Canine phaeochromocytoma: a guide to diagnosis and treatment

Phaeochromocytomas are neuroendocrine tumours arising from chromaffin cells of the adrenal medulla. Clinical signs are primarily associated with excessive catecholamine secretion and, to a lesser extent, with the space-occupying or invasive nature of the tumour. The diagnosis of phaeochromocytoma relies on clinical suspicion, biochemical testing, diagnostic imaging and histopathology. Biochemical testing mainly depends on the measurement of levels of plasma or urinary metanephrines, with normetanephrine demonstrating superior diagnostic performance compared to metanephrine. Adrenalectomy is the treatment of choice, but may not be possible in cases with extensive local invasion, concurrent disorders or distant metastasis. Contrast-enhanced computed tomography is recommended for surgical planning and metastasis screening. Vascular invasion is frequently observed, yet surgery remains a viable option in many cases. Recent studies question the necessity of alpha-blockade before surgery, and randomised controlled clinical trials are necessary to evaluate this. Long-term survival is often seen in dogs that survive the perioperative period. For patients in which surgery is not deemed feasible, medical treatment with tyrosine-kinase inhibitors may be considered. Given the current scarcity of effective medical treatment, there is an urgent need to identify novel therapeutic options. This review provides recommendations on the diagnosis and management of canine phaeochromocytoma.

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Marit F van den Berg DVM Dipl. ECVIM-CA PhD candidate. Department of Clinical Sciences, Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands. Email: m.f.vandenberg@uu.nl
Sara Galac DVM PhD Associate Professor. Department of Clinical Sciences, Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands.

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A phaeochromocytoma is a catecholamine-producing neuroendocrine tumour of chromaffin cells of the adrenal medulla. It occurs most often in older dogs, with an average age between 10.5 and 12 years, and there is no apparent breed or sex predilection (Reusch, 2015; Galac, 2017). Catecholamines (dopamine, adrenaline and noradrenaline) are synthesised from phenylalanine through a series of enzymatic conversions. Noradrenaline is converted to adrenaline by the cytoplasmic enzyme phenylethanolamine-N-methyltransferase. The expression of phenylethanolamine-N-methyltransferase is dependent on glucocorticoids so its expression is mainly localised to chromaffin cells of the adrenal medulla, which have a high exposure to cortisol because of centripetal (ie, from outside to inside) blood flow from the adrenal cortex (Eisenhofer et al, 2001). Upon sympathetic stimulation, catecholamines are secreted into the circulation from their secretory vesicles by exocytosis and exert their physiological effects by activation of adrenergic α- and β-receptors. The most important physiological effects include an increase in blood pressure, increase in heart rate and contractility, decrease in gastrointestinal motility and increase in levels of blood glucose and fatty acids (Reusch, 2015; Galac, 2017).

Dogs with a phaeochromocytoma may present with concurrent endocrine neoplasias, with the most frequently reported combinations being adrenocortical tumours and pituitary adenomas (Beatrice et al, 2018), resembling human multiple endocrine neoplasia syndrome. Information on the genetic background of canine phaeochromocytoma is limited, but there have been reports of mutations in the succinate dehydrogenase complex in dogs, mirroring findings in humans (Korpershoek et al, 2019).

Table 1. Clinical signs in dogs with phaeochromocytomas

Category	Clinical signs	Remarks
Cardiorespiratory	Panting	Catecholamine-induced
	Dyspnoea	Related to acute cardiac failure, pulmonary metastasis or large tumour size
	Tachycardia	Catecholamine-induced (increased heart rate and contractility)
	Arrhythmias	Usually tachyarrhythmias, but bradyarrhythmias (atrioventricular block) have been reported as well
	Collapse	Caused by tumour rupture or arrhythmias
	Hypertension	Patients usually present with ocular manifestations (acute blindness, intraocular haemorrhage), but hypertensive encephalopathy is possible as well
Neuromuscular	Weakness	Catecholamine-induced (hypermetabolic state)
	Muscle tremors	Catecholamine-induced
	Anxiety	Catecholamine-induced
	Seizures	Can be caused by hypertensive encephalopathy, catecholamine-induced vasospasms or brain metastasis
	Ataxia or paresis	Reported as a result of metastasis in the vertebral canal
Non-specific	Lethargy	Catecholamine-induced
	Weight loss	Catecholamine-induced (hypermetabolic state), cancer cachexia
	Hyporexia	Can be caused by nausea or abdominal pain
Miscellaneous	Polyuria or polydipsia	Catecholamine-induced (secondary decreased release and activity of antidiuretic hormone) and/or primary polydipsia (abdominal pain or mass effect)
	Abdominal pain	As a result of mass effect or tumour rupture
	Nausea or vomiting	Catecholamine-induced (activation α-adrenergic receptors in chemoreceptor trigger zone)
	Diarrhoea	Catecholamine or hypertension-induced
Invasiveness or large tumour size	Abdominal distention	Large tumour size, ascites, intra-abdominal haemorrhage
	Caudal vena occlusion	Hind limb oedema, ascites, and distension of the caudal epigastric veins are reported. Clinical signs may be absent because of development of collateral circulation
	Aortic thromboembolism	Patients can present with lack of femoral pulse, cold distal limbs, paraparesis, painful and weak hind limbs
Tumour rupture	Retroperitoneal or intra-abdominal haemorrhage	Signs of haemorrhagic shock, abdominal pain

