Small

ADRENAL DISEASE IN CATS

Rachel Korman BVSC MANZCVS (Int Med) FANZCVS (Fel Med)
CVE Co-Tutor for Feline Medicine DE
luckykorman@gmail.com

C&T No. 5823

Adrenal disease is uncommon in cats and as usual, like all things cat, they do adrenal disease differently to dogs. As a clinician, if you are not aware of the clinical scenarios, you may miss some of these cases that can be rewarding (or sometimes plain terrifying) to treat.

The adrenal glands are located craniomedial to each kidney. The outer portion is the cortex, consisting of three functionally distinct layers:

- Zona glomerulosa (producing aldosterone)
- Zona fasiculata (producing glucocorticoids) and the
- Zona reticularis (producing sex hormones).

The central portion of the adrenal gland is the medulla, responsible for catecholamine synthesis namely adrenalin, noradrenaline and dopamine. Functional differences between layers are due to specific cell-surface receptors and there is cross over between layers. Aldosterone synthesis in the zona glomerulosa is triggered by angiotensin activity and hyperkalemia. Glucocorticoid production is driven by adrenocorticotrophic hormone (ACTH) from the anterior pituitary.

This article focuses primarily on adrenal dependent hyperadrenocorticism (HAC), hyperaldosteronism, other sex steroid secreting tumours and pheochromocytoma.

Hyperadrenocorticism

Hyperadrenocorticism occurs due to a functional tumour in the pituitary gland (pituitary dependent) or adrenal gland (adrenal dependant). Most cats (75-80%) have a pituitary tumour secreting ACTH. These are typically due to an adenoma rather than carcinoma. A smaller number of cats with HAC have a functional adrenal tumour (20-25%).

Adrenal tumours represent 0.2% of all feline tumours. Most cats with a functional adrenal tumour (FAT) have a benign adenoma of the cortex (65%), however malignant tumours are seen. Rarely, different tumours in each adrenal gland occur. In contrast to dogs, most cats with HAC tend to be female (78%), which is similar in humans. It occurs in middle-aged to older cats.

Common historical and physical examination findings include:

- Polyuria, polydipsia, polyphagia
- Pot-bellied appearance
- Weight gain or weight loss despite a good appetite
- Muscle wasting
- Hepatomegaly
- Abdominal enlargement
- Plantigrade stance and weakness
- Dermatological changes
  - > Unkempt hair coat
  - > Patchy alopecia
  - > Skin fragility and
  - > Secondary infections.

Skin fragility can be dramatic and severe—skin tearing can occur simply with jumping or grooming and can be very difficult to manage. Alopecia is typically bilateral and symmetrical and prominent subcutaneous vasculature can be seen.

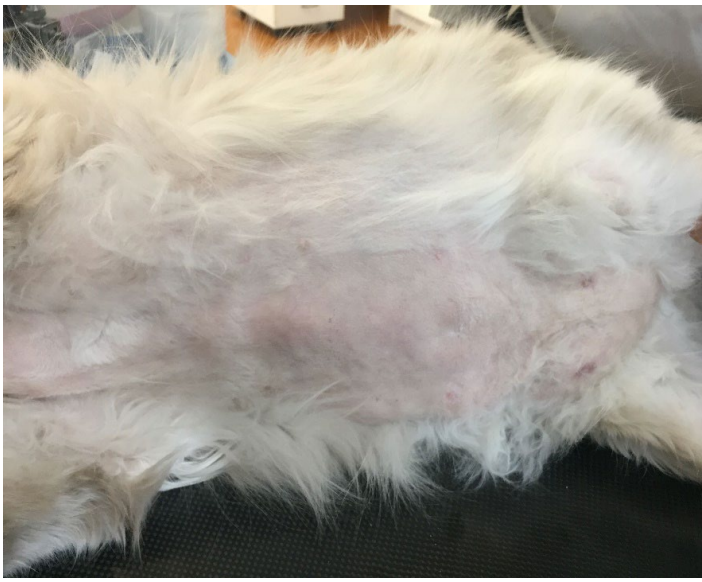

Figure 1. Cats with hyperadrenocorticism may show symmetrical alopecia and prominent subcutaneous vasculature

Clinical pathology changes are varied and non-specific. Glucocorticoids decrease insulin sensitivity and increase hepatic gluconeogenesis. Cats appear more sensitive to these effects than dogs and diabetes is common (80-90% of cats with HAC). Affected cats often have cortisol-induced insulin resistance and require high doses of insulin, although often not to the extent seen with acromegalic cats.

