CPD article

Approach to an incidental adrenal mass

Adrenal glands represent important endocrine organs. Disorders of these can present in many vague, often non-specific ways; this presents a dilemma for the clinician when an abnormal adrenal gland is detected on imaging. This article aims to explore the evidence for approach to adrenal masses in the dog and cat, including defining an adrenal gland mass, the logical approach to the mass, and treatment options.
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Adrenal masses may be identified in a patient where the significance is unknown; this is likely to occur more frequently with more widely available advanced diagnostic imaging. The approach to the identified mass may be unclear, in particular when the patient has presented with vague/lack of clinical signs compatible with a functional mass. The same dilemma exists in people; as a result guidelines have been developed. Adaptations of these guidelines based upon prevalence data in the dog and cat can be applied to our patients.

How and when might we identify an adrenal mass?

Adrenal masses are most likely to be identified using abdominal ultrasound in practice; however, they may also be detected using abdominal radiography, computed tomography (CT) scanning, and magnetic resonance imaging (MRI).

With abdominal ultrasound the left adrenal gland can be found craniomedial to the left kidney, ventrolateral to the aorta and between the origin of the craniomesenteric and left renal arteries, and is peanut-shaped. The right adrenal gland is craniomedial to the hilus of the right kidney, dorsal or dorsolateral to the vena cava and between the origin of the cranial mesenteric and right renal arteries, and is comma-shaped. Identification may be aided by the knowledge that the phrenicoabdominal vein crosses the mid-portion of both glands (see *Figure 1* for an example of an incidental right-sided adrenal mass found on ultrasound) (Barthez et al, 1998).

There is a large range of normal-sized adrenals in the dog, and the left adrenal is generally slightly larger than the right. Normal dimensions described include the range of length 10.7–50.0 mm and transverse diameter 3.0–16.0 mm; studies have proposed the maximum adrenal transverse diameter as the most reliable method to assess for adrenomegaly, and propose a cut-off of 7.4 mm as the maximal transverse diameter. Authors acknowledged overlap

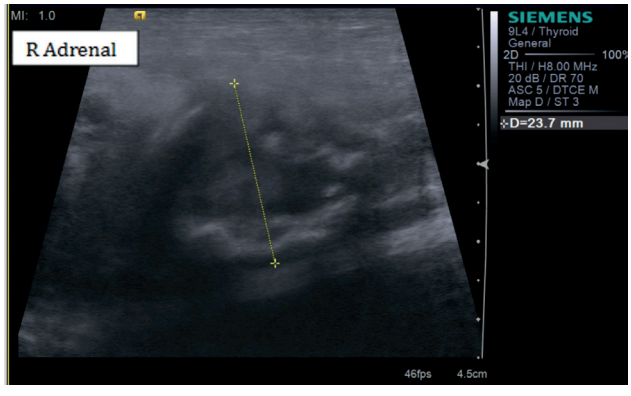

Figure 1. Adrenal masses may be detected as an incidental finding on abdominal ultrasound.

but concluded that this cut-off provided a sensitivity of 77% and specificity of 80–91% for the identification of adrenal gland enlargement (in this case in the context of pituitary-dependent hyperadrenocorticism) (Barthez et al, 1998). Interestingly, and perhaps more reliably, a more recent study proposed cut-offs for different sized dogs, with normal being a thickness of the caudal pole of the adrenal gland in the sagittal plane of ≤0.54 cm for dogs <10 kg, ≤0.68 cm for dogs 10–30 kg, and ≤0.80 cm for dogs >30 kg body weight (Soulsby et al, 2015). In the cat, adrenal glands are proportionally larger, with the range of normal length described as 4.5–13.7 mm and transverse diameter 2.9–5.3 mm (Barthez et al, 1998).

Adrenal masses can be identified as a change in shape of the gland produced by abnormal tissue (which typically grows in a concentric fashion). Small masses might only affect a small portion of the gland, whereas larger masses typically result in global enlargement. Adrenal masses can be unilateral or bilateral and are most likely to be due to tumours or hyperplasia, although haematomas, abscesses, and granulomatous disease

have been described, rarely, in small animals. Adrenal tumours affecting the dog include adrenocortical adenoma, carcinoma, phaeochromocytoma, and metastatic neoplasia (Barthez et al, 1998).

Once a unilateral adrenal mass has been identified, staging is advised as a tumour is considered most likely. Staging should include full assessment of the mass, in particular assessment for local or vascular invasion (especially of the caudal vena cava); imaging of the contralateral adrenal gland; and imaging of the remainder of the abdomen and the thorax.