(Gilson et al, 1994; Barthez et al, 1997; Reusch, 2015; Galac, 2017)

Clinical manifestations

Clinical signs are primarily associated with excessive catecholamine secretion and, to a lesser extent, with the space-occupying or invasive nature of the tumour (*Table 1*). Clinical signs may be present continuously or may be intermittent or paroxysmal as a result of episodic hormone secretion (Reusch, 2015; Galac, 2017). Approximately 50% of affected dogs show hypertension at the time of investigation. Phaeochromocytomas frequently invade surrounding structures, particularly the caudal vena cava, which can eventually lead to caudal vena cava occlusion. In a small number of dogs, spontaneous tumour rupture with retroperitoneal or intra-abdominal haemorrhage has been documented (Whittemore et al, 2001; Enright et al, 2022). The presence of metastatic disease can lead to organ-specific clinical signs, such as central nervous system symptoms associated with brain metastasis, or paresis and ataxia related to metastasis in the vertebral canal (Platt et al, 1998). Dogs with 'clinically silent' phaeochromocytomas do not display any symptoms related to catecholamine excess (Constantinescu et al, 2022). However, in many instances, these patients may show subtle or non-specific signs that clinicians could easily overlook, especially in the case of concurrent disease.

Diagnosis

The diagnosis of a phaeochromocytoma relies on clinical suspicion, biochemical testing and diagnostic imaging findings (*Figure 1*). In addition, an adrenal mass may be identified incidentally ('incidentaloma') on imaging not performed for suspected adrenal disease and can result in the diagnosis of a phaeochromocytoma. These incidental adrenal masses were found in 9.3% of dogs during abdominal computed tomography (Baum et al, 2016) and 4%

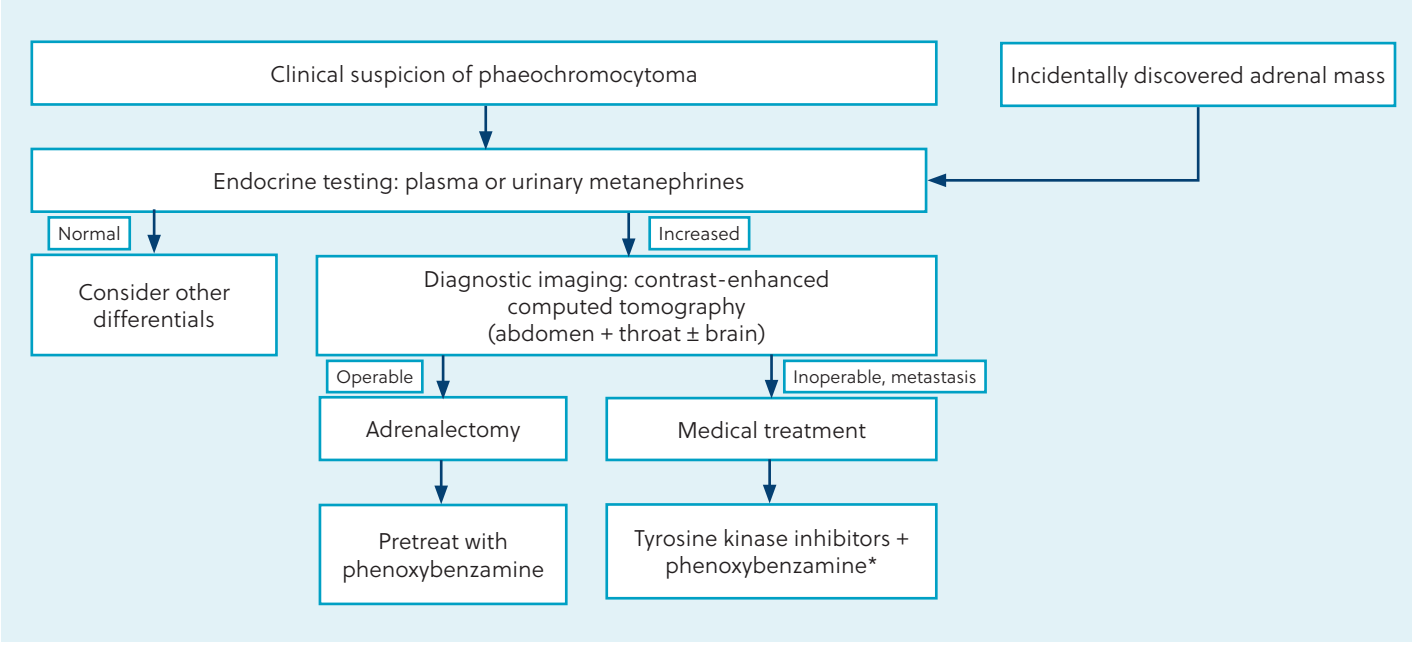

*Figure 1. Diagnostic and therapeutic approach for a dog suspected of having a phaeochromocytoma. *Phenoxybenzamine is recommended to control clinical signs of catecholamine excess such as hypertension. The dose should be gradually increased until clinical signs are effectively managed or until reaching a final dose of approximately 1 mg/kg every 12 hours.*

of dogs during abdominal ultrasonography (Cook et al, 2014). The diverse range of clinical manifestations demands a high level of clinical awareness for diagnosis. The definitive diagnosis relies on histopathology and immunohistochemistry using neuroendocrine markers.