Hypercholesterolemia is common. Increases in ALKP as seen in dogs with HAC are less common

due to a lack of the steroid-induced isoenzyme and a shorter half-life of the enzyme in cats. Increases in ALKP occur in only 30% of cats compared with 90% of dogs and appear correlated with diabetic control.

Haematology findings variably include lymphopenia, eosinopenia and a neutrophilic leukocytosis. Urinalysis may reveal glucosuria. Despite obvious PUPD, many cats retain urine specific gravity > 1.020.

Pituitary-adrenal axis testing should always be interpreted together with patient history and clinical and laboratory findings. No single diagnostic test is perfect. If results are equivocal but clinical signs are strongly suggestive, then alternative testing methods should be considered, or repeated at a later stage. HAC is rare in cats and false positive results in cats without disease (or suggestive clinical signs) are common. The low dose dexamethasone suppression test (LDDST) remains the best screening test for HAC in cats due to its high sensitivity (false negative unlikely), however the dexamethasone dose required is different to dogs. When using the canine dose (0.01 mg/kg) many healthy cats fail to suppress cortisol production, so to increase test specificity, a 10x higher dexamethasone dose is used. Occasionally, cats with HAC can have a normal LDDST (i.e. suppression occurs). If clinical signs are highly suggestive of HAC, then alternative testing is considered.

Treatment considerations determine whether further testing to differentiate PDH from FAT is necessary. If a client is not likely to pursue surgical treatment (e.g. adrenalectomy in the case of FAT) or radiation treatment (e.g. for a pituitary mass), then differentiating whether disease is pituitary or adrenal based will not change treatment options (e.g. medical therapy with trilostane).

Treatment for HAC is determined by location (e.g. pituitary or adrenal), owner considerations (e.g. willingness for surgery, finances) and patient co-morbidities (e.g. skin fragility, diabetic stabilisation).

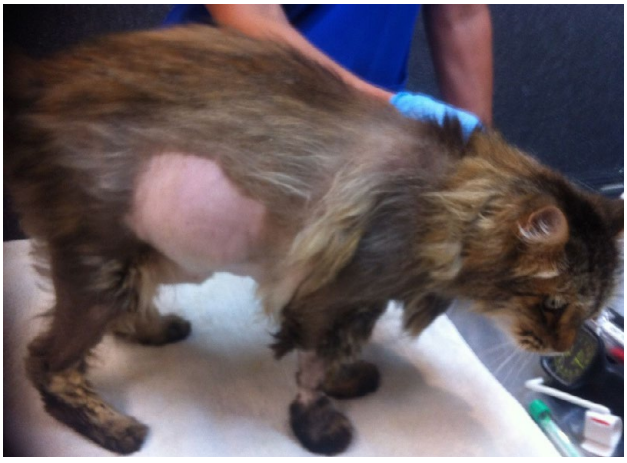

Figure 2. Cat with a functional adrenal tumour demonstrating a pot-bellied appearance and plantigrade stance

The preferred treatment for unilateral functional adrenal tumours is surgical adrenalectomy which may be curative. The size and side of the adrenal affected doesn't appear to affect outcome, although practically, the left adrenal has an easier surgical approach. Surgical time over 4 hours was a negative prognostic indicator. Clinical signs tend to resolve over 4-8 weeks. Significant complications can occur secondary to poor wound healing, immunocompromise and skin fragility. Approximately 50-70% of cats achieve survival times over 1 year. Development of HAC from the contralateral gland has been reported. Surgical management of pituitary dependent HAC can include bilateral adrenalectomy or transphenoidal hypophysectomy or radiation therapy.

