nodular lesion in the body of the spleen in another, and a salivary mucocoele excision (n=1).

Anaesthetic and surgical times were available for 8 dogs and ranged from 110 to 300 min (mean 217.5 min, median 232.5 min) and 60 to 215 (mean 161.25 min, median 187.5 min), respectively.

4. Histopathological evaluation

The adrenal specimens were submitted to histopathological examination in 13 dogs (81%). Of these, 8 (62%) were diagnose with adrenocortical abnormalities including carcinoma (n=4), adenoma (n=2), myelolipoma with nodular cortical hyperplasia (n=1), and extensive haemorrhage within the gland displacing the cortex and medulla without neoplastic evidence (n=1). The remaining 5 animals (38%) had medullary neoplasms identified, including phaeochromocytoma (n=4) and neuroblastoma (n=1). The 3 dogs (19%) without histopathological diagnosis were presented as emergencies and were euthanised during surgery. The owners declined necropsy.

The dog with a caval 'true' thrombus had an adrenocortical adenoma. Also, the largest tumour (maximum diameter of ~12 cm), which caused ipsilateral ureter extrinsic compression and aorta wall invasion, was diagnose as a neuroblastoma. The 4 dogs with adrenal *incidentalomas* were diagnosed with adrenocortical adenoma (n=1), extensive haemorrhage within the gland (n=1), and phaeochromocytoma (n=2).

Other histopathological diagnoses included glycogen-like vacuolar hepatopathy (n=5) consistent with hyperadrenocorticism, chronic hepatitis (n=1), hepatocellular carcinoma (n=1), benign nodular lymphoid hyperplasia and extramedullary haematopoiesis (n=1), voluminous splenic haematoma (n=1), hydroureteronephrosis (n=1) caused by extrinsic compression of the ureter by the tumour, neoplastic invasion of the renal pelvis and extrinsic compression of the kidney by the tumour (n=1), neoplastic invasion of the peri-neural and -adipose tissue (n=1).

Adrenal gland abnormalities were locally invasive in 6 dogs (38%), including 1 carcinoma, 1 phaeochromocytoma, 1 neuroblastoma, and 3 without histopathological diagnosis. The tissues invaded were the CVC with a tumour thrombus (n=2), aorta wall (n=1), ipsilateral renal pelvis (n=1), renal vasculature (n=3), adrenal peri-neural and -adipose tissue (n=2), and muscle wall (n=1).

Metastases were not identified in any of the dogs at time of surgery (0%). Yet, a necropsy performed in the only dog that died in the postoperative period (4 days after surgery) revealed presence of metastasis in the right cervical lymph node originating from a phaeochromocytoma. Therefore, it is arguable that distant spread could have already been present at time of surgery, altering this rate to 6%. In the long-term, metastases were diagnosed in an additional dog during necropsy and sites included the precordial area, mediastinal lymphatic centre area, and liver – the primary tumour was a neuroblastoma.

5. Outcome

Intraoperative complications were registered in 13 dogs. Twelve (92%) had intraoperative complications including an iatrogenic tear and subsequent repair of the CVC (n=1), prolonged CVC occlusion for approximately 8 min (n=1), minor (n=4) and major (n=5) haemorrhage, hypotension (n=5), tachycardia (n=6), and cardiac arrest (n=1). Postoperative complications developed in 67% of dogs who survived surgery (8/12) and included acute renal insufficiency (n=1), hypoadrenocorticism (n=1), pancreatitis (n=4), hypertension (n=1), cardiac arrhythmias (n=1), dyspnoea (n=1), DIC (n=1), diarrhoea (n=1), anorexia (n=1), wound breakdown (n=1).

Twelve (75%) dogs survived surgery. Causes of intraoperative death included hypovolaemic shock following an iatrogenic tear of the CVC (n=1), and perceived lack of complete resectability (n=3) attributed to a combination of complicating factors – the mass's friable

nature (n=2), presence of major haemorrhage (n=3), extensive degree of local invasiveness into the surrounding tissues in general (n=1) or into the CVC (n=2), and suspected metastatic spread to the spleen (n=1). The owners of the 3 latter patients (with perceived lack of complete resectability) were contacted at that point, and they elected euthanasia and declined necropsy or histopathological evaluation. During the postoperative period, 1 additional dog was euthanised following the development of a series of complications – hypertension, cardiac arrhythmias, dyspnoea, and DIC. Necropsy revealed haemothorax and -abdomen, pulmonary congestion, extensive subcutaneous haemorrhages, diffuse tubular necrosis and glomerular and interstitial fibrosis, hepatic necrosis with calcification, pyogranulomatous inflammation of the peripancreatic adipose tissue, and metastasis from the original adrenal phaeochromocytoma to the right cervical lymph node. Median hospitalisation times for those who survive surgery were 4 days (mean 3.8 days, range 2 to 5 days).