Clinical pathology

The findings of complete blood count, serum biochemistry and urinalysis in dogs with a phaeochromocytoma are non-specific. However, they are important to rule out other diseases or identify concurrent disease. In some dogs with a phaeochromocytoma, laboratory results are completely normal (Reusch, 2015; Appelgrein et al, 2020). Most consistent haematological abnormalities include anaemia and leukocytosis or stress leucogram. Increased levels of liver enzymes are the most frequent biochemical abnormality (Reusch, 2015). Additional reported biochemical abnormalities include azotaemia, hypercholesterolemia, hyperglycaemia, hypoalbuminaemia, hyperphosphataemia, hyponatraemia and hypokalaemia (Gilson et al, 1994; Barthez et al, 1997). However, it is important to realise that concurrent diseases could contribute to these findings. Urinalysis may reveal hyposthenuria or isosthenuria, proteinuria and haematuria. Hyposthenuria or isosthenuria may result from the inhibitory effect of catecholamines on the release and activity of antidiuretic hormone, while proteinuria may be caused by hypertension-induced glomerular damage (Reusch, 2015).

Biochemical testing

Within adrenal medullary chromaffin cells, there is a continuous leakage of adrenaline and noradrenaline from their secretory vesicles into the cytoplasm, where they are converted to metanephrine and normetanephrine (together referred to as 'metanephrines') by the enzyme catechol-O-methyltransferase before being released into the circulation (Eisenhofer et al, 2023). Catecholamines and metanephrines undergo varying degrees of sulphate conjugation and, subsequently, are primarily eliminated by the kidneys and excreted in urine.

Biochemical testing for phaeochromocytomas in dogs has only been carried out for the past 10–15 years and has consisted of evaluation of plasma and urinary levels of catecholamines and metanephrines, as well as urinary vanillylmandelic acid (Gostelow et al, 2013; Salesov et al, 2015; Soler Arias et al, 2021; van den Berg et al, 2023a). The current recommendation for biochemical testing for phaeochromocytomas includes measuring plasma or urinary metanephrines (Reusch, 2015). Because catecholamine secretion is often episodic and even negligible in some tumours, measurement of metanephrines is superior because of their continuous intratumoural production (van Berkel et al, 2014; Eisenhofer et al, 2023). Additionally, as a result of the absence of catechol-O-methyltransferase in sympathetic nerves, the O-methylated metanephrines demonstrate higher specificity for chromaffin cells and phaeochromocytomas compared to catecholamines or other catecholamine metabolites (Eisenhofer et al, 2023). Measuring levels of free metanephrines offers superior diagnostic accuracy compared to total (free plus conjugated) metanephrines. This is because the free metanephrines are primarily produced within adrenal chromaffin and phaeochromocytoma cells, whereas sulphate conjugation mainly takes place in the gastrointestinal tract (Peitzsch et al, 2013). Urinary vanillylmandelic acid testing is not recommended in regions where metanephrine assays are available.

The methods used for measuring catecholamine metabolites in dogs have become increasingly accessible, primarily encompassing high-pressure liquid chromatography with electrochemi-

cal detection and liquid chromatography-tandem mass spectrometry. Today, liquid chromatography-tandem mass spectrometry is the method of choice for low-cost, high-throughput, precise and accurate measurement of metanephrines (Eisenhofer et al, 2016). With liquid chromatography-tandem mass spectrometry, analytical interferences are rarely a problem, while high-pressure liquid chromatography with electrochemical detection is prone to interferences (Eisenhofer et al, 2023). For example, amoxicillin and acetaminophen have been reported to cause false positive increases of normetanephrine in humans by high-pressure liquid chromatography with electrochemical detection, but not by liquid chromatography-tandem mass spectrometry (Eisenhofer et al, 2023). "Recently, reference intervals for plasma and urinary free metanephrines, determined by liquid chromatography-tandem mass spectrometry, were reported in healthy dogs (*Table 2*) (van den Berg et al, 2023a). Since liquid chromatography-tandem mass spectrometry displays good consistency among different laboratories (Peitzsch et al, 2021), practitioners can confidently use these reference ranges if this is the analytical method used by their external reference laboratory.