Severe hyperplasia can result in bilateral adrenal masses in atypical cases of pituitary-dependent hyperadrenocorticism, with hyperplasia of both glands up to 3 cm in size described (Barthez et al, 1998). Bilateral tumours can also be found with adrenocortical or medullary tumours, with an incidence of around 6% of phaeochromocytomas in dogs (Bouayad et al, 1987; Gilson et al, 1994; Barthez et al, 1997), or pituitary and concurrent adrenal masses (Francis et al, 1992).

What can we learn from human medicine?

Incidentally identified adrenal masses also represent a management dilemma in human medicine. A study revealed adrenal incidentalomas on autopsy in 6.5% of individuals (Hedeland et al, 1968); in particular, functional masses resulting in subclinical Cushing's syndrome are recognised with increasing frequency. Ultimately the majority of adrenal masses are identified to be non-functional adenomas (80%), with the remainder reflecting functional masses associated with subclinical Cushing's syndrome (5%), phaeochromocytoma (5%), aldosteronoma (1%), adrenocortical carcinoma (<5%) and finally non-functional tumours that may represent metastatic disease from anywhere in the body (2.5%), myelolipoma, benign cysts, and ganglionomas (see *Figure 2*) (Young, 2007).

Ultimately the decision-making process is guided by three key questions. Is the tumour functional (hormonally active)? Does it have radiological features of malignancy? Finally, does the patient have a history of a previous malignant lesion?

Question 1: is the tumour functional?

By definition, 'incidental' adrenal mass excludes patients with overt evidence of hyperadrenocorticism. Considerations for occult functional tumours in human medicine are (Young, 2007):

Subclinical Cushing's syndrome

- Diagnosed with a dynamic dexamethasone suppression test
- Optimal management unknown, but recommend surgery in younger patients (<40 years) with perioperative glucocorticoids
- Some evidence that adrenal masses that are initially non-secretory develop cortisol hypersecretion up to 4 years later; as a result, repeat hormonal screening is recommended on a yearly basis for 4 years following diagnosis of an adrenal mass.

Clinically silent phaeochromocytoma

- Often present as incidental findings (58% of people in one study), otherwise most commonly present with hypertension

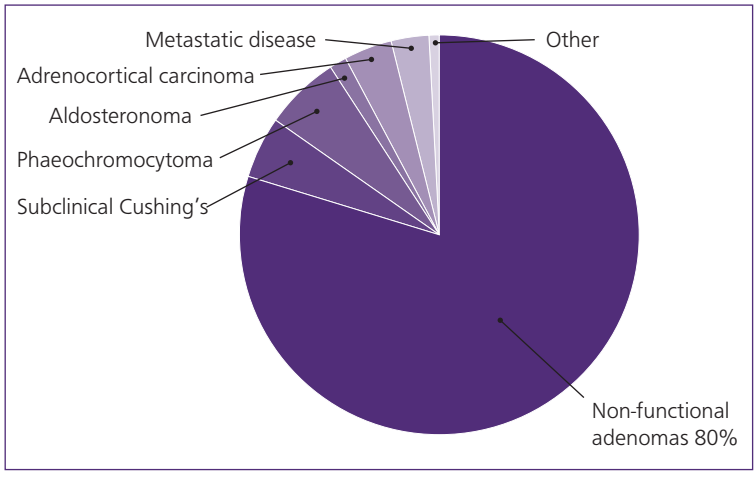

Figure 2. The vast majority of incidental adrenal masses in humans are ultimately non-functional adenomas.

Hyperaldosteronism

- Lower incidence but should be investigated in the presence of hypertension. Serum potassium concentration is not a helpful screening test, because of poor sensitivity and specificity.
- Diagnosed by plasma aldosterone to renin ratio.

Other hormonally active processes

- Sex hormone secretion results in clinical signs (hirsutism, virilisation), therefore screening with incidental masses is not recommended
- Congenital adrenal hyperplasia with adrenal hyperplasia is an uncommon cause of uni/bilateral adrenal masses. An adrenocorticotropic hormone (ACTH) stimulation test with measurement of precursors (17-hydroxyprogesterone) is not recommended unless there are signs of hyperandrogenism or bilateral adrenal masses.

Question 2: does the tumour have radiological features of malignancy?