Overall, 11 (69%) dogs survived the immediate postoperative period, with a median follow-up period of 415 days (range 14-1173 days). One dog was lost to follow-up at 14 days, 7 more dogs died in the long-term, and 3 were known to be still alive at the end of the study.

In total, of the 12 dogs who were known to have died (intra- and postoperatively, and during the long-term period), 8 (67%) were considered to have died of adrenal tumour-related (TR) causes and 4 (33%) of non-adrenal tumour-related (NTR) causes (**Table 6**). An overall median survival time of 419 days was obtained through Kaplan-Meier life table-analysis (**Graphic 1**).

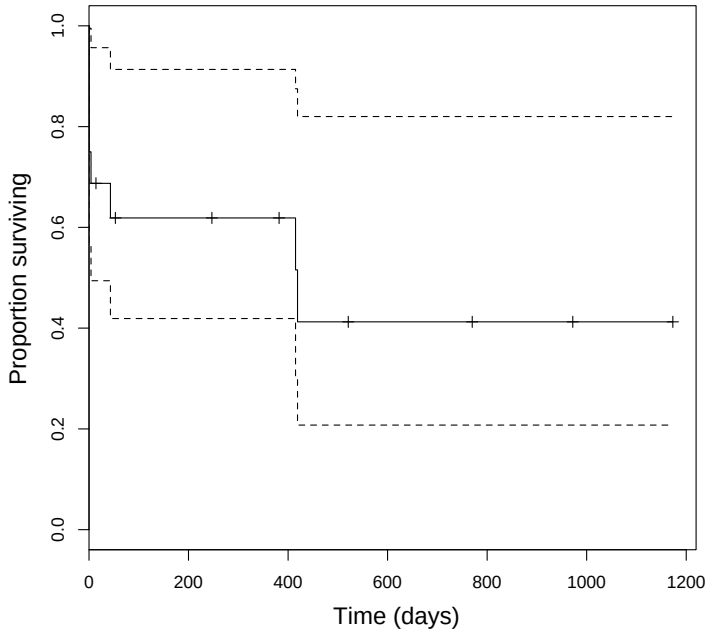
Table 6. Summary data for all 16 dogs undergoing adrenalectomy.

Dog	Histopathological diagnosis	Maximum diameter*	Survival time (days)	Status	Cause of death	
1	Unknown	50 mm	0	Dead	TR	Tumour rupture & AAH (E)
2	Unknown	50 mm	0	Dead	TR	Tumour rupture & AAH (E)
3	Unknown	40 mm	0	Dead	TR	Tumour rupture & AAH (E)
4	Myelolipoma	50 mm	0	Dead	TR	Hypovolaemic shock
5i	Phaeochromocytoma	35 mm	4	Dead	TR	Postoperative complications (E)
6	Phaeochromocytoma	40 mm	14	Alive	NA	Lost to follow-up
7	Neuroblastoma	121 mm	43	Dead	TR	Metastatic disease (E)
8i	Phaeochromocytoma	25 mm	53	Alive	NA	
9	Phaeochromocytoma	33 mm	247	Alive	NA	
10i	Haemorrhage	35 mm	382	Dead	NTR	Congestive heart failure (E)
11	Carcinoma	25 mm	415	Dead	TR	Chronic liver disease (E)
12	Carcinoma	35 mm	419	Dead	TR	Chronic pancreatitis, diabetes (E)
13i	Adenoma	52 mm	521	Dead	NTR	Recurrent uterine infection (E)
14	Carcinoma	20 mm	770	Alive	NA	
15	Carcinoma	45 mm	972	Dead	NTR	Severely compromised mobility (E)
16	Adenoma	28 mm	1173	Dead	NTR	Hepatocellular carcinoma (E)

Caption: AAH= acute tumour haemorrhage; E=euthanasia; i=*incidentaloma*; NA=non-applicable; TR=adrenal tumour-related; NTR=non-adrenal tumour related. *Size of tumour is characterised as the maximum diameter observed due to unavailability of standardised measurements or use of the same techniques; hence, the dimensions here presented were based on mixture of US, CT, or macroscopic measurements.

In the long-term, local recurrence was not identified in any of the dogs (0%). On the other hand, metastases to the precordial area, mediastinal lymphatic centre area, and liver were diagnosed in 9% of long-term survivors (1/11). Overall metastatic rate of this study was 13% (2/16).

