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PHEOCHROMOCYTOMA IN DOGS AND CATS

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Pheochromocytomas are endocrine tumors of neuroectodermal origin that arise from chromaffin cells (pheochromocytes) of the sympathoadrenal system. These tumors are most often solitary and are located in or about the adrenal gland. Those tumors arising from chromaffin cells outside the adrenal gland are referred to as extraadrenal pheochromocytomas or paragangliomas. The majority of pheochromocytomas described in the veterinary literature have been adrenal in origin and have ranged in size from 0.4 to 15 cm and from 2.0 to 7.0 cm diameter in the dog and cat, respectfully. Some of these tumors, by way of their ability to produce and excrete the polypeptide hormones epinephrine, norepinephrine, and occasionally dopamine, are considered functional neoplasms. Others are nonfunctional but may be capable of producing clinical signs by virtue of their space-occupying nature. Even with the more recent appearance of reviews of canine pheochromocytomas,[3, 15, 27] this neoplasm is still considered rare in dogs and only two references describing the tumor in a total of five cats could be found.[9, 18] Although sporadic case reports involving paragangliomas in the dog and cat exist,[29, 30] their occurrence is still considered extremely rare.

Pheochromocytomas are a great diagnostic and therapeutic challenge to the veterinary clinician. Recent case reviews of pheochromocytomas in the dog revealed that anywhere from 27% to 85% of the diagnoses were made postmortem.[3, 11, 15] Similar reviews in the human literature report the incidence of postmortem diagnosis to range from

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34% to 75%.[5] Several reasons exist for the low rate of antemortem diagnosis. Most of the clinical signs produced by pheochromocytomas either result from the direct presence and space-occupying nature of the tumor or are secondary to the excretion of excessive amounts of catecholamines. The pattern of secretion of pheochromocytomas can be persistent but more often is paroxysmal and the pharmacologic effects of the catecholamines excreted can be numerous and variable in each individual animal patient. Thus, the variety of clinical signs coupled with the paroxysmal nature of the disease allows the clinical appearance to be easily confused with many more common disorders.

Pheochromocytomas are frequently reported in conjunction with other, often serious, concomitant disorders.[11] Many of these concomitant disorders have been the primary focus of the clinician and symptoms of an underlying pheochromocytoma have been either overlooked or ascribed to the more recognizable disorder. Many of these patients with an unsuspected pheochromocytoma were referred because they showed no response to symptomatic or specific therapy directed at these other disorders.[11]

Pheochromocytomas may also occur as part of the multiple endocrine neoplasia (MEN) syndrome. This syndrome refers to a group of familial syndromes in humans involving hyperplasia or neoplasia in two or more endocrine glands. Several different types of MEN have been described in people. A case of MEN has been described in a dog affected with medullary carcinoma of the thyroid gland, pheochromocytoma, and parathyroid hyperplasia similar to MEN type IIa of humans.[31]

PATHOPHYSIOLOGY

Chromaffin cells or pheochromocytes are capable of amine precursor uptake and decarboxylation (APUD); the pheochromocytoma is an example of an APUDoma. A basic understanding of the production, degradation, and pharmacologic effects of the polypeptide hormones produced by some pheochromocytomas will allow for a more meaningful understanding of the various historical and clinical signs, and serves as a background for introducing some of the diagnostic tests available to the clinician.

Production

The synthesis of epinephrine and norepinephrine begins with the hydroxylation of tyrosine by the enzyme tyrosine hydroxylase (Fig. 1). The product formed is dihydroxyphenylalanine (DOPA), which is further enzymatically converted to dihydroxyphenylethylalanine (dopamine). Dopamine is then transported into the intracellular vesicles or granules of the chromaffin cell and is converted to norepinephrine by the enzyme dopamine β-hydroxylase. In adrenal medullary cells, norepinephrine can undergo methylation and be converted into epinephrine. This same biosynthetic pathway is shared both by normal and neoplastic adrenal medullary cells.

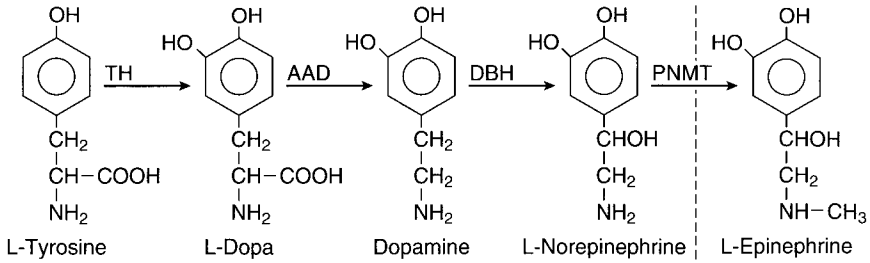

Figure 1. Catecholamine biosynthetic pathway. The formation of norepinephrine occurs through a series of enzymatic transformations of tyrosine precursors. The production of epinephrine occurs in the adrenal medulla and in neurons of the central nervous system and peripheral ganglia, which utilize epinephrine as a neurotransmitter. TH, Tyrosine hydroxylase (rate-limiting enzyme); AAD, aromatic–L-amino acid decarboxylase; DBH, dopamine beta-hydroxylase; PNMT, phenylethanolamine–N–methyltransferase. (*From* Landsberg L, Young JB: Catecholamines and the adrenal medulla. *In* Bondy PK, Rosenberg LE (eds): Metabolic Control and Disease, ed 8. Philadelphia, WB Saunders, 1980, pp 1621–1693.)