Computed tomography scanning is the imaging modality of choice for assessing adrenal incidentaloma, although use of MRI and positron emission tomography (PET) scan have been described. Features described as compatible with malignancy include the attenuation on CT scan (greater than 10 Hounsfield units is most likely consistent with a malignant mass), size (greater than 4 cm is more likely to be malignant), and evidence of extracapsular or vascular invasion (Lee et al, 1991).

Question 3: does the patient have previous history of a malignant lesion?

Metastatic adrenal involvement is uncommonly identified at diagnosis of primary neoplasia (2.5%); however, some tumours are known to be predisposed to adrenal metastasis in the course of disease (lung, breast, kidney, stomach and lymphoma). Metastatic masses in the adrenal glands are typically heterogenous with irregular margins, and are present bilaterally in up to 15% of cases. Fine needle aspirate collection has been described in patients where a diagnosis of metastasis is unclear, although risks are recognised

(including haemorrhage, pneumothorax, abdominal pain, haematuria, pancreatitis) and evaluation for phaeochromocytoma before biopsy is advised, given the potentially fatal consequences of sampling these functional masses (Lee et al, 1991).

Approach in the dog

A very similar approach is recommended in the dog, and similarly the cat. Note that in the cat, functional adrenal masses are proportionately different in underlying cause to those in dogs, with hyperaldosteronism the most common cause, followed by hyperadrenocorticism.

Question 1: is the tumour functional?

Hyperadrenocorticism

As with people, the most common functional adrenal mass in the dog is adrenocortical in origin. Although patients may not have presented for evaluation for hyperadrenocorticism, further interrogation may support a clinical suspicion, particularly compatible history (polyuria/polydipsia (PU/PD), polyphagia, panting), clinical examination findings (pot-bellied appearance, hair coat changes, hypertension; see *Figure 3*), and laboratory findings (stress leucogram, thrombocytosis, increased alkaline phosphatase (ALKP), cholesterol, and proteinuria).

Urine creatinine cortisol ratio (UCCR) and the low-dose dexamethasone suppression test (LDDST) represent superior screening tests (tests to rule out hyperadrenocorticism when negative) to the ACTH stimulation test, given their improved sensitivity, but are less specific. All tests must be interpreted in light of clinical signs, given false positive results in the presence of non-adrenal illness (in particular diabetes mellitus) (Lee et al, 1998).

The treatment of choice for adrenal-dependent hyperadrenocorticism is adrenalectomy. This can be performed laparascopically or via coeliotomy. It is often advised (although not always) that patients should have 2–3 weeks of trilostane therapy before surgery, with an aim of post-treatment cortisol 55–170 nmol/litre. The major cause of mortality in dogs undergoing adrenalectomy with concurrent hyperadrenocorticism is thromboembolism, and Cushing's syndrome is a known risk factor for hypercoagulability syndrome; however, there is so far minimal evidence for resolution of the hypercoaguable state following trilostane therapy. Some clinicians recommend heparin or anti-platelet therapy before or after surgery; this is currently not employed at the author's institution, because of the challenges and controversies with titrating and monitoring effect of these drugs. In addition, surgically managed dogs require adrenal supplementation in the short- to mid-term follow-up period, because of contralateral adrenal gland suppression.

Medical management is an alterative treatment, and therapy with trilostane and mitotane have been described (median survival times 15.6 and 14 months respectively (Arenas et al, 2014)), although survival is reduced compared to dogs with pituitary-dependent disease, in particular in the presence of metastasis at the time of diagnosis (North and Banks, 2009; Behrend et al, 2013). Publications have not directly compared survival between surgical and medical management options; however, perioperative mortality is anticipated to be 6–19%, with a risk of recurrence of hyperadrenocorticism in the minority of dogs (Anderson et al, 2001; Lang et al, 2011).

Bottom line: in a dog with an adrenal mass consider the likelihood of hyperadrenocorticism by taking a thorough history, paying particular attention to water intake, appetite and exercise tolerance, followed by a thorough clinical examination including attention to muscle mass, haircoat, and blood pressure. If suspicious then a UCCR from a pooled sample (over 3 days) distant from any stress could be collected; if this is high the author would suggest a LDDST. If there is a clinical suspicion of hyperadrenocorticism the options of medical management versus surgery can then be discussed with the owner.