Besides analytical interferences, many other factors can influence catecholamine and metanephrine measurements, potentially leading to false positive test results. Of drugs that can pharmacodynamically cause false positive results, metoclopramide, α-blockers (such as phenoxybenzamine), β-blockers (such as atenolol), calcium-channel blockers (such as amlodipine) and sympathomimetics (such as ephedrine and phenylpropanolamine) are particularly relevant to veterinary medicine (Reusch, 2015). Phenoxybenzamine, a non-selective α-blocker used in the preoperative medical management of phaeochromocytomas, is a well-known cause of false positive increases in plasma normetanephrine (van Berkel et al, 2014; Eisenhofer et al, 2023). Consequently, biochemical testing for phaeochromocytoma should be performed before starting this drug. Endogenous and exogenous glucocorticoids may increase catecholamine production (Galac, 2017). Because of the overlap in clinical signs between dogs with hypercortisolism and those with phaeochromocytomas, hypercortisolism is an important differential diagnosis.

Studies have demonstrated that normetanephrine exhibits better diagnostic performance than metanephrine in both plasma and urine for differentiation between dogs with phaeochromocytomas and those with other diseases, including hypercortisolism (Gostelow et al, 2013; Salesov et al, 2015; van den Berg et al, 2023a). Currently, there is no consensus regarding the preferred use of plasma or urine for metanephrine measurements in terms of diagnostic accuracy. In the past, it was customary to stabilise urinary metanephrines by acidifying the urine. However, both human and canine studies have demonstrated that acidification is unnecessary for accurate measurement of urinary metanephrines (Willemsen et al, 2007; Sasaki et al, 2021). In addition, urinary metanephrines seem to be stable at room temperature for several days (Sasaki et al, 2021). In dogs, it is unknown how stable plasma metanephrines are after blood collection. In humans, blood should be kept at 4°C and must be centrifuged within 6 hours. Plasma metanephrines remain stable if plasma is kept at 4°C for 3 days, but storage or shipment of longer duration must be at –20°C or lower (Willemsen et al, 2003). In dogs, it is recommended to centrifuge the blood immediately, and to ship the plasma samples on dry ice (Reusch, 2015).

Table 2. 95% reference intervals for biochemical tests in healthy dogs, measured by liquid chromatography-tandem mass spectrometry

Bodily fluid	Metanephrine	95% reference intervals
Plasma (nmol/litre)	Normetanephrine	0.9–3.6
	Metanephrine	0.4–2.5
	3-methoxytyramine	0.3–1.3
Urine (nmol/mmol)	Normetanephrine / creatinine	16.8–97.4
	Metanephrine / creatinine	8.0–65.6
	3-methoxytyramine / creatinine	27.9–136.0

(van den Berg et al, 2023a)

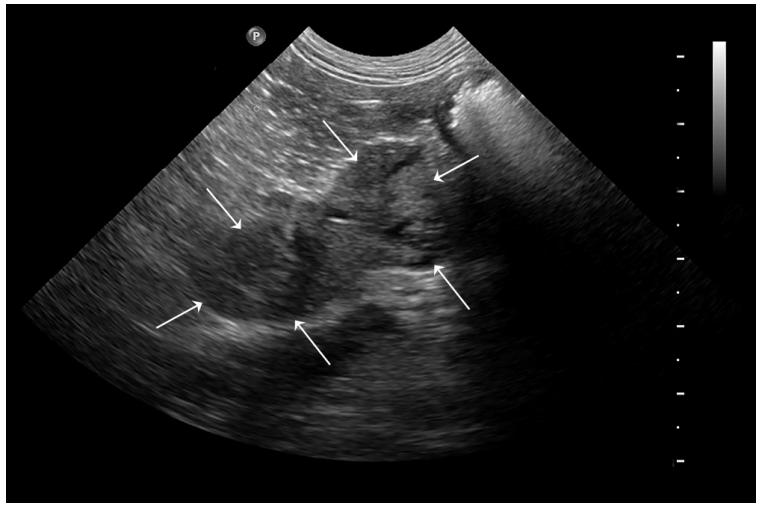

Figure 2. Long-axis ultrasonographic image of a phaeochromocytoma of the left adrenal gland (arrows) showing heterogeneous echogenicity.

Diagnostic imaging

Once the biochemical diagnosis of a phaeochromocytoma is made, patients should undergo diagnostic imaging. Because of its widespread availability and non-invasive nature, abdominal ultrasonography is the primary method for evaluating phaeochromocytomas in dogs. The shape, size, architecture and symmetry of the adrenals can be assessed, as well as local invasion into surrounding structures and the presence of abdominal metastasis (Reusch, 2015). Phaeochromocytomas do not display a characteristic sonographic appearance; they can be identified as rounded masses with well-defined or irregular borders, or as solitary or multiple adrenal nodules (Pagani et al, 2016). The echogenicity shows substantial variability, with hypoechoic, isoechoic or hyperechoic patterns being observed. Additionally, echogenicity may appear either homogeneous or heterogeneous (*Figure 2*) (Pagani et al, 2016). Tumour size varies greatly, ranging from a few millimetres to >10 cm in diameter (Reusch, 2015; Enright et al, 2022). Most phaeochromocytomas are unilateral, with a contralateral adrenal gland that is

normal in size and shape, but bilateral phaeochromocytomas may occur (Reusch, 2015).