In the normal adrenal cell, a rising level of cytoplasmic norepinephrine can suppress its own production through negative feedback on the rate-limiting enzyme tyrosine hydroxylase. This normal feedback inhibition may uncouple in the pheochromocytoma patient. Several explanations exist for this uncoupling. Some evidence suggests that some of these tumors possess an above-normal rate in the activity of tyrosine hydroxylase, which in turn is associated with an increased rate of catecholamine biosynthesis.[19] Alternatively, the tumor may degrade and metabolize norepinephrine at a rate fast enough to prevent its accumulation and subsequent feedback inhibition.[21]

Secretion

The normal adrenal gland in humans and dogs secretes predominantly epinephrine.[11, 21] Epinephrine constitutes 80% to 85% of catecholamine production by the normal adrenal in humans and dogs, whereas norepinephrine is the primary secretory product in cats.[11] Most pheochromocytomas in human patients excrete predominantly norepinephrine or a mixture of norepinephrine and epinephrine. Rarely, these tumors will excrete epinephrine exclusively. Dopamine excretion has also been described in association with malignant pheochromocytomas in humans.[21] Unfortunately, similar excretion patterns for epinephrine, norepinephrine, and dopamine have not been elucidated for tumors occurring in dogs or cats.

Some pheochromocytomas in humans contain and excrete other

peptides including somatostatin,[45] calcitonin,[26] vasoactive intestinal peptide,[41] corticotropin-releasing hormone,[33] growth hormone–releasing hormone,[33] adrenocorticotropic hormone (ACTH),[35] α–melanocyte-stimulating hormone,[16] parathyroid-like hormone,[12] atrial natriuretic peptide,[40] and opioid peptides.[45] Although pituitary-dependent hyperadrenocorticism was diagnosed in 66% of cases reported recently in a study identifying pheochromocytoma in association with hyperadrenocorticism in a small number of dogs,[42] the question of whether pheochromocytomas have the ability to produce ACTH or other hormones in the dog or cat has yet to be answered and requires further study.

The underlying mechanisms responsible for catecholamine release from pheochromocytomas are not well understood. Pheochromocytomas are distinguished from the normal adrenal gland by their lack of innervation. Catecholamine excretion is not mediated by neural impulses and is thought to occur mainly by diffusion in contrast to the exocytosis of storage granules in the normal adrenal gland.[7] Why some pheochromocytomas secrete in a constant manner and others paroxysmally is unclear. Pheochromocytomas are also capable of secreting in response to certain drugs and chemicals, changes in tumor blood flow, and direct physical pressure.[21]

Action

The clinical signs experienced by animal patients with pheochromocytomas largely result from the physiologic effects of catecholamines on their receptors (Tables 1 and 2). Catecholamine receptors exist in two main categories, α and β, and these are subdivided into α-1, α-2, and β-1, β-2. These various subtypes of receptors differ in their response to the catecholamines epinephrine and norepinephrine. The α-1, α-2, and β-1 receptors respond equally to epinephrine and norepinephrine, whereas the β-2 receptors are found to respond more favorably to epinephrine.

Hypertension, either sustained or paroxysmal, is responsible for many of the clinical signs in humans with pheochromocytoma. This hypertension is primarily due to an increase in peripheral vascular resistance resulting from stimulation of α-1 receptors causing vasoconstriction. Catecholamine activation of β-1 receptors can result in a significant tachyarrhythmia detectable on auscultation of affected patients. Pheochromocytomas again can differ in the quantity and type of catecholamine excreted. Although some or many of the clinical signs can be explained based on the effects of catecholamines on receptors, predicting the precise pattern of secretion based on clinical features alone is still very difficult.[21]

Prolonged stimulation of catecholamine receptors can lead to a progressive diminution in response by the tissue to subsequent stimulation. This progressive diminution in response has been referred to as desensitization or tachyphylaxis. Desensitization resulting from a decrease in catecholamine receptor number is referred to as down-regulation. Down-regulation has been demonstrated for both α-1 and β-1 receptors in rats harboring pheochromocytomas.[34, 38] Desensitization without any detectable alteration in receptor number has been demonstrated for α-2 and β-2 receptors in the same subjects, suggesting postreceptor mechanisms may be responsible for the observed tachyphylaxis.[34, 37, 38] Desensitization or down-regulation of catecholamine receptors has yet to be documented in the canine or feline patient with a pheochromocytoma.

Table 1. PHARMACOLOGIC EFFECTS OF CATECHOLAMINES ON RECEPTOR ORGANS

Receptor Organ	Receptor Type	Response
Heart		
Sinoatrial node	Beta-1	Increased heart rate
Atrial	Beta-1	Increased contractility, conduction velocity
Atrioventricular node and conduction system	Beta-1	Increased conduction velocity
Ventricles	Beta-1	Increased contractility, conduction velocity
Arterioles		
Coronary, renal, skeletal muscle, abdominal viscera	Alpha-1, Beta-2	Constriction, Dilation
Skin and mucosa, cerebral, pulmonary, salivary glands	Alpha-1	Constriction
Systemic veins	Alpha-1	Constriction
Bronchial smooth muscle	Beta-2	Relaxation
Urinary bladder		
Detrusor muscle	Beta-2	Relaxation
Trigone and sphincter	Alpha	Contraction
Stomach		
Motility	Alpha, Beta-2	Decreased motility
Sphincters	Alpha	Contraction
Intestine		
Motility	Alpha, Beta-2	Decreased motility
Sphincters	Alpha	Contraction
Liver	Alpha, Beta-2	Glycogenolysis
Pancreatic acini	Alpha	Decreased secretion
Eye		
Radial muscle of iris	Alpha-1	Contraction (mydriasis)
Adipose tissue	Beta-2	Lipolysis

Adapted from Feldman EC, Nelson RW: Canine and Feline Endocrinology and Reproduction, ed 2. Philadelphia, PA, WB Saunders, 1996, p 308.