Phaeochromocytoma

Arising from the catecholamine-secreting chromaffin cells in the adrenal medulla, phaeochromocytomas are considered rare (0.1% of canine tumours). They have a high tendency to be malignant (50% display distant metastasis or vascular invasion at the time of diagnosis). Cases often present with vague clinical signs such as weakness, lethargy, and panting. The presence of PU/PD in some patients reflects a particularly challenging work-up and may result in overlooking phaeochromocytoma in favour of investigations directed at hyperadrenocorticism. Some patients may present with acute abdominal crisis because of spontaneous

Figure 3. Clinical suspicion of a functional adrenal mass must be considered in approach to these cases.

tumour rupture and retroperitoneal haemorrhage. Hypertension has been reported in around 50% of dogs presenting with phaeochromocytoma (Barthez et al, 1997).

There are no pathognomic findings on routine blood tests, although a mild anaemia, increase in ALKP and raised cholesterol are not uncommon. Studies have recently identified urine and plasma normetanephrine to be sensitive and specific for the diagnosis of phaeochromocytoma. There is an argument for collecting the urine from an at-home sample or sampling the blood promptly during hospitalisation (within 30 minutes); however sample requirements (urine needs to be acidified to pH 2 within 30 minutes and samples need to be immediately frozen and shipped on dry ice) mean this can be challenging; further studies concluded that results were satisfactory on samples from hospitalised animals (Kyles et al, 2003).

Surgery is the management of choice when distant metastasis is excluded and the presence of tumour thrombus does not preclude surgery. Pre-treatment with phenoxybenzamine was found to influence survival, so is recommended for 2 weeks in all patients. Medical management with phenoxybenzamine is an alternative, and titration of drug therapy every 2–3 days, from 0.25 mg/kg BID up to 1 mg/kg BID or until signs are controlled, is advised (Salesov et al, 2015).

Bottom line: in an adrenal mass in a dog, in particular if there is evidence of vascular invasion of the vena cava, consider the possibility of a phaeochromocytoma in patients with non-specific signs including excessive panting, perhaps PU/PD without the other hallmarks of hyperadrenocorticism, and in cases with intermittent hypertension and evidence of target organ damage (e.g. on retinal examination). Hormonal tests can screen for this, and trial therapy with phenoxybenzamine in a case with a high suspicion may help with the index of suspicion.

Hyperaldosteronism

Hyperaldosteronism is the most common functional tumour in cats, but is rare in the dog; screening for this is reserved for patients with compatible signs. It occurs most commonly as a result of adenoma or carcinoma, although bilateral hyperplasia has been reported. Unregulated aldosterone release results in excessive sodium retention and potassium depletion through its action on the kidney. Excessive sodium retention does not tend to result in significantly increased serum sodium levels, but does result in systemic hypertension. In contrast, hypokalaemia is often detected and results in the classic presentation of muscle weakness in affected patients.

Animals may also present with PU/PD (thought to be because of partial nephrogenic diabetes insipidus because of hypokalaemia or excessive mineralocorticoid). Laboratory findings include mildly increased sodium, hypokalaemia and metabolic alkalosis. A canine assay for renin (aldosterone:renin ratio (ARR) is gold standard) is currently available (Nationwide (Specialist) Laboratories). Surgery is the treatment of choice after medical stabilisation. Alternatively medical therapy can be continued; this consists of potassium supplementation, mineralocorticoid blockers (spironolactone) and anti-hypertensives (amlodipine/angiotensin converting enzyme inhibitor or angiotensin receptor blocker) (Herrera et al, 2008).

Bottom line: consider hyperaldosteronism in cases with hypertension and hypokalaemia. In dogs this is rare.

Question 2: are there features of malignancy?

Similar to in people, radiological findings in the dog are considered to guide suspicion of a malignant lesion. If the mass is more than 4 cm in size, or there is evidence of vascular or capsular invasion, a malignant lesion is deemed more likely and surgical intervention if appropriate is advised. Masses of <4cm but greater than 2 cm are more likely to be malignant than are masses <2 cm, and represent the 'grey zone' where some centres will recommend surgery. If the lesion is smaller with no evidence of invasion then monitoring is reasonable, with a view to intervention if dynamic change is identified. A paper identified a mean survival time (MST) of 29.8 months (range 1–96 months) in dogs with non-cortisol-secreting adrenal tumours that were not treated with surgery; larger size was found to be negatively associated with survival (Breitschwerdt et al, 1985).

Question 3: is there evidence of disseminated neoplasia?