Among other adrenal masses, cortisol-secreting adrenocortical tumours are most observed, and they may exhibit a similar sonographic appearance, making them an important consideration in the differential diagnosis. In comparison to adrenocortical tumours, phaeochromocytomas are reported to invade adjacent vessels more often and to exhibit mineralisation less frequently (Besso et al, 1997; Davis et al, 2012). While atrophy of the contralateral adrenal gland is expected in case of unilateral cortisol-secreting tumours, this may not be evident on ultrasonography (Besso et al, 1997). Studies indicate that contrast-enhanced ultrasound can be used to differentiate between adrenocortical tumours and phaeochromocytomas (Bargellini et al, 2016; Nagumo et al, 2020; Burti et al, 2023). The most consistent finding is a shorter mean transit time in phaeochromocytomas compared to adrenocortical tumours.

Vascular invasion and the presence of a tumour thrombus are reported in 33–82% of dogs with a phaeochromocytoma, and most commonly involve the phrenicoabdominal vein and caudal vena cava (*Figures 3–5*) (Herrera et al, 2008; Barrera et al, 2013; Enright et al, 2022). There could be a potential association between tumour size and thrombosis (Massari et al, 2011), but further investigation in a larger number of dogs is necessary to confirm this. Invasiveness does not necessarily indicate malignancy, as it may simply reflect the expansion of a large tumour mass into less resistant structures (Zini et al, 2019).

In humans with phaeochromocytomas, computed tomography is the first-choice imaging modality beacuse of its excellent spatial resolution for thorax and abdomen (Lenders et al, 2014). Contrast-enhanced computed tomography allows precise evaluation of tumour size, shape and architecture, and surpasses ultrasonography in its ability to detect vascular invasion (Schultz et al, 2009; Gregori et al, 2015). In addition, it is superior to thoracic radiographs for detecting pulmonary metastasis (Armbrust et al, 2012) and can serve to show the brain when central nervous system symptoms are present. Phaeochromocytomas may be seen as rounded or lobulated soft-tissue masses in the mid-dorsal abdomen, often exhibiting heterogenous enhancement and irregular contours (*Figures 4* and *5*) (Gregori et al, 2015; Yoshida et al, 2016; Pey et al, 2022).

Although various studies have evaluated the accuracy of computed tomography characteristics in predicting tumour type in dogs with adrenal tumours, overlapping characteristics between tumour types limit the potential for reliably distinguishing them based on computed tomography alone (Gregori et al, 2015; Yoshida et al, 2016; Pey et al, 2022). Nevertheless, these computed tomography criteria can be considered in the diagnostic evaluation of dogs with adrenal tumours. Compared to adrenocortical carcinomas, phaeochromocytomas rarely show intratumoural cal-

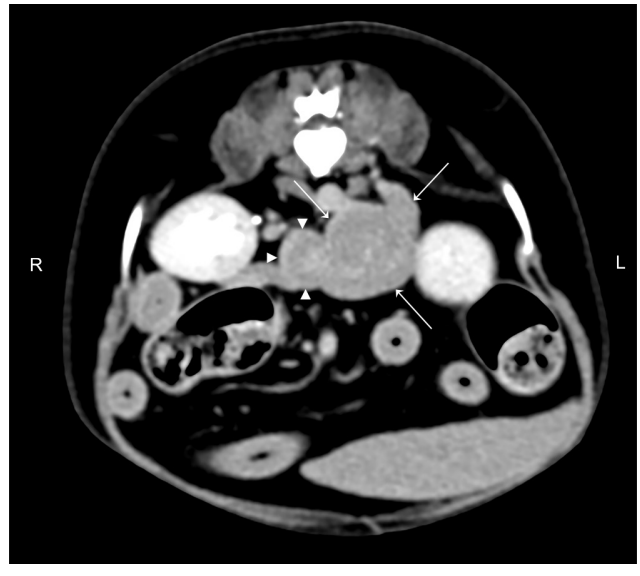

Figure 4. Transverse post-contrast computed tomography image in soft tissue window at the level of the mid-abdomen. The left adrenal gland is markedly enlarged and demonstrates heterogeneous contrast enhancement (arrows). Vascular invasion in the caudal vena cava is visible (arrowheads).

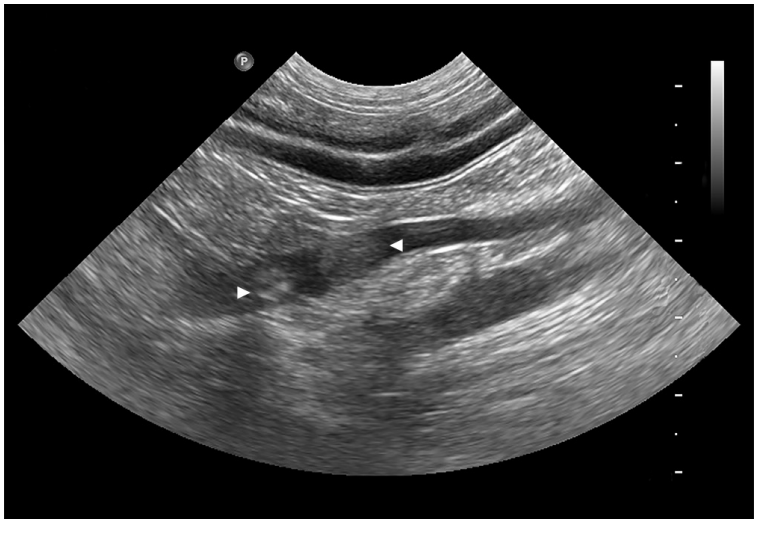

Figure 3. Ultrasonographic image of vascular invasion of the caudal vena cava. The heterogeneous tumour thrombus (arrowheads) originated from a phaeochromocytoma in the left adrenal gland.