Degradation

The physiologic effects of catecholamines are terminated by a commonly shared catabolic enzyme system that is present in both neuronal and extraneuronal tissues. Catecholamines are converted by the enzyme

Table 2. PHARMACOLOGIC EFFECTS OF CATECHOLAMINES ON HORMONE SECRETION

Endocrine Organ	Hormone	Secretory Effect	Receptor
Thyroid			
Follicles	T_4, T_3	Increased	Beta
C cells	Calcitonin	Increased	Beta
Parathyroid	Parathyroid hormone	Increased	Beta
Pancreatic islets			
Alpha cells	Glucagon	Increased	Beta
Beta cells	Insulin	Decreased	Alpha
Delta cells	Somatostatin	Increased	Beta
Gastric antrum	Gastrin	Increased	Beta
Adrenal cortex	Aldosterone	Decreased	?DA
Ovary	Progesterone	Increased	Beta
Testis	Testosterone	Increased	Beta
Pineal	Melatonin	Increased	Beta
Kidney			
Juxtaglomerular apparatus	Renin	Increased	Beta
Unknown	Erythropoietin	Increased	Beta

Adapted from Landsberg L, Young JB: *In* Wilson JD, Foster DW (eds): Textbook of Endocrinology, ed 8. Philadelphia, PA, WB Saunders, 1992, p 655.

monoamine oxidase (MAO) and/or by catechol-O-methyltransferase (COMT) into their metabolites, which include metanephrine, normetanephrine, vanillylmandelic acid (VMA), and 3,4 dihydroxymandelic acid (Fig. 2). Whereas COMT is primarily extraneuronal with some of the enzyme present intraneuronally, MAO is present in both locations.[21]

Neuronal inactivation of locally released catecholamines occurs after catecholamine reuptake by the axonal membrane and is particularly important at postganglionic sympathetic nerve endings. Extraneuronal uptake plays a larger role in the uptake and conversion of circulating catecholamines and occurs in a wide variety of cells in several organs, particularly the liver and kidney. The mechanisms involved in extraneuronal uptake and the exact relation between uptake and metabolism are not well understood. The kidney metabolizes circulating catecholamines with COMT and MAO and can excrete all metabolites in addition to a small percentage of unchanged amines in the urine, where these metabolites and amines are capable of being measured to help aid in the diagnosis of a pheochromocytoma. The liver also contains COMT and MAO and is capable of conjugating catecholamines and catecholamine metabolites with sulfate or glucuronide and excreting them in bile, but the quantitative significance of this route is unknown.[21]

ANAMNESIS AND CLINICAL SIGNS

Most of the clinical signs produced by pheochromocytomas either result from the direct presence and space-occupying nature of the tumor

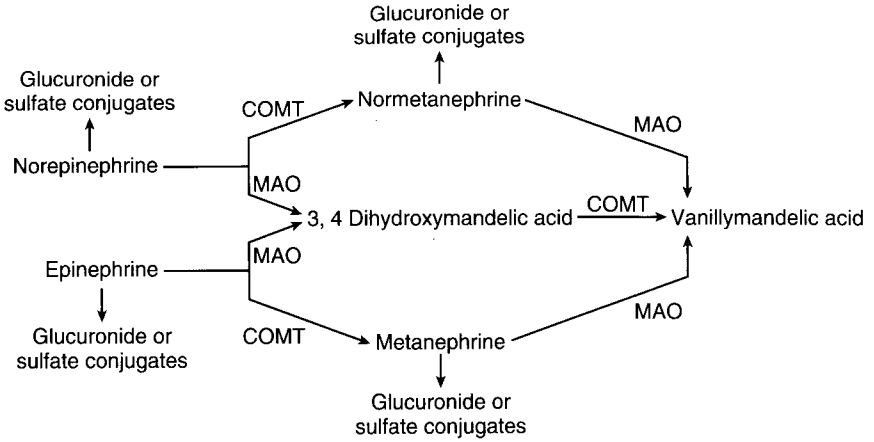

Figure 2. Catabolic pathways for catecholamines. Unchanged catecholamines and their metabolites are excreted primarily in the urine. Hepatic conjugation may also contribute, though to a lesser extent. MAO, monoamine oxidase; COMT, catechol–o–methyl transferase. (*From* Levine RJ, Landsberg L: *In* Bondy PK, Rosenberg LE (eds): Duncan's Diseases of Metabolism, ed 7. Philadelphia, WB Saunders, 1974, p 1196.)

or are secondary to the excretion of excessive amounts of catecholamines. The duration of clinical signs can range from days to years before presentation.[44] The clinical signs, arranged by frequency of occurrence reported in dogs with pheochromocytomas and compiled from a number of retrospective studies, are listed.[3, 9, 11, 15, 27, 39, 44]

Weakness	Hind limb edema
Collapse	Abdominal distension
Anorexia	Acute blindness
Lethargy	Epistaxis
Vomiting	Restlessness
Polypnea	Anxiety
Cough	Pacing
Dyspnea	Ataxia
Polyuria	Seizures
Polydipsia	Tremors/shaking
Diarrhea	Cyanosis
Weight Loss	Adipsia

Although the number of documented feline cases of pheochromocytoma are few, polyuria, polydipsia, lethargy, and anorexia are the clinical signs reported most frequently in this species. Other reported clinical signs in cats include seizures and intermittent vomiting.[9, 18] Because many of the clinical signs of pheochromocytomas are intermittent and can mimic or be obscured by symptoms of other coexisting disorders, the diagnosis of a pheochromocytoma requires a high degree of clinical alertness.