Unlike in people, presence of adrenal involvement in neoplasia at the initial time of diagnosis is not uncommon in the dog and cat (21% and 14.8% respectively), therefore screening should be performed, in particular in the presence of bilateral adrenal masses or heterogenous mass-lesions (Barthez et al, 1998).

Bottom line: features of malignancy, including primary mass size, vascular invasion, and disseminated disease, can be assessed for during screening.

A final word on the cat

Imaging in cats is slightly different in that incidental adrenal gland mineralisation is common (33%) and therefore must not be over-interpreted. Cats also can develop enlarged adrenal glands in later life; the underlying cause is unknown but this is particularly well described in hyperthyroid patients. In contrast to dogs, hyperaldosteronism is the most common functional adrenal mass in the cat. Affected cats typically present with refractory hypokalaemia (resulting in muscle weakness) and hypertension (Schulman, 2010; Arenas et al, 2013). An ARR can be supportive of hyperaldosteronism; however, in cats with ARR results within the reference range, the literature suggests that a fludrocortisone suppression test may be valuable (Djajadiningrat-Laanen et al, 2013). Diagnosis of hyperaldosteronism (Conn's disease) in cats with bilateral adrenomegaly is complicated, as often older cats, in particular those with primary hypertension, can have bilateral adrenal gland hyperplasia (Barthez et al, 1998). Surgical management appeared to be associated with improved survival in a small case series, with extended survival for those that underwent curative surgery and survived the perioperative period (Ash et al, 2005). Hyperadrenocorticism and sex hormone tumours are worth considering in cats with relevant clinical signs (Boland and Barrs, 2017).

KEY POINTS

- When considering the significance of an adrenal mass the clinician should consider:
  - Could this be a functional mass?
  - Does the mass have features of malignancy?
  - Is there evidence of disseminated neoplasia?
- Hormonal screening tests in animals with adrenal masses should be interpreted in light of index of clinical suspicion.
- The low-dose dexamethasone suppression test is a superior screening test compared to the adrenocorticotropic hormone stimulation test.
- Phaeochromocytoma in dogs can cause vague signs; hypertension, sometimes intermittent, is often a feature.
- Hyperaldosteronism is the most common functional tumour in cats; surgical management appears to be associated with a superior outcome to medical therapy.

Bottom line: Hyperaldosteronism is the most common cause of a functional adrenal mass in cats; in cats presenting with hypokalaemia or hypertension this should be considered. Determining the ARR before starting spironolactone in these cases is useful.

Conclusions

With advances in abdominal imaging, in particular the use of CT scanning more commonly, there is likely to be an increased incidence of detection of adrenal masses. A logical approach to these lesions can be employed, and a decision to perform functional tests, recommend surgical excision, or suggest monitoring can be supported by evidence in humans, dogs and cats. CA

Conflict of interest: none to declare.

Note: Some of the medications described in this article are not licensed.

References

Anderson CR, Birchard SJ, Powers BE et al. Surgical treatment of adrenocortical tumors: 21 cases (1990-1996). J Am Anim Hosp Assoc. 2001;37(1):93–97. https://doi.org/10.5326/15473317-37-1-93

Arenas C, Pérez-Alenza D, Melián C. Clinical features, outcome and prognostic factors in dogs diagnosed with non-cortisol-secreting adrenal tumours without adrenalectomy: 20 cases (1994-2009). Vet Rec. 2013;173(20):501. https://doi.org/10.1136/vr.101691

Arenas C, Melián C, Pérez-Alenza MD. Long-term survival of dogs with adrenal-dependent hyperadrenocorticism: a comparison between mitotane and twice daily trilostane treatment. J Vet Intern Med. 2014;28(2):473–480. https://doi.org/10.1111/jvim.12303

Ash AR, Harvey AM, Tasker S. Primary hyperaldosteronism in the cat: a series of 13 cases. J Feline Med Surg. 2005;7(3):173–182. https://doi.org/10.1016/j.jfms.2004.08.007

Barthez PY, Marks SL, Woo J, Feldman EC, Matteucci M. Pheochromocytoma in dogs: 61 cases (1984–1995). J Vet Intern Med. 1997;11(5):272–278. https://doi.org/10.1111/j.1939-1676.1997.tb00464.x

Barthez PY, Nyland TG, Feldman EC. Ultrasonography of the adrenal glands in the dog, cat, and ferret. Vet Clin North Am Small Anim Pract. 1998;28(4):869–885. https://doi.org/10.1016/S0195-5616(98)50082-4