Graphic 1. Kaplan-Meier life table analysis for overall median survival time of 419 days in 16 dogs undergoing adrenalectomy (censored cases are represented by vertical bars).



Resolution of clinical signs was assessed in dogs who survived the postoperative period, with exclusion of those with adrenal *incidentalomas* because these patients had clinical signs non-related to the adrenal abnormality or no clinical signs at all. Hence, 6 of 8 dogs (75%) had resolution of clinical signs. However, in 2 patients (25%) new clinical signs were registered which resulted directly from the adrenal disease (both had adrenocortical carcinomas removed) and/or the undertaken procedure itself: long-term chronic liver disease in one; and chronic pancreatitis and subsequent diabetes in another. Both dogs were supportively managed accordingly until a point where their condition had deteriorated considerably, and euthanasia was elected. With regard to the first dog mentioned, the possibility of metastatic disease as the cause or contributing factor of the chronic hepatic compromise was not totally discarded, in consideration of the US aspect of the liver and detection of adrenal peri-neural and -adipose invasion at time of adrenalectomy. Furthermore, because of this latter argument, the dog was submitted to one session of chemotherapy with carboplatin postoperatively, to which the patient reacted poorly and, consequently, chemotherapy was no longer pursued. Therefore, it is also possible that this treatment may have contributed to the aggravation of the liver damage.

Recurrence of clinical signs related to the adrenal disease occurred in 1 case (1/8), at 43 days after surgery, and was attributed to the metastatic spread of the adrenal neuroblastoma,

diagnosed through necropsy following euthanasia. The dog had similar clinical signs to initial presentation and more, including prostration, anorexia, asthenia, general weakness associated to nonspecific pain, faecal incontinence, refusal to seat, an intense pain on abdominal palpation. A chemotherapy protocol after surgical removal of the primary tumour had been offered and declined at that time.

In regard of the dogs with adrenal *incidentalomas* (n=4), whereas two had good long-term outcomes (one survived for 382 days and another for 521 days, and both died of NTR causes), one was still alive and well at 53 days postoperatively, and a fourth dog died 4 days after surgery following the occurrence of a series of complications already outlined. It is possible that these were consequential to a productive phaeochromocytoma, although no signs of activity were noted beforehand; thus, surgical manipulation might have triggered those events by causing a catecholamine surge, for instance.

V. DISCUSSION

Age, gender, weight, and breed of the population of this study were consistent with previous reports of similar spectrum (Anderson et al., 2001; Barrera et al., 2013; Herrera et al., 2008; Kyles et al., 2003; Lang et al., 2011; Massari et al., 2011; Schwartz et al., 2008; van Sluijs et al., 1995). The only major difference detected involved the age range, specifically the minimum age registered, which can easily be explained by the fact that one animal had a neuroblastoma, an adrenal tumour which typically occurs in young animals rather than in middle-aged to older individuals like adrenocortical tumours and phaeochromocytomas (Rosol & Gröne, 2016; Reusch, 2015). If that dog was to be excluded, age would vary between 7.9 to 15 years old (mean 10.4 years); thus, in accordance with other case series. Weight-wise it was interesting to see that 81% of dogs weighed more than 15 kg. Massari et al. (2011) had reported that 40.4% of their canine population with adrenal tumours weighted more than 15 kg, compared to 36.5% weighing 15 kg or less. Moreover, Reusch & Feldman (1991) had also noted that 46% of their dogs with ATs weighed more than 20 kg in comparison to 77% of dogs with PDH who weighted < 20 kg. Although these results might suggest a tendency for adrenal tumours to occur with increased frequency in larger breed dogs, it is also possible that these findings were influenced by elevated body condition scores, which were not determined in any case.

Predictably, considering the advanced age of these patients (Reusch, 2015), a high proportion of dogs (75%) had history of concurrent diseases or other neoplasms. Coexistence of non-adrenal diseases may interfere with results of functional tests (Cameron et al., 2010; Gostelow et al., 2013; Salesov et al., 2015) and, more importantly, may influence prognosis, especially on long-term. For instance, upon removal of cortisol-producing ATs, clinical signs of atopy or degenerative joint disease may be unmasked as cortisol concentrations decrease (Behrend, 2015). Yet, here, none of the dogs had pre-diagnosed conditions associated with the necessary severity to cause that negative impact on outcome, i.e., they did not preclude adrenalectomy.