The paroxysm or crisis is the classic manifestation of the pheochromocytoma. It is the physiologic consequence of catecholamine release from the tumor and the subsequent stimulation of adrenergic receptors. Severe headache and palpitations (with or without tachycardia) along with excessive and inappropriate perspiration are commonly observed symptoms characterizing this paroxysm in humans. Episodes or paroxysms are often separated by symptom-free intervals. The frequency and length of the paroxysm is not well documented in veterinary patients; in humans, paroxysms can occur from several times a month to several times a day and can last from 1 minute to several hours, but usually last less than 1 hour.[6] Many of the clinical signs expressed in the paroxysm are the result of systemic hypertension produced by the catecholamines. In some veterinary patients, the paroxysm can be severe enough to cause acute fulminating clinical signs that are rapidly progressive and potentially fatal. These clinical signs can include acute collapse, cardiovascular shock, pulmonary edema, ventricular fibrillation, cyanosis, epistaxis, cerebral hemorrhage, and seizures.[39]

A correlation between tumor size and clinical manifestations in the dog has been suggested by one case review.[3] In this study, small noninvasive tumors confined to the adrenal medulla or slightly larger tumors produced minimal signs and were all diagnosed incidentally on necropsy. This is in contrast to the experience with humans, wherein small tumors are frequently found to liberate large amounts of physiologically active catecholamines into the circulation, cause clinical manifestations, and allow diagnosis at an early stage.[21] Large pheochromocytomas in people sequester catecholamines with relatively little physiologic catecholamine secretion. Significant amounts of catecholamine are stored and metabolized within the larger tumor to VMA, metanephrine, and normetanephrine.[7] Most of these tumors are therefore capable of reaching a larger size before becoming clinically evident. Because many of the clinical signs listed are very subtle, often vague, and easily overlooked by most pet owners, many of our veterinary patients with small pheochromocytomas probably remain undiagnosed, allowing their tumors to attain a larger size prior to detection.

PHYSICAL EXAMINATION

Unfortunately, as with clinical signs, no findings on the physical examination are specific for the diagnosis of a pheochromocytoma. At the time of diagnosis, most of the affected dogs are older, with a mean age of 10.5 years (range 1 to 26 years).[3, 11, 15, 27] No breed or sex predilection has been reported. The findings on physical examination again reflect either the local invasiveness of the tumor or its ability to excrete excessive catecholamines. Because the secretion of catecholamines and the subsequent hypertension produced can be episodic, the findings described may or may not be present at the time of physical examination.

Findings attributable to excessive catecholamine release can include

abnormal lung sounds. Increased bronchovesicular or alveolar sounds can occur as a result of pulmonary hypertension, causing congestion and edema. Many of these animals will also be tachypneic on auscultation. Pulmonary edema can also be cardiogenic in origin. Cardiac auscultation may reveal a tachycardia, arrhythmia, or systolic murmur.[11, 15]

Other physical findings related to catecholamine excess include pyrexia and hyperemic mucous membranes. Ophthalmologic findings may include mydriasis, retinal hemorrhages, and retinal detachment with associated blindness in patients with severe hypertension. Several nonspecific neurologic findings have also been reported, including head tilt, nystagmus, strabismus, and seizures. Focal neurologic deficits have also been reported and are probably the result of cerebrovascular hemorrhage.[39, 44]

Physical examination findings can also reflect the space-occupying nature of the tumor. A palpable abdominal mass was reported in 25% of the cases in one review.[44] In contrast to what is reported in the human literature, a large number of dogs with pheochromocytoma have local invasion of the tumor into surrounding structures, particularly the posterior vena cava. The incidence of local invasion into the vena cava with tumor thrombus formation ranges from 15% to 38%.[3, 11, 15] Obstruction of the posterior vena cava may cause venous distention posterior to the obstruction resulting in ascites, peripheral edema of the hind limbs, and gross distention of the caudal superficial epigastric veins located over the ventral abdominal wall. In some cases, local invasion of the tumor has resulted in a disruption of vascular integrity leading to acute abdominal hemorrhage manifested by abdominal pain and pale mucous membranes.

DIAGNOSIS

Diagnosis of pheochromocytoma requires substantial knowledge of the clinical syndrome and a high index of suspicion in the individual patient. The challenge of diagnosis stems from the ambiguity of clinical signs, the lack of specificity in routine diagnostic tests, the presence of other conditions obscuring the diagnosis, and, possibly, the secretion of biologically active hormones other than catecholamines.[4, 13] The situation is further complicated by the lack of established hormonal testing in the dog and cat and limitations in imaging techniques.

Routine Laboratory Evaluation

Results of routine laboratory work including complete blood count, biochemical profile, and urinalysis are rarely helpful in establishing a diagnosis.[11, 15, 22, 39] The hemogram is normal in many dogs. In some dogs, anemia may occur as a result of chronic disease or hemorrhage from the tumor.[11, 15, 22, 39] Conversely, hemoconcentration may be evident in some

patients. Thrombocytosis may occur with chronically bleeding tumors.[15] Catecholamine release results in decreased neutrophil margination and may cause a neutrophilic leukocytosis.[22] Leukocytosis may also occur in association with necrosis and inflammation of the tumor.