Medical management for HAC can also be considered. Ketoconazole is not an effective or safe treatment for HAC in cats. Mitotane (an adrenocorticial cytotoxic agent targeting the ZF and ZR) is less effective than trilostane in cats. Monitoring is difficult as ACTH stimulation testing is less likely to change with treatment and clinical signs often progress. As cats demonstrate a sensitivity to chlorinated hydrocarbons, side effects are common.

Metyrapone is an adrenal steroid synthesis inhibitor, inhibiting the enzyme steroid 11-B-monooxygenase and may permit rapid correction of HAC. It may be useful for pre-surgical stabilization prior to adrenalectomy but is difficult to source.

Trilostane is a competitive inhibitor of 3 β-hydroxysteroid dehydrogenase, an enzyme essential for synthesis of cortisol and all other steroids. Trilostane treated cats often have improvement, but not resolution of clinical signs or diabetic control. Doses range between 10-30 mg/cat PO q 12-24 hours with a starting dose of 1-2 mg/kg/day. Optimal timing for assessment of ACTH stimulation post-pill is unknown but 2-4 hours seems reasonable. A post ACTH stimulation cortisol of between 50-150 mmol/l is suggested. Repeat blood sampling can be difficult in patients with skin fragility syndrome. If skin fragility syndrome is present it may be best to choose a conservative trilostane dosage and limited blood monitoring. A recent study assessing compounded trilostane found that 38% of tested products were not the prescribed strength.

Test	Protocol	Interpretation	Comments
Urine cortisol: creatinine ratio (UCCR)	2 morning, home caught urine samples, pooled	High – HAC possible Normal – HAC unlikely	Useful rule out test. If positive further investigation required. Low specificity means false positives are common. A high sensitivity means false negatives are rare. NOTE: early DM treatment increases UCCR
Low Dose Dexamethasone Suppression Test (LDDST)	0.1 mg/kg IV Cortisol measurement t =0, 4, 8 hrs	Failure of suppression - HAC possible	High sensitivity Low specificity
ACTH stimulation test	5 µg/kg or 125 ug/ cat tetracosactide or co-syntrophin (synthetic ACTH) IV Cortisol measurement t=0, 60 min	Post ACTH > upper end RI = HAC possible; lack of stimulation – sex hormone adrenal disease possible	Low sensitivity means false negatives are possible. 75% of cats with HAC will have a normal ACTH stimulation test. Moderate specificity means false positives are possible e.g. stress, non-adrenal illness

ACTH stim adrenocorticotrophic hormone stimulation test; DM diabetes mellitus; IV intravenous; LDDST low dose dexamethasone suppression test; RI reference interval; t time; UCCR urine cortisol:creatinine ratio.

Test	Protocol	Interpretation	Comments
LDDST	0.1 mg/kg IV Cortisol @ *t* =0, 4, 8 hrs	4hr cortisol < 40 nmol/l or 4 or 8 hr > 40nmol/l but < 50% of the baseline value PDH more likely	
HDDST	1 mg/kg dexamethasone IV Cortisol @ *t* = 0,4, 8 hrs	Suppression >50% suggests PDH Suppression >50% FAT unlikely	50% PDH do not suppress
UCCR with oral dexamethasone	2 morning home collected urine samples. Immediately after 2nd urine sample 0.1 mg/kg dexamethasone PO q 8 hrs (0800, 1600, 2000), 3rd urine sample on morning 3rd day	Suppression suggests PDH	75% PDH suppress 25% PDH do not suppress If less than 50% suppression, cannot differentiate
ACTH stim test	5 µg/kg or 125 µg/cat tetracosactide or co-syntrophin (synthetic ACTH) IV Cortisol measurement *t*=0, 60 min	Marked increase or high normal – PDH more likely Low or low normal – FAT more likely	
Endogenous ACTH	Assay available in Australia but not validated in cats. Samples submitted to Michigan frozen and difficulties with thaw in transit, but high results are still significant.	Increased all cats with PDH, decreased all cats with FAT	Healthy cats below limit of detection so cannot be used as screening Expensive
Radiography		Large adrenal mass maybe visible. Mineralisation common in healthy cats	Normal does not exclude
Ultrasound	Adrenal height in healthy cats generally < 0.5 cm Length 0.45-1.4 cm Sick cats with non-adrenal illness height < 0.5 cm (but up to 0.7 cm in one study) and length 0.7 cm to 1.9 cm)	Bilateral symmetrical enlargement suggests PDH. Unilateral adrenal mass & atrophy of contralateral gland suggests FAT. Presence of vascular invasion suggests carcinoma.	93% sensitivity for differentiation PDH from ADH Adrenomegaly also seen with hyperthyroidism, acromegaly, lymphoma and hyperaldosteronism. Bilateral tumours can occur.
CT scan		Assessment for pituitary or adrenal mass. Adrenal mass maybe visible but doesn't equate with functionality (ie production of hormones)	45% PDH have a normal CT or MRI