In regard of clinical presentation, there was a considerably high proportion (3/16) of dogs presented as surgical emergencies due to tumour rupture and AAH in comparison to others studies of similar design – 8/60 (Lang et al., 2011) and 4/86 (Barrera et al., 2013). Additionally, and even though traumatic and non-traumatic rupture of adrenal tumours resulting in intraabdominal or retroperitoneal bleeding has been considered a rather rare event, reported in a total of 20 cases (Barrera et al., 2013; Evans et al., 1991; Lang et al., 2011; Santamarina et al., 2003; Vandenbergh et al., 1992; Whittemore et al., 2001; Williams & Hackner, 2001). Hence, this study might suggest that this scenario is more common than previously thought.

Yet, it should be beared in mind that these results might also be coincidental. The described clinical signs were identical to previous reports.

On the other hand, for patients undergoing elective adrenalectomies, clinical signs that lead to the investigations were neither numerous and, sometimes, nor exuberant, with PU/PD being the most common complaint. This was probably a result of heightened awareness of HAC, which makes dogs being examined at much earlier stages of disease development and, in turn, clinical manifestations will be more subtle and less prevalent in individual dogs; likewise, reference ranges of functional testing might need to be readjusted (Behrend et al., 2013).

With regard to phaeochromocytoma-orientated functional assays, in here, 4 dogs had assays performed. Results of urinary catecholamines and metanephrines were supportive of productive phaeochromocytomas in 2 dogs. Yet, both animals also had ACTHST suggestive of HAC, and histopathological examination yield a diagnose of adrenocortical carcinoma. This situation exemplifies the previously pointed out difficulty in differentiating animals with HAC and phaeochromocytoma through these tests, considering that results of dogs with HAC can overlap with those with phaeochromocytomas (Quante et al., 2010). For the other 2 patients, plasma free or total metanephrines were measured, and results were deemed non-supportive of productive phaeochromocytomas – one had an adrenocortical carcinoma and the other a phaeochromocytoma diagnosed through histopathological evaluation. For this latter dog, although it is possible that the medullary tumour was non-functional since it was incidentally discovered with no clinical signs associated, it is also feasible that because of its small dimensions (25 mm in maximum diameter) these results were below the sensitivity of the test (Reusch, 2015). Besides, even if the phaeochromocytoma was indeed non-functional at that stage, there was no way to tell if it would or not become functionally active with time.

In this study, 25% (4/16) of dogs had adrenal *incidentalomas*, discovered through imaging methods such as US and CT, which is a considerably high proportion to take into account, also in comparison with other studies: 3/39 (Kyles et al., 2003), 2/60 (Lang et al., 2011). Nevertheless, this event is not surprising and has been predicted by other authors (Baum et al., 2016; Cook et al., 2014; Myers, 1997). Previously, it has been argued that there might be a ~14-30% chance of an adrenal *incidentaloma* being malignant and they might become functionally active with time (Cook et al., 2014). Moreover, for any mass measuring ≥ 20 mm in maximum diameter, the likelihood of malignancy (Cook et al., 2014; Labelle et al., 2004) and growth potential (Arenas et al., 2013) might also be high. In here, half of the dogs with *incidentalomas* had no clinical signs and the other half had non-related manifestations. Moreover, whereas functional testing performed in 2 dogs confirmed the suspected inexistence

of productive activity, one of the dogs not tested died after development of postoperative complications which were suspicious of a productive phaeochromocytoma – this patient was also the only one of the 4 with confirmed malignancy upon discovery of distant spread at necropsy. Still, malignancy rate of *incidentalomas* could actually have been superior (2/4) if the other dog with a phaeochromocytoma was to be included, especially in consideration of the argument that phaeochromocytomas are typically reckoned to be malignant in dogs (Reusch, 2015). Overall, 75% of patients diagnosed with adrenal *incidentalomas* presented an inherent potential to cause a problem: in respect of their proven malignancy and suspected functionality; high likelihood of malignancy; or large dimensions (52 mm in maximum diameter) associated with the prospect of an eventual rupture, even though the tumour was benign (adrenocortical adenoma).

Intraoperative complications rate in this study was high (92%) and superior to the highest rate previously reported (83%) (Barrera et al. 2013). This proportion has ranged from 15 to 83% in three different studies (Barrera et al., 2013; Kyles et al., 2003; Lang et al., 2011), which is likely due to the use of different criteria to include or exclude a specific complication. While this explanation might also justify the higher rate of intraoperative complications in this study, surgeon's experience should also be considered as a relevant factor since the procedure was undertaken by different surgeons with equally different levels of experience.