Liver enzyme elevations may be present on the biochemical profile but do not correlate with the presence of hepatic metastases.[11, 15] Hypercholesterolemia has been recognized in dogs with pheochromocytoma and may occur due to catecholamine-induced lipolysis with subsequent conversion of free fatty acids to cholesterol in the liver or may be associated with concurrent diseases such as hyperadrenocorticism.[11, 15] Urinalysis may show proteinuria resulting from hypertensive glomerulopathy.

A small number of dogs with pituitary-dependent hyperadrenocorticism may have pheochromocytomas.[42] Signs and laboratory work consistent with hyperadrenocorticism may lead to the impression that an adrenal mass is of adrenal cortical origin. This may confuse the diagnosis. The origin of the adrenal mass must be recognized, because anesthetic and therapeutic considerations are quite different.

Glucose intolerance occurs in some people with this disease. The mechanism for glucose intolerance is probably the suppression of insulin release (α-adrenergic stimulation) combined with hepatic gluconeogenesis and glycogenolysis (β-adrenergic stimulation). Dogs with diabetes and concurrent pheochromocytoma have been recognized.[11] The role of the tumor in regulation of diabetes in these dogs is not known. In humans, elevation of blood lactate in the absence of lactic acidosis is frequently recognized.[4]

Blood Pressure and Cardiac Evaluation

Hypertension may occur intermittently or continuously in association with pheochromocytoma. About 90% of humans with pheochromocytoma have hypertension but in many (approximately 50%) it occurs episodically.[4, 13, 25] Indirect blood pressure measurements may be helpful in identifying dogs and cats with pheochromocytomas. The prevalence of hypertension in canine patients with pheochromocytomas (systolic blood pressure > 160 mm Hg; diastolic blood pressure > 100 mm Hg) differs greatly (25% to 86%) in various reports.[13, 15, 39] This discrepancy between reports probably stems from the episodic nature of hypertension and infrequent blood pressure measurement. Dogs that have indirect blood pressure evaluations usually have some clinical indication for the procedure, whereas blood pressure determination is routine in humans. Repeated blood pressure evaluations may be necessary to document hypertension in some patients.

Echocardiography may reveal left ventricular hypertrophy consistent with systemic hypertension.[15] Electrocardiographic changes may include sinus tachycardia, arrythmias, and evidence of cardiac chamber enlargement.[11, 39]

Imaging

Radiographs of the abdomen reveal a mass in the perirenal area in 30% to 56% of cases.[11, 15] Approximately 10% of pheochromocytomas may show evidence of mineralization radiographically, as will adrenal cortical tumors.[11, 22] Abdominal detail is occasionally decreased due to the presence of fluid (hemorrhage or ascites).[11, 15, 22] Abnormal hepatic contours, hepatomegaly, and displacement of the kidneys may also occur.[11, 15, 34] Thoracic radiographs may reveal changes secondary to hypertension, including cardiac enlargement and pulmonary congestion or edema.[11, 15] Metastases have been recognized in the lungs radiographically in approximately 11% of dogs with pheochromocytoma.[15]

Contrast radiography may have a role in determining the extent of invasion of pheochromocytomas. Excretory urography may help to establish whether invasion of the adjacent kidney exists. Nonselective venography may be used to assess the integrity of the caudal vena cava (Fig. 3).

An adrenal mass can be identified with ultrasonography in 65% to 83% of cases[11, 15] (Fig. 4). Furthermore, ultrasonography may be helpful in clinical staging. Identification of invasion of the kidney or vena cava and identification of intraabdominal metastases have been reported.[11] Normal ultrasonography does not rule out the presence of a pheochromocytoma or the absence of invasion and metastasis, however.[11, 15]

Computed tomography (CT) is considered the best technique for localizing a pheochromocytoma in people, with a sensitivity and specificity of 85% to 98% and 70%, respectively.[20] Tumors as small as 0.5 to 1

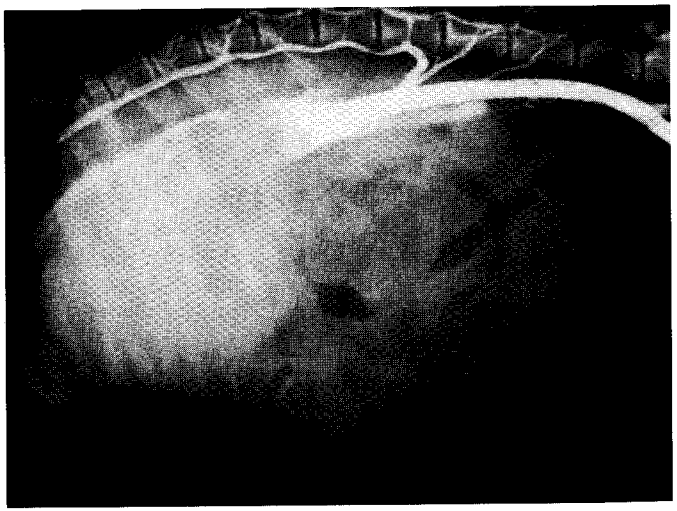

Figure 3. Nonselective venogram in a dog with a pheochromocytoma. There is evidence of obstruction of the caudal vena cava secondary to invasion or thrombosis. Collateral circulation is evident.