ACTH stim adrenocorticotrophic hormone stimulation test; CT contrast tomography;

IV intravenous; LDDST low dose dexamethasone suppression test; MRI magnetic reasonance imaging; PDH pituitary dependent hyperadrenocorticism; t time; UCCR urine cortisol:creatinine ratio.

Adverse effects of trilostane include anorexia, lethargy, weight loss, pancreatitis and hypoadrenocorticism. The median survival time in one study of 15 trilostane treated cats was 617 days (this included both PDH and FAT). The author has treated one cat with HAC, Ehrler Danos syndrome and severe skin fragility with trilostane alone for a number of years. Overall, the drug appears well tolerated.

Sex-steroid Producing Adrenocortical Tumours

Adrenal tumours may secrete hormones other than cortisol either in isolation or combined with other sex steroids and/or aldosterone. Progesterone is the more common hormone secreted. Progesterone is the precursor hormone for androgens, oestrogens, aldosterone and cortisol. Progesterone competes with cortisol for cortisol binding protein and with androgens and oestrogens for sex hormone binding proteins. Increased progesterone concentration leads to a high level of unbound cortisol and other sex hormones. Progesterone is also an insulin antagonist. Ultimately, clinical signs of HAC (e.g. PUPD, endocrine alopecia, skin fragility) and DM are most common.

In most cats with sex steroid producing tumours, results of the pituitary adrenal axis testing are normal to suppressed. Diagnosis relies on demonstration of increased concentrations of one or more adrenal sex steroids on an ACTH stimulation test. Unfortunately, other than progesterone assays, commercial access to other sex steroid hormone assays (e.g. 17-OH progesterone) in Australia is not available.

Overproduction of sex hormones can occur without glucocorticoid effects, resulting in signs of oestrus or male characteristics.

Primary Hyperaldosteronism

Aldosterone is the predominant mineralocorticoid secreted by the adrenal cortex. It regulates body sodium and potassium balance and maintains intravascular fluid volume and acid-base status. Primary hyperaldosteronism is the autonomous production of aldosterone due to a functional adrenal tumour. Secondary hyperaldosteronism occurs as a physiological response to renin-angiotensin-aldosterone system (RAAS) stimulation (e.g. an appropriate response to dehydration, hypotension, or reduced renal perfusion). Renin concentration should be reduced with primary hyperaldosteronism and increased with secondary hyperaldosteronism.

Primary hyperaldosteronism is the most common adrenal disease in middle aged to older cats. Most cats present with blindness caused by systemic hypertension or severe weakness (which may be episodic) due to hypokalemia (hypokalaemic polymyopathy). Lethargy, depression, neck ventroflexion, muscle pain, PUPD and stiffness are also identified.

Diagnosis is based on clinical signs, serum biochemistry (e.g. hypokalemia), plasma aldosterone concentration, adrenal imaging (presence of an adrenal tumour) and histopathology of adrenal tissue.