Nevertheless, it is consensual that complications can be worrisome. In fact, in this study, one of these (an iatrogenic tear of the CVC) resulted in death. A situation of this nature could be prevented by placing Rumel tourniquets systematically, independently of existence or not of CVC invasion, which would be tightened if such an event was to occur. However, in practice, accomplishing their placement can be challenging, with risk of causing rupture as well, not to mention that is time-consuming which might affect outcome – Herrera et al. (2008) found that the longer the surgical time, the poorer the survival of dogs with phaeochromocytomas. In contrast, another complication of note in this study was a prolonged CVC occlusion for approximately 8 minutes, from which the patient had a full haemodynamic recovery. This case agrees with previous reports supporting the ability of canine patients to survive prolonged acute CVC occlusions (Halwagi et al., 2017; Horvath & Bender, 1961; Hunt et al., 1992).

Postoperative complications have been reported to develop in 30 to 51% of dogs following adrenalectomy (Barrera et al., 2013; Kyles et al., 2003; Lang et al., 2011; Schwartz et al., 2008). Here, they occurred in 67% of patients and, similarly to the results presented by Schwartz et al. (2008), 38% (3/8) developed more than 1 complication. Pancreatitis was the most commonly diagnosed complication (4/13), observed in 25% (3/12) of right-sided procedures and 25% (1/4)

of left-sided. Despite the fact that right-sided adrenalectomy requires greater manipulation of the pancreas, pancreatitis developed in similar rates for each side intervened. Furthermore, other studies have helped deconstructed the preconception that pancreatitis would be exclusive of (Schwartz et al., 2008) or more common in dogs undergoing right-sided adrenalectomy, particularly by finding that side of surgery was not statistically significantly associated with the development of pancreatitis (Barrera et al., 2013). In the population here studied, it also appeared that postoperative complications occurred more frequently in dogs with ATs (5/6) compared to those with phaeochromocytomas (2/4). However, previous studies found no significant differences (Barrera et al., 2013; Kyles et al., 2003).

Overall perioperative mortality (including all dogs that died in surgery and in the postoperative period) was 31%. This rate is slightly higher compared to a range varying from 12 to 26% for dogs with adrenal tumours in general undergoing adrenalectomy, reported in preceding case series (Barrera et al., 2013; Kyles et al., 2003; Lang et al., 2011; Massari et al., 2011; Schwartz et al., 2008). Yet, the population here presented had a higher proportion of dogs (19%) undergoing surgery due to tumour rupture and AAH compared to other authors, as formerly discussed. What is more, Lang et al. (2011) found that dogs with AAH had a significantly increased risk of perioperative mortality in comparison to those that underwent elective adrenalectomy, with a reported mortality rate of 50%. Plus, even though the 3 dogs with AAH in this study were euthanised intraoperatively, it is likely that they would have reached that outcome anyway in the postoperative period, according to Lang et al. (2011). Therefore, if only those undergoing elective procedures were to be considered, mortality would compare favourably to previous case series (15%).

When all adrenal gland tumours are considered, overall MST reported has varied from 375 to 953 days (Lang et al., 2011; Massari et al., 2011; Schwartz et al., 2008), and in one study 65% survived more than 1 year following surgery, up to 1941 days (~5 years) (Massari et al., 2011). Here, a comparable overall MST of 419 days was reached (**Graphic 1**). Moreover, at the end of this study, 64% of dogs who survived the postoperative period had lived for more than 1 year, and up to 1173 days (~3 years). And also, of those who had not reached 1 year of survival, only 1 had died of TR causes, and of the remaining 3, one was lost to follow-up and two were still alive and well (**Table 6**).

Adrenalectomy offers at least as good a prognosis as chronic medical management. In fact, even with its limitations, medical therapy with trilostane and mitotane in dogs with ADH can be a viable alternative to surgery, with reported MST of 353 and 102 days (Helm et al., 2011), respectively; and of 14.0 and 15.6 months (Arenas et al., 2014), respectively. In another study,

regarding the course of dogs with non-cortisol-secreting tumours without adrenalectomy, MST was 17.8 months (552 days) (Arenas et al., 2013). Even though these MST can sometimes be similar or superior to surgical reports, this retrospective study inclusively, most case series have reported higher MST especially if dogs survive the short-term period: with adrenocortical adenomas, MST were 688 days (Schwartz et al., 2008); with adrenocortical carcinomas, MST were 778 or 992 days if they survived the postoperative period (Anderson et al., 2001), 230 days overall (Schwartz et al., 2008), 360 days (Massari et al., 2011), and 48 months (Barrera et al., 2013); with adrenal tumours in general, MST were 690 days overall (Schwartz et al., 2008), 375 or 492 days if they survived the postoperative period for elective procedures, 208 or 844 days for emergency procedures (Lang et al., 2011), and 953 days overall (Massari et al., 2011). Furthermore, no successful medical treatment exists for phaeochromocytomas in detriment of the surgical route, and most dogs succumb to the disease and associated complications rather quickly (Reusch, 2015).