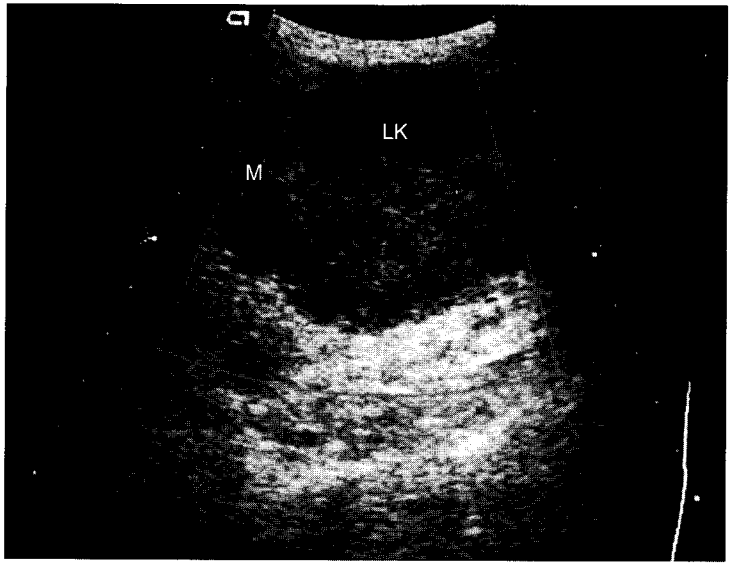

Figure 4. Ultrasonographic image of a canine pheochromocytoma. A mass (M) cranial to the left kidney (LK) was demonstrable in this study.

cm in diameter may be identified with CT.[4, 13, 20, 25] Additionally, the presence of metastasis and invasion may be assessed. This technique may also be used in dogs (Fig. 5). Routine use of CT in the dog and cat is hindered by the requirement for anesthesia, limited availability, and expense. Therefore, ultrasonography is preferred by many veterinary clinicians. Magnetic resonance imaging (MRI) may be helpful in localizing tumors and determining the extent of disease.[4, 13, 20, 25] Magnetic resonance imaging may have an advantage over CT in ability to further characterize tissue and distinguish histologic types of adrenal tumors[4, 20] (see also the article by Dr. Myers elsewhere in this issue).

Nuclear scintigraphy with[123] Iodine metaiodobenzylguanidine (I-MIBG) is a useful technique for localizing pheochromocytomas in humans.[4, 13, 20, 25] Localization of I-MIBG in neoplastic chromaffin tissue results from its similarity in structure to epinephrine. In contrast, the amount of uptake in normal chromaffin cells often is insufficient for visualization.[13] This method is commonly used in clinical staging of people and may be used therapeutically in patients with metastatic disease.[23, 25] I-MIBG scintigraphy has been performed for the diagnosis of a pheochromocytoma in a dog.[2] Unfortunately, lack of availability, expense, and time required to prepare the I-MIBG preclude the routine use of this technique in the veterinary patient.[2] Scintigraphy using somatostatin (octreotide) compares favorably to I-MIBG for localization and staging of pheochromocytomas in people. This technique may have application in veterinary medicine as well[36] (see also, the article by Myers).

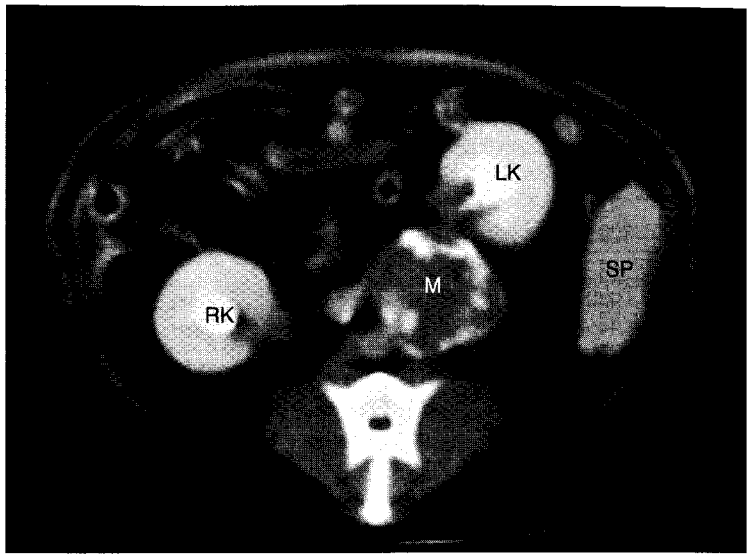

Figure 5. CT of the abdomen of a dog with pheochromocytoma. A mass is visible medial to the left kidney. LK = left kidney; RK = right kidney; SP = spleen; M = mass (pheochromocytoma).

Detection of Excessive Catecholamines

Specific diagnostic techniques for pheochromocytoma are aimed at identifying elevated circulating catecholamines or urinary metabolites of catecholamines. These techniques have been infrequently used in the canine and feline patient because of limited availability, lack of reference ranges, expense, and the inconvenience of 24-hour urine collection. These methods may be useful in patients in whom a tumor is not identified with imaging techniques, but in whom a pheochromocytoma is strongly suspected.

Identification of Urine Metabolites

Rationale. Circulating catecholamines are metabolized by renal and hepatic enzymes (COMT and MAO) (see Fig. 2). Unchanged catecholamines and metabolites (metanephrine, VMA, and normetanephrine) are excreted in the urine in quantities proportional to production.