Most cats have elevated aldosterone concentrations, although occasional

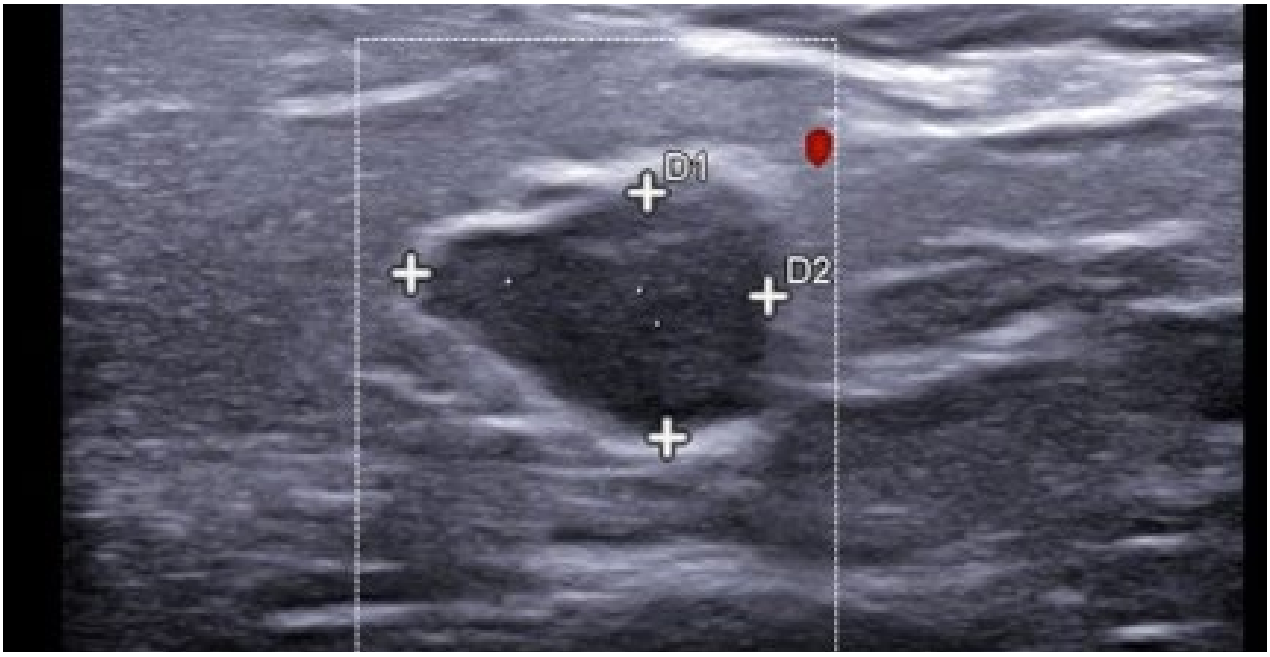

Figure 3. An ultrasound image showing an enlarged caudal pole of the left adrenal in a cat

patients may demonstrate inappropriate plasma aldosterone compared to potassium concentration. A hyperkalemic patient should have low aldosterone, so if aldosterone is at the top end of normal this would be inappropriate. Aldosterone concentration is difficult to interpret in patients with a renal azotemia (e.g. elevated creatinine and reduced urine specific gravity). This is where assessment of a plasma renin: aldosterone ratio would be ideal, however unfortunately plasma renin assays are not commercially available in Australia.

Frequently when treating patients with hyperaldosteronism, hypokalemia is refractory to supplementation. This should increase suspicion for the disease. Serum sodium concentrations are frequently normal or very mildly increased.

Functional adrenal tumours are unilateral adenomas in 50% of cats and the majority of remaining cats have unilateral adrenal carcinomas. Hyperaldosteronism may also be seen in cats without obvious adrenal tumours. One paper described hyperaldosteronism in 11 older cats with rapid onset hypokalemic paresis and blindness due to retinal detachment. Half of these cats were only mildly hypokalemic, however these patients presented with severe hypertension. Primary hyperaldosteronism was diagnosed on the basis of plasma aldosterone and plasma renin activity and ratio calculation. Imaging included ultrasound and CT and revealed no or only minor changes. Histopathology included nodular hyperplasia of the ZG, ZF and ZR and renal hyaline arteriolar sclerosis, glomerular sclerosis, tubular atrophy and interstitial fibrosis. Progressive renal disease (often remaining hypophosphatemic) occurred in many cats, likely secondary to incompletely suppressed renin activity.