Metastatic rate at surgery was questionable (0 or 6%), and in the long-term, while local recurrence was not identified in any of the dogs, distant spread was diagnosed in 1 of 11 dogs (9%) that survived long-term. Overall metastatic rate of this study was 13%. These are quite low rates and comparable to other studies (Anderson et al., 2001; Barrera et al., 2013; Kyles et al., 2003; Massari et al., 2011; Schwartz et al., 2008). Possible explanations include an improvement in preoperative diagnostics, leading those dogs with metastasis to non-surgical treatment options and, therefore, being excluded; or it may result from the real number of eventual metastases being underestimated, considering that necropsy was rarely pursued. If 2 additional dogs with suspected metastatic lesions (one with suspected spleen metastasis who was euthanised at surgery; and another who developed chronic liver disease in the long-term for which US aspect of the liver and presence of invasion of adrenal peri-neural and -adipose tissue at time of surgery granted cause for suspicion), but without histopathological confirmation, were to be included, metastatic rate would be 25%. A similar conclusion was drawn by Barrera et al. (2013) in their case series.

Previous investigators have evaluated prognostic factors, namely predictors for short-term survival, for dogs with different types of adrenal gland neoplasms undergoing adrenalectomy. Preoperative variables significantly associated with shorter survival times included adrenal gland tumour size (particularly, when the major axis length was $\geq$ 5cm), vein thrombosis, extensive invasion of the CVC (into or beyond the hepatic hilus), weakness, lethargy, increased blood urea nitrogen concentration, thrombocytopenia, increased partial thromboplastin time, increased aspartate transaminase, hypokalaemia, presence of metastases, and presence of AAH (Barrera et al., 2013; Lang et al., 2011; Massari et al., 2011; Schwartz et al., 2008).

Intraoperative variables significantly associated with shorter survival times included blood loss requiring transfusion, and concurrent nephrectomy (Barrera et al., 2013; Schwartz et al., 2008). Postoperative variables significantly associated with shorter survival times were development of pancreatitis, acute renal failure, DIC, hypotension, and hypoxemia (for which PTE is a possible cause, although it could not be confirmed due to the retrospective nature of the studies) (Barrera et al., 2013; Schwartz et al., 2008).

In this study, although no statistical comparisons were feasible, these cases may serve as supportive examples of formerly identified prognostic factors in the referred literature. Nonetheless, they are representative of individual animals.

Size-wise, 3 of 5 dogs with tumours measuring ≥ 5 cm in maximum diameter died in surgery. Two had acute adrenal haemorrhage – an event that for each 1 mm increase in tumour size suffers a 6% increase in odds of occurrence (Lang et al., 2011). The third dog had a 50-mm myelolipoma, which because of its dimensions and very intimate association with the CVC, lead to an iatrogenic rupture of the vessel, culminating in hypovolaemic shock, cardiac arrest, and death. This case, along with another case of a 52-mm adrenocortical adenoma, serve as examples of the fact that even benign adrenal tumours may grow into considerably large dimensions, comparable to those of malignant masses. Therefore, large neoplasms may not only generate difficulties on their own by making surgical resection more challenging and risky in terms of causing iatrogenic injuries, but also by their augmented intrinsic potential to rupture and generate AAH – also a factor associated with a poorer outcome (Lang et al., 2011). Additionally, vein thrombosis has also been significantly associated with a tumour major axis length of ≥ 5 cm, and represents another characteristic which can potentially cause a negative impact on outcome (Massari et al., 2011). Regarding the 2 remaining dogs with tumours measuring ≥ 5 cm in maximum diameter, one had a neuroblastoma and died at 43 days postoperatively after recurrence of clinical signs and diagnosis of metastases; though Massari et al. (2011) found no significant association between presence of metastasis and a tumour major axis length of ≥ 5 cm. The other patient had an adrenocortical adenoma, survived for 521 days, and died from NTR causes.

Even though the cases reported here support the role of tumour size as an influencing outcome factor, on its own or through inherent associations with equally negative prognostic impact, it should be considered that size measurements in this study were unavoidable obtained through a mixture of methods. As a result, dimensions hereby reported might have been misjudged. For instance, underestimation of measurements is a well-known phenomenon associated with US (Behrend, 2015; Pagani et al., 2016).