Behrend EN, Kooistra HS, Nelson R, Reusch CE, Scott-Moncrieff JC. Diagnosis of spontaneous canine hyperadrenocorticism: 2012 ACVIM consensus statement (small animal). J Vet Intern Med. 2013;27(6):1292–1304. https://doi.org/10.1111/jvim.12192

Boland LA, Barrs VR. Peculiarities of feline hyperadrenocorticism: update on diagnosis and treatment. J Feline Med Surg. 2017;19(9):933–947. https://doi.org/10.1177/1098612X17723245

Bouayad H, Feeney DA, Caywood DD, Hayden DW. Pheochromocytoma in dogs: 13 cases (1980-1985). J Am Vet Med Assoc. 1987;191(12):1610–1615

Breitschwerdt EB, Meuten DJ, Greenfield CL et al. Idiopathic hyperaldosteronism in a dog. J Am Vet Med Assoc. 1985;187(8):841–845

Djajadiningrat-Laanen SC, Galac S, Boevé MH et al. Evaluation of the oral fludrocortisone suppression test for diagnosing primary hyperaldosteronism in cats. J Vet Intern Med. 2013;27(6):1493–1499. https://doi.org/10.1111/jvim.12216

Francis IR, Gross MD, Shapiro B, Korobkin M, Quint LE. Integrated imaging of adrenal disease. Radiology. 1992;184(1):1–13. https://doi.org/10.1148/radiology.184.1.1609063

Gilson SD, Withrow SJ, Wheeler SL, Twedt DC. Pheochromocytoma in 50 dogs. J Vet Intern Med. 1994;8(3):228–232. https://doi.org/10.1111/j.1939-1676.1994.tb03222.x

Hedeland H, Ostberg G, Hokfelt B. On the prevalence of adrenocortical adenomas in an autopsy material in relation to hypertension and diabetes. Acta Med Scand. 1968;184(3):211–214. https://doi.org/10.1111/j.0954-6820.1968.tb02445.x

Herrera MA, Mehl ML, Kass PH et al. Predictive factors and the effect of phenoxybenzamine on outcome in dogs undergoing adrenalectomy for pheochromocytoma. J Vet Intern Med. 2008;22(6):1333–1339. https://doi.org/10.1111/j.1939-1676.2008.0182.x

Kyles AE, Feldman EC, De Cock HEV et al. Surgical management of adrenal gland tumors with and without associated tumor thrombi in dogs: 40 cases (1994-2001). J Am Vet Med Assoc. 2003;223(5):654–662. https://doi.org/10.2460/javma.2003.223.654

Lang JM, Schertel E, Kennedy S et al. Elective and emergency surgical management of adrenal gland tumors: 60 cases (1999-2006). J Am Anim Hosp Assoc. 2011;47(6):428–435. https://doi.org/10.5326/JAAHA-MS-5669

Lee MJ, Hahn PF, Papanicolaou N et al. Benign and malignant adrenal masses: CT distinction with attenuation coefficients, size, and observer analysis. Radiology. 1991;179(2):415–418. https://doi.org/10.1148/radiology.179.2.2014283

Lee JE, Evans DB, Hickey RC et al. Unknown primary cancer presenting as an adrenal mass: frequency and implications for diagnostic evaluation of adrenal incidentalomas. Surgery. 1998;124(6):1115–1122. https://doi.org/10.1067/msy.1998.92009

North SM, Banks TA. Tumours of the endocrine system. In: North SM, Banks TA (eds). Small Animal Oncology. Amsterdam: Elsevier; 2009:265–279

Salesov E, Boretti FS, Sieber-Ruckstuhl NS et al. Urinary and plasma catecholamines and metanephrines in dogs with pheochromocytoma, hypercortisolism, nonadrenal disease and in healthy dogs. J Vet Intern Med. 2015;29(2):597–602. https://doi.org/10.1111/jvim.12569

Schulman RL. Feline primary hyperaldosteronism. Vet Clin North Am Small Anim Pract. 2010;40(2):353–359. https://doi.org/10.1016/j.cvsm.2009.10.006

Soulsby SN, Holland M, Hudson JA, Behrend EN. Ultrasonographic evaluation of adrenal gland size compared to body weight in normal dogs. Vet Radiol Ultrasound. 2015;56(3):317–326. https://doi.org/10.1111/vru.12236

Young WF. The incidentally discovered adrenal mass. N Engl J Med. 2007;356(6):601–610. https://doi.org/10.1056/NEJMcp065470