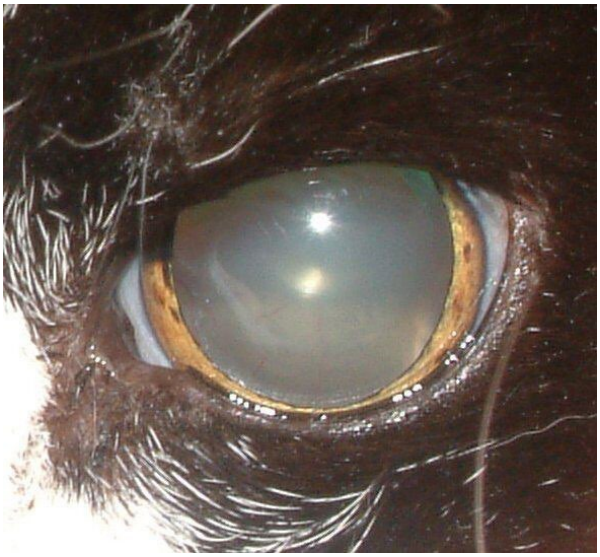

Figure 4. Cats with hyperaldosteronism can present with blindness associated with bullous retinal detachment and hyphaema

Management of hyperaldosteronism can be medical or surgical. Medical management utilises spironolactone as an aldosterone receptor antagonist. Side effects such as facial pruritis were identified in a cohort of Maine Coons receiving the medication for cardiac disease but has not been reported in other breeds. The author has treated a patient with hyperaldosteronism who developed severe facial pruritis two weeks after starting spironolactone. Clinical signs resolved on cessation of the medication. Amlodipine is used

Figure 5. Cats with hyperaldosteronism can present with marked weakness and ventroflexion due to hypokalemia