Vein thrombosis was identified as a significant prognostic factor for decreased survival in one study (Massari et al., 2011). Conversely, others have found that CVC invasion did not significantly affect short-term morbidity or mortality, provided that the surgeon was familiarised with appropriate techniques (Kyles et al., 2003) and the tumour thrombus did not extend into or beyond the hepatic portion of the CVC (Barrera et al., 2013). In this group of dogs, two had CVC invasion unexpectedly discovered at surgery along with acute adrenal haemorrhage. In their situations, because the surgeon's experience dictated that only partial resections (without thrombectomy) could be accomplished, and in consideration of the poor outcome associated with acute adrenal haemorrhage, euthanasia was elected. Therefore, these cases serve more as an example to stress how the surgeon's experience with the surgical procedure and associated techniques may affect outcome as well, rather than the mere existence of a CVC thrombus.

Presence of metastasis at time of surgery was possibly present in one dog (6%), confirmed histologically at 4 days after surgery when the animal was euthanised and submitted to necropsy. Another dog had suspected metastatic lesions in its spleen at time of surgery, though it could not be confirmed, as he was euthanised at that time – he had also a ruptured tumour, acute adrenal haemorrhage, and extensive local invasion into surrounding tissues. Both these situations exemplify how detection of metastasis at surgery can affect short-term survival.

Likewise, presence of acute adrenal haemorrhage in this study was registered in 3 dogs, all of which ended up being euthanised for a combination of reasons. Although these results are suggestive of AAH as a negative prognostic factor for short-term survival, it should be noted that in the study by Lang et al. (2011) none of the dogs died intraoperatively. Still, it is likely that they would have reached that outcome in the postoperative period anyway, as it was previously argued in here.

In regard of intraoperative complications, major haemorrhage requiring transfusion was noted in 5 dogs, 3 of which were cases presented with AAH and another had major haemorrhage as a result of iatrogenic injury of the CVC – all 4 died intraoperatively. As such, these cases are supportive of major haemorrhage as prognostic factor, even though for the animals with AAH it is questionable if there were other variables to have weighed more in the decision for euthanasia. Conversely, a fourth animal who had major haemorrhage due to concurrent liver lobectomy lived a completely different path. Not only did he survived the short-term period, but he also presented the longer survival time of this retrospective study, having died of NTR causes at 1173 days following adrenalectomy.

Concurrent nephrectomy was identified as negative prognostic factor by Schwartz et al. (2008), however, later on Barrera et al. (2013) did not find nephrectomy to be a direct risk factor for decreased survival rate. However, MST was negatively affected because it was associated with development of renal failure, which in turn, was identified as a risk factor for death in the short-term. This might explain why the 3 dogs in this study, who had concurrent nephrectomy, did not seem to have affected short-term survival – one was alive and well when was lost to follow-up at 14 days after surgery; another survived for 43 days and died following development of metastatic disease; and a third patient was euthanised at surgery but for other reasons – since none developed renal failure.

In the postoperative period, pancreatitis was diagnosed in 4 dogs. Two were still alive and well at 53 and 770 days, and two had died at 521 days postoperatively from NTR causes and at 419 days from TR causes. In fact, for this latter case, the dog had a chronic form of pancreatitis, which eventual lead to euthanasia, and this scenario had started in the postoperative period as an acute form of pancreatitis. Therefore, for this case, it is possible that the development of pancreatitis affected its long-term survival but not its short-term.

These results do not particularly support the factor as of short-term prognostic value. Still, the use of different criteria to diagnose the complications might explain it. For instance, some of the cases here presented were diagnosed on the basis of clinical signs and response to therapy, rather than obtaining confirmation with canine-specific pancreatic lipase immunoreactivity assay and ultrasonographic evaluation for every single case. On the other hand, Schwartz et al. (2008) noted that all dogs that developed pancreatitis also had acute renal failure; hence, there is a chance that the predominating factor was actually the acute renal failure rather than the pancreatitis. In here, even though one dog developed transient acute renal insufficiency in the postoperative period, none had renal failure.

DIC developed in one patient in the postoperative period, together with hypertension, cardiac arrhythmias and dyspnoea, which due to their combined severity lead to the euthanasia of the animal. This example shows how DIC might contribute to or directly compromise short-term survival.

Finally, Herrera et al. (2008) found that age of their dogs with phaeochromocytomas had a significant negative effect on survival, i.e., for every 1-year age increase, the odds of 10-day survival decreased by 33%. In this study, patients with phaeochromocytomas were approximately 7, 8, 10, and 15 years old. The two younger animals were still alive and well at 53 and 247 days, postoperatively. In regard of the two older dogs, one (the 10-year old) was lost to follow up at 14 days, and the other (the 15-year old) died secondarily to a series of

postoperative complications; thus, representing an example which is in accordance with what was reported by Herrera et al. (2008).