Method. Twenty-four hour urine collection is performed with the patient at rest. Urine is immediately acidified with hydrochloric acid (pH < 3) and refrigerated.[11, 20] The laboratory performing the assay should be contacted for instructions on sample handling. Spot urine samples may be used with catecholamine values expressed in μg/mL creatinine.[11, 20]

Interpretation. No reference ranges exist for dogs or cats and these assays have been infrequently performed. In humans, normal total

urinary catecholamines are less than 100 to 150 μg/day.[11, 20] In patients with pheochromocytoma, values exceed 250 μg/day.[8] Normal human VMA and metanephrine values are less than 6.5 mg/day and less than 1.3 mg/day, respectively.[20]

False Positives. Exercise, excitement, foods containing vanilla, radiographic contrast agents, and potentially other medications may result in abnormally elevated urine catecholamine levels.[4, 11, 20]

False Negatives. Improper sample handling and intermittent secretion of catecholamines by the tumor may result in false-negative values. Additionally, the specific catecholamine secreted by a tumor and the metabolites produced in an individual patient may vary. Therefore, sensitivity of these tests are increased when multiple catecholamines or metabolites are measured. Finally, impaired renal function may decrease catecholamine excretion, resulting in lower values.[11, 20]

Identification of Serum Catecholamines

Rationale. Plasma catecholamine (norepinephrine, epinephrine, dopamine) levels may be continuously or intermittently elevated in patients with pheochromocytoma.

Method. Plasma is collected from a heparinized blood sample. The plasma should be separated and transported immediately to the lab on ice or frozen within 1 hour.[20] The laboratory performing the assay should be contacted for specific instructions on sample handling.

Interpretation. These assays are not recommended as the sole means of diagnosis due to wide variability in serum levels of catecholamines. No reference ranges exist for dogs and these assays have been infrequently performed. In normal humans, plasma catecholamines measure less than 500 pg/mL for norepinephrine and less than 100 pg/mL for epinephrine.[20] Plasma levels greater than 1500 pg/mL for norepinephrine and 300 pg/mL for epinephrine are consistent with a pheochromocytoma.[20]

False Positives. Stress and excitement elevate levels.[20]

False Negatives. Tumors may secrete intermittently. The type of catecholamine secreted by the tumor may vary.[11, 20]

Clonidine Suppression Test

Rationale. Clonidine is an α_2-agonist drug. Administration of clonidine should decrease neurologically mediated release of catecholamines. Because pheochromocytomas secrete catecholamines independent of neurogenic input, levels of catecholamines in the blood stream are not decreased with clonidine administration.[20]

Method. In humans, blood pressure and serum catecholamine levels are measured before and 3 hours after administration of clonidine per os at 0.3 mg per 70 kg of body weight.[20]

Interpretation. Catecholamine levels drop below 500 pg/mL or decrease by 50% in normal patients and do not fall in patients with pheochromocytoma.[20] Blood pressure usually falls in both groups of patients. This test is generally best performed in patients with high serum catecholamine levels, as the results are influenced by the magnitude of serum catecholamine levels. Fluctuation in catecholamine levels with intermittent secretion by the tumor may influence results.

False Positives. Sensitivity is higher in humans (97%) when the criteria used is a drop in the catecholamine level by 50%. The specificity is only 67% when this method is used.[20] Therefore, increased false positives are possible.

False Negatives. When the criteria used for interpretation of the test is catecholamine levels dropping below 500 pg/mL, then the sensitivity drops to 87%, but the specificity is high (93%).[20] Therefore, the number of false negatives increases slightly.

Phentolamine Suppression Test

Rationale. When hypertension results from a pheochromocytoma, α-adrenolytic agents result in a lowering of blood pressure. Phentolamine is an α-adrenergic antagonist that may be administered intravenously.[20]

Method. A hypertensive patient is monitored to obtain a stable baseline arterial blood pressure. Phentolamine is administered at 0.5 to 1.5 mg as an intravenous bolus. Blood pressure is monitored every 30 seconds for 3 minutes then every minute for 7 minutes.[20] Severe hypotension may result in shock. Patients must be monitored very closely.

Interpretation. The result is considered positive if blood pressure decreases more than 35 mm Hg systolic and 25 mm Hg diastolic for at least a 5-minute duration.[20]

False Positives. Very common. Patients with other causes of hypertension may have positive results.[20]

Histamine, Tyramine, Metoclopramide, and Glucagon Provocation Tests

Rationale. These agents result in increased secretion of catecholamines by the pheochromocytoma.[20] Metoclopramide may induce secretion of catecholamines and precipitate a crisis in patients with pheochromocytoma. It should, therefore, be avoided in these patients. Additionally, if signs consistent with a hypertensive crisis are seen in association with metoclopramide administration, the patient should be evaluated for a pheochromocytoma.

Method. Not recommended due to the possibility of inducing a life-threatening hypertensive crisis.

SURGICAL MANAGEMENT

Surgery is the treatment of choice for pheochromocytomas in dogs as in humans. When complete resection is not possible, surgical debulk-

ing may be of benefit in controlling clinical signs temporarily. Resection of these tumors may be technically difficult. Pheochromocytomas often invade surrounding structures. En bloc resection may involve removal of the adjacent kidney and portions of the caudal vena cava. Clearly, an experienced surgeon is needed. Other methods of adrenalectomy including the transperitoneal laparoscopic approach have gained favor among some physicians[17] and may play a potential role in the future care of veterinary patients with nonmalignant tumors. At the time of surgical resection, a thorough exploratory laparotomy is indicated to determine if metastases are present and to rule out the presence of other tumors. In rare cases, both adrenal glands may be involved.