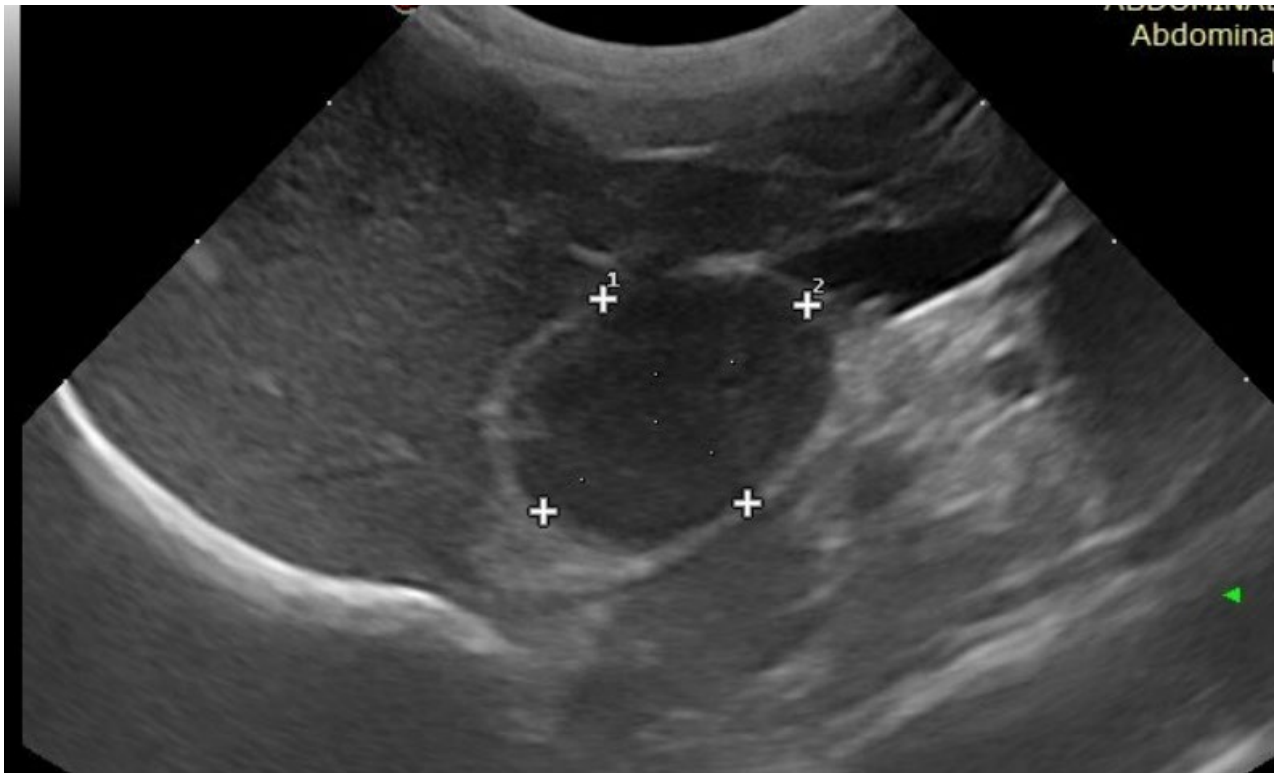

Figure 6. A large right adrenal tumour identified on ultrasound in a cat. The tumour was later confirmed as a pheochromocytoma

for hypertensive patients and substantial dosing maybe required. Potassium gluconate or potassium citrate is used to treat hypokalemia.

Survival times can be long with medical management alone. Two of three cats receiving medical management only (amlodipine, spironolactone and potassium gluconate) survived for 304 and 984 days. These cats were eventually euthanased because of chronic kidney failure. The third cat was euthanased after 50 days as it could not be medicated.

Surgical adrenalectomy is best performed by experienced surgeons. Stabilisation with medical therapy prior to adrenalectomy is recommended. Reported survival times are between 240-1803 days. Peri-operative haemorrhage is not uncommon and intensive care during the post-operative period is strongly recommended.

Catecholamine Secreting Adrenal Tumours

In dogs, pheochromocytomas cause episodic catecholamines secretion and evidence of systemic hypertension can be intermittent. Few cases are reported in the literature of catecholamine secreting adrenal tumours (pheochromocytomas) in cats, although one has recently been seen at the author's practice. This patient presented with severe neurological signs (obtundation, non-ambulatory tetraparesis) secondary to severe hypertension and suspected intracranial haemorrhage. The patient received treatment with amlodipine (for hypertension), atenolol (for a persistent tachycardia) and the neurological signs resolved over a 3 week period. Adrenal imaging revealed a unilateral adrenal mass. Although reference intervals are not reported for plasma normetanephrine in cats, the patient's plasma normetanephrine was significantly higher than levels in a single case report for a cat with a pheochromocytoma. Histopathology following adrenalectomy confirmed pheochromocytoma and the patient's normetanephrine levels reduced markedly following surgery. The patient survived for a further 10 months post-operatively.

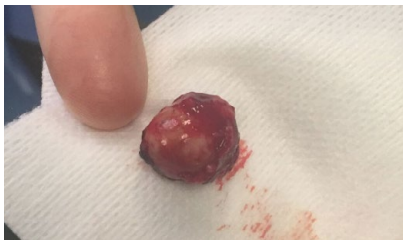

Figure 7. Adrenalectomy in cats is technically challenging and should be performed by experienced surgeons

References:

1. Clinical findings, diagnostics and outcome in 33 cats with adrenal neoplasia (2002-2013).
   Daniel G et al, *J Feline Med Surg.* 2016 Feb;18(2):77-84
2. Treatment of aldosterone-secreting adrenocortical tumors in cats by unilateral adrenalectomy: 10 cases (2002-2012).
   Lo AJ *et al, J Vet Intern Med.* 2014 Jan-Feb;28(1):137-43.
3. Ultrasonographic appearance of adrenal glands in healthy and sick cats.
   Combes A *et al, J Feline Med Surg.* 2013 Jun;15(6):445-57.
4. Primary hyperaldosteronism in the cat: a series of 13 cases.
   Ash RA *et al, J Feline Med Surg.* 2005 Jun;7(3):173-82.