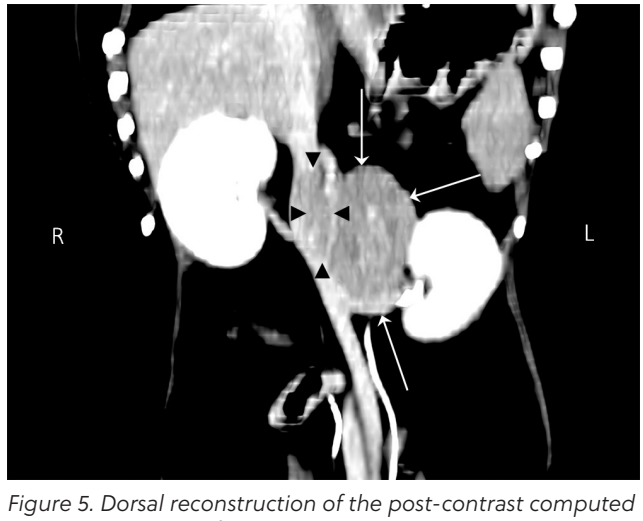

Figure 5. Dorsal reconstruction of the post-contrast computed tomography study of the phaeochromocytoma shown in **Figure 4**. *The arrows point to the tumour and the arrowheads show the vascular invasion into the caudal vena cava.*

cification, have higher precontrast attenuation values, are more likely to exhibit vascular invasion and demonstrate longer tumour thrombi (Gregori et al, 2015; Yoshida et al, 2016; Pey et al, 2022).

Fine needle aspiration

Once an adrenal mass has been identified, it is tempting to consider obtaining a fine needle aspiration to distinguish tumour types or confirm malignancy. Two studies evaluated the safety of percutaneous ultrasound-guided fine-needle aspirations of adrenal lesions in dogs (Sumner et al, 2018; Pey et al, 2020). Of 69 dogs in total, complications were reported in five dogs (one ventricular tachycardia, three haemorrhages and one death as a result of acute respiratory distress syndrome). Some of these complications could be attributed to relevant concomitant disease, specifically pericardial effusion in the dog with ventricular tachycardia and laryngeal paralysis in the dog that died of respiratory distress (Sumner et al, 2018; Pey et al, 2020). The diagnostic accuracy of fine-needle aspirations in distinguishing between phaeochromocytomas and adrenocortical tumours ranged from 87% to 100% (Bertazzolo et al, 2014; Pey et al, 2020). However, cytology is not reliable in distinguishing benign from malignant lesions, nor does it provide information about the functional status of the tumour. In human medicine, both fine-needle aspiration and core needle biopsy of phaeochromocytomas are contraindicated because of the potential for serious complications (such as severe hypertension, severe pain or haematoma) and increased surgical challenges (Vanderveen et al, 2009). Although fine-needle aspiration of the adrenal gland appears to be relatively safe in dogs, the risks should be weighed carefully against benefits.

Histopathology

The definitive diagnosis of a phaeochromocytoma is based on histological examination and immunohistochemistry. Histologically, phaeochromocytomas are characterised by neoplastic cells arranged in lobules or nests separated by fine fibrovascular septa. Additionally, diffuse growth surrounded by thick acellular bands of fibrosis can be seen (Zini et al, 2019). There might be compression of the adrenal cortex and disruption of the adrenal capsule, along with areas of necrosis and haemorrhage, especially in large tumours. Distinguishing between adrenocortical and adrenomedullary origin can be challenging, and immunohistochemistry utilising various neuroendocrine markers, such as chromogranin A and synaptophysin, is employed to reinforce the diagnosis of phaeochromocytoma (Reusch, 2015; Galac and Korpershoek, 2017). Capsular and vascular invasion are seen in the majority of canine phaeochromocytomas but are not reliable indicators of malignancy (Zini et al, 2019).

Treatment

Preoperative medical management

If surgery is feasible, preoperative medical management can be started in consultation with the referral institution before referring patients for adrenalectomy. Intraoperative tumour manipulation can lead to cardiovascular instability because of episodic hypersecretion of catecholamines, which can result in severe complications such as hypertensive crises and cardiac arrhythmias (Reusch, 2015). The aim of preoperative medical management is to mitigate these complications by blocking the effects of catecholamines for at least 1–2 weeks before surgery. Phenoxybenzamine, an irreversible antagonist of both α-1 and α-adrenergic receptors, effectively blocks the α-adrenergic response to circulating adrenaline and noradrenaline and is used most often (Lenders et al, 2014; Reusch, 2015).