Overall, and most importantly, this study allows a reinforcement of the idea that if dogs survive the immediate perioperative period, long-term outcome is generally good with possibility of prolonged survival times, as local or distant tumour recurrence appears to be low, as previously reported (Anderson et al., 2001; Barrera et al., 2013; Barthez et al., 1997; Gilson, Withrow, & Orton, 1994; Kyles et al., 2003; Lang et al., 2011; Massari et al., 2011; Schwartz et al., 2008; van Sluijs et al., 1995).

Limitations of this study were associated with its retrospective design, occasionally resulting in incomplete clinical and follow-up data, especially for dogs treated early in the study period. Furthermore, the reduced number of eligible cases, the variability existent in the selected group regarding the histological type of adrenal lesions, concurrency of other neoplastic lesions, and performance of surgical procedures on top of adrenalectomy, prevented unravelling more precise information concerning outcome of specific adrenal tumours or surgical techniques.

Indeed, such missing data and heterogeneity of the one available, resulted in an even smaller effective sample size, precluding further statistical analysis with reliability beyond a general descriptive exploration and a straightforward survival analysis through a Kaplan-Meier estimate allowing characterization of death in the population over time. Besides, a comprehensive survival analysis was also compromised by animals lost to follow-up, animals recently intervened thus limiting information regarding their long-term outcome, occasional bias in discriminating cause of death between pre-established groups (necropsy was seldom performed), and a high proportion of cases succumbing of NTR causes.

Additionally, and notwithstanding the discussed evidence, it is recognised that outcome might have been potentially biased by variation in clinicians' recommendations and owners' decisions (for instance, regarding a patient’s fittingness for undertake surgery), and surgical technique. Indeed, the technical difficulties that adrenalectomy imposes and their degree of influence on outcome cannot be undervalued, and the fact that, in this study, different surgeons with equally different degrees of experience undertook the procedure might have impacted outcome as well. Moreover, follow-up examinations were also completed by different veterinarians which might have affected the diagnosis of some complications since confirmation testing was not always performed for every case. Also, outcome could not be always objectively evaluated, sometimes having to rely on general satisfaction and feedback from owners.

Even with its limitations, these results are, nonetheless, reflective of routine clinical situations.

VI. CONCLUSION

Overall, this study emphasizes the conception that if dogs survive the immediate perioperative period, long-term outcome is generally good with possibility of prolonged survival times, as local or distant tumour recurrence appears to be low, just like has been previously reported (Anderson et al., 2001; Barrera et al., 2013; Barthez et al., 1997; Gilson, Withrow, & Orton, 1994; Kyles et al., 2003; Lang et al., 2011; Massari et al., 2011; Schwartz et al., 2008; van Sluijs et al., 1995).

In this study, 25% of dogs had adrenal *incidentalomas* discovered through imaging methods. In spite of this rate representing a considerably high proportion to reflect on, it does not exemplify an absolute unexpected finding. What is more, 75% of these had potential to be problematic in consideration of their proven malignancy and suspected functionality, high likelihood of malignancy, or large dimensions with potential to rupture (even though the tumour was benign). In reality, there is no way to tell how an *incidentaloma* will evolve over time, and surgical intervention sooner rather than later might be the safest way to guaranty a good prognosis. Still, it is recognised that not all dogs will be fitting candidates to adrenalectomy in consideration of their advance age and inherent concurrent frailties.

It should be also outlined that a substantial proportion of dogs (19%) in this case series were presented as medical and surgical emergencies due to a ruptured tumour and acute adrenal haemorrhage, which might indicate that these scenarios are more common than previously thought. Furthermore, surgeon's awareness of this situations might be critical as their experience and knowledge in how to surgical manage them can have an important effect on outcome, as also suggested by this study.

In sum, and in spite of its limitations, this retrospective investigation serves as an example of previously argued outcome predictors to consider when approaching these cases: age of patients with phaeochromocytomas, size of tumour, surgeon's experience in dealing with CVC invasion, presence of metastasis at surgery, acute adrenal haemorrhage, major intraoperative haemorrhage, and postoperative DIC. It also promotes awareness of adrenal *incidentalomas* and emergency clinical presentations. In addition, one can infer that having the experience and knowledge to surgical handle the adrenal glands might be a vital competence even for surgeons working at majorly first-opinion institutions which also offer a first-line of surgical options and referral work, in consideration of the three clinical cases here presented as candidates of emergency exploratory laparotomies due to an haemoabdomen of unknown origin, and only later attributed to an unexpected ruptured adrenal tumour.

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