In humans with a phaeochromocytoma, current international guidelines recommend preoperative medical treatment with α-adrenergic receptor blockers, but this approach is now being challenged as a result of controversies over the lack of evidence (Wang et al, 2023). One study demonstrated significantly reduced perioperative mortality in dogs pretreated with phenoxybenzamine (13%) in comparison to untreated dogs (48%) (Herrera et al, 2008). Conversely, pretreatment with an α-blocker was not associated with increased survival in another study (Enright et al, 2022). A separate study involving 13 dogs undergoing surgery for phaeochromocytomas revealed minimal perioperative complications and a low mortality rate, even without prior α-blocker therapy (Appelgrein et al, 2020). While this demonstrates the feasibility of not using preoperative α-blockade in specialised centres with expertise in adrenalectomy and high-level anaesthetic monitoring and care, it is important to interpret these findings cautiously and not to misconstrue them as evidence that α-blockade can be safely omitted in all patients and under any circumstances. At present, preoperative α-blockade is still advised at the authors' institution. The current recommendation is to start with a dose of 0.25 mg/kg phenoxybenzamine every 12 hours. In case of hypertension, the dose is gradually increased every 2–3 days until normotension is achieved or until reaching a final dose of approximately 1 mg/kg every 12 hours. If there is no hypertension, the dose of 0.25 mg/kg every 12 hours is continued until surgery. The last dose is administered the evening before surgery. Should the dog exhibit signs of hypotension (weakness, lethargy, syncope) or other adverse events (tachycardia, vomiting), the dosage of phenoxybenzamine should be decreased. As an alternative to phenoxybenzamine, treatment with selective α-1 blockers (such as prazosin and terazosin) can be considered. For patients experiencing tachyarrhythmias, β-blockers (such as atenolol) can be initiated. However, these should never be initiated before α-blockade, because this can result in severe hypertension (Galac, 2017).

Surgical treatment

Where possible, phaeochromocytomas should be removed surgically, because surgery alleviates clinical signs linked to excessive catecholamine secretion but also avoids potential complications arising from uncontrolled tumour growth (Galac, 2017). Surgery may be prevented by extensive local invasion, distant metastasis or serious concurrent disorders. For patients with vascular invasion, the possibility of undergoing adrenalectomy remains viable (*Figure 6*), as several studies have indicated that tumour invasion into the vena cava does not impact perioperative mortality rates (Kyles et al, 2003; Herrera et al, 2008; Lang et al, 2011). Nonetheless, extensive vascular invasion, particularly tumour thrombi extending beyond the hepatic hilus, may be associated with a

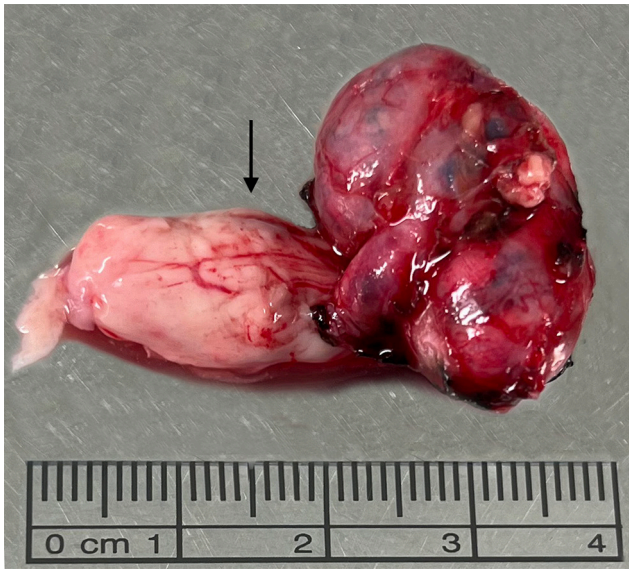

Figure 6. Phaeochromocytoma of the left adrenal gland with a tumour thrombus in the caudal vena cava (arrow). An adrenalectomy with caudal vena cava venotomy was performed through an open laparotomy (median celiotomy) approach.

higher perioperative mortality (Barrera et al, 2013). Particularly in cases of vascular invasion, adrenalectomy should only be performed by highly skilled surgeons experienced in appropriate techniques. Significant prognostic indicators for survival of dogs who undergo adrenalectomy for phaeochromocytoma include the absence of intraoperative arrhythmias, prior phenoxybenzamine treatment, younger age and a short surgical duration (Herrera et al, 2008).

Irrespective of vascular invasion, dogs that survive the perioperative period frequently experience long-term survival (Lang et al, 2011; Barrera et al, 2013; Enright et al, 2022). In a study assessing short- and long-term outcomes of 53 dogs undergoing adrenalectomy for a phaeochromocytoma, the median survival was 1150 days (Enright et al, 2022). In another study, survival rates at 1, 2 and 3 years were 83%, 60% and 60%, respectively, in 27 dogs that underwent adrenalectomy for a phaeochromocytoma (Barrera et al, 2013). To achieve a favourable outcome, the presence of a skilled surgeon, experienced anaesthesia team and dedicated postoperative care is essential (Galac and Korpershoek, 2017; Hayes, 2022).

Adrenalectomy can be performed laparoscopically or by an open laparotomy. The decision between an open or laparoscopic approach depends on tumour size, the presence of vascular invasion and the surgeon's experience (Pitt et al, 2016; Cavalcanti et al, 2020; Hayes, 2022; van Bokhorst et al, 2023). Laparoscopy is suitable for masses up to 5 cm in diameter that have not invaded the caudal vena cava (Pitt et al, 2016; Cavalcanti et al, 2020).

Postoperatively, patients should be monitored for cardiac arrhythmias, hyper- and hypotension and haemorrhage (Galac, 2017). Following unilateral adrenalectomy, hormonal supplementation therapy is unnecessary.

Medical treatment

When surgery is not deemed feasible or is prevented for other reasons, medical treatment is warranted. The use of toceranib phosphate, a tyrosine kinase inhibitor, has been described in a small retrospective study involving five dogs with inoperable, metastatic or recurrent phaeochromocytomas (Musser et al, 2018). Of these dogs, one exhibited a partial response, while the remaining four dogs displayed stable disease for a period of 11–61 weeks (Musser et al, 2018). At the authors' institution, toceranib phosphate is administered orally 3 times a week (on Monday, Wednesday and Friday) at a dose of 2.75 mg/kg, rounded to the nearest available tablet size. Dogs should be monitored for adverse events (such as vomiting, diarrhoea, gastrointestinal bleeding) and monitoring should include measurement of albumin, creatinine, liver enzymes (alanine aminotransferase, aspartate aminotransferase), phosphate, haematocrit, neutrophil count and proteinuria (Plumb, 2018).

Medical treatment with phenoxybenzamine is recommended to control the clinical signs of catecholamine excess. The dose should be gradually increased until clinical signs (such as hypertension) are effectively managed or until reaching a final dose of around 1 mg/kg q12h (Reusch, 2015).

Apart from toceranib phosphate, there are no other tumour-targeted drugs for dogs with phaeochromocytomas. A recent study on transcriptomics of canine phaeochromocytoma and paraganglioma identified several promising therapeutic targets, such as dopamine receptor D2 and pleiotrophin (van den Berg et al, 2023b). Of interest, dopamine receptor D2 is also highly overexpressed in human phaeochromocytoma and paraganglioma, and dopamine receptor D2 antagonists are being evaluated in phase II clinical trials in patients with metastatic phaeochromocytoma and paraganglioma (Anderson et al, 2022).

Administration of 131I-metaiodobenzylguanidine was documented in one dog, resulting in clinically stable disease for 4 months (Bommarito et al, 2011). Recently, stereotactic body radiation therapy for treatment of phaeochromocytomas was evaluated in eight dogs – a favourable outcome with complete resolution of clinical signs was seen in all dogs and, based on tumour size, two dogs demonstrated complete remission and two dogs demonstrated partial remission (Linder et al, 2023).

Conclusions

Dogs with phaeochromocytomas may present with a wide variety of clinical symptoms, making the diagnosis challenging. The diagnosis should be made based on clinical suspicion, biochemical testing and diagnostic imaging findings. Biochemical testing should include measurement of metanephrines rather than catecholamines. The more widespread availability of techniques for metanephrine measurement and establishment of reference intervals for metanephrines in healthy dogs facilitate biochemical testing for phaeochromocytoma and further research into this area. For dogs with a phaeochromocytoma, surgery is the treatment of choice, and dogs surviving the perioperative period can experience prolonged survival. While preoperative medical management with α-blockers (like phenoxybenzamine) is currently recommended, randomised controlled clinical trials are essential to assess the actual necessity of α-blockade. When surgery is not feasible, medical treatment involves administration of phenoxybenzamine to manage the clini-

cal signs of catecholamine excess, along with the implementation of tyrosine kinase inhibitors. Given the current scarcity of effective medical treatment options, it is imperative to conduct in vitro and in vivo studies to ascertain whether the recently identified therapeutic targets possess the potential to evolve into future treatment options. In addition, future studies on whole-exome or whole-genome sequencing will be needed to fully elucidate the genetic basis of canine phaeochromocytoma. CA

Conflicts of interest

The authors declare that there are no conflicts of interest.

KEY POINTS

- Because clinical signs can be subtle, non-specific and intermittent, a high level of clinical awareness is necessary for accurate diagnosis of phaeochromocytoma.
- Biochemical testing should include measurement of plasma or urinary metanephrines.
- Contrast-enhanced computed tomography is recommended for surgical planning and metastasis detection.
- Vascular invasion into the caudal vena cava is commonly observed but does not necessarily exclude the possibility of surgery or imply malignancy.
- Adrenalectomy is the preferred treatment, but it is a challenging and high-risk procedure that should exclusively be performed by skilled surgical and anaesthesia teams.
- Current medical treatment options include tyrosine kinase inhibitors, and future research endeavours should focus on identification of novel therapeutic alternatives.

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