MEDICAL MANAGEMENT

Preoperative and Anesthetic Management

Pheochromocytoma patients may be poor anesthetic risks as a result of hypertension and arrhythmias.[14] Surgical manipulation may aggravate these conditions further. When the tumor is excised, the decrease in circulating catecholamines may lead to pronounced hypotension. Management of the pheochromocytoma patient in these crucial periods is still controversial in humans and little is known about the effects of various treatment regimens in the veterinary patient. In general, the goals of preoperative treatment are to control hypertension and arrythmias as well as achieve and maintain adequate vascular volume.[32]

Preoperatively, attempting to normalize blood pressure with α-antagonist drugs over a 2 to 3 week period may be of value.[11, 20] The rationale for this is to minimize the risk of a hypertensive crisis during anesthetic induction or during surgical manipulation. In addition, restoration of plasma volume in the patient with chronic vasoconstriction through preoperative medication may ameliorate postoperative hypotension. Currently, there is no evidence available to support any difference in the outcome of surgery in humans when the patient is treated preoperatively.[13]

The drug of choice for preoperative α-blockade is phenoxybenzamine, a nonselective, noncompetitive α_1-antagonist. Advantages of this drug include a long duration of action and noncompetitive blockade of α-adrenergic receptors. Phenoxybenzamine is administered at a dose of 0.2 to 1.5 mg/kg in the dog, and 0.5 mg/kg in the cat orally twice a day. A low dose should be used initially with gradual increase to achieve normotension.[20, 30] Alternatively, a selective, competitive, α_1-antagonist such as prazosin may be used (0.5 to 2.0 mg/kg orally two to three times daily).

β-Blocking agents may be used to control arrhythmias or tachycardia, but should never be used without concurrent α-blockade to avoid exacerbating hypertension with loss of the β_2-vasodilatory effects. Propranolol may be administered orally at a dose of 0.15 to 0.5 mg/kg three times daily in the dog, and 0.4 to 1.2 mg/kg two to three times daily in the cat. Labetalol is a combined α-antagonist and β-antagonist drug that has been used in human patients. The ratio of α and β activity for this drug is not ideal in the management of most pheochromocytoma patients because its β effects predominate such that hypertension continues to be problematic.

Concerning choice of anesthetic regimen, premedication with atropine should be avoided due to the potential to aggravate tachycardia.[32] A safer choice as an anticholinergic is glycopyrrolate.[32, 39] Diazepam or narcotics such as oxymorphone are preferable as premedication to phenothiazines such as acepromazine.[32] Acepromazine may result in severe hypotension.[32] For induction, narcotic agents or propofol are preferable to the arrhythmogenic barbiturates.[32] Isoflurane is preferable to halothane as a maintenance agent because halothane may potentiate catecholamine-induced arrhythmias.[32, 39]

Close attention to patient stability, particularly with direct arterial blood pressure monitoring, during the anesthetic period is essential to successful surgical outcome. To treat a hypertensive crisis in the perioperative period, phentolamine (0.02 to 0.1 mg/kg IV as needed), can be used. Alternatively, direct vasodilatory agents such as sodium nitroprusside (5 to 15 mg/kg/min continuous rate infusion) may be of value. Arrhythmias and extreme tachycardia may be treated with intravenous β-blockers such as propranolol (0.02 to 0.1 mg/kg IV over 2 to 3 minutes) or esmolol (slow bolus: 500 mg/kg, or infusion: 50 to 200 mg/kg/min). Esmolol is preferred because the short half life allows for closer control than may be achieved with propranolol.[32] Hypotension is best treated through volume expansion with crystalloids, colloids, or blood products as indicated.[32] If hypotension is unresponsive to fluid therapy, pressor agents such as dobutamine may be of value.[32, 39]

Postoperative Management

Postoperatively, the biggest concern is hypotension. Volume expansion is the best treatment for this complication because the vasculature is usually desensitized in pheochromocytoma patients to the effects of pressor agents. Blood pressure monitoring postoperatively is indicated. Most patients should become normotensive within 24 to 48 hours of surgery.[32] When resection of the tumor is incomplete, hypertension and arrhythmias are managed as in the preoperative setting. Some human patients continue to have residual hypertension, despite complete tumor excision.

Chronic Long-term Management

When surgical resection is incomplete or when the patient has metastatic disease, continued management with adrenergic antagonist drugs may be necessary. These agents are discussed above under preoperative management. α-Methyltyrosine has been used in humans and may play an important role in chronic therapy by permitting lower dosages of phenoxybenzamine to be used and reducing the side effects

of long-term α-blockade.[32] α-Methyltyrosine decreases catecholamine synthesis by inhibiting the rate-limiting enzyme tyrosine hydroxylase. Use of this agent in the canine or feline patient has not been reported and the dosage may need to be extrapolated from that used in humans (0.3 to 4.0 g/day). Calcium channel blockers may be of use in controlling hypertension. In addition to direct vasodilatory affects, these agents block synaptic calcium channels, thereby decreasing catecholamine release.[32]

Chemotherapy has been used in people, but has not been described in the dog or cat. The combination of dacarbazine, cyclophosphamide, and vincristine has had some success in humans.[4, 13, 20, 25] Induction of a hypertensive crisis after chemotherapy administration has been reported in humans with pheochromocytoma,[46] indicating that chemotherapy may be of some risk in these patients and may require hospitalization and blood pressure monitoring.

^{131}I-MIBG has also been used in people with disseminated tumor.[23, 25] The treatment appears to result in limited short-term responses. The value of this therapy in the dog or cat is unknown.

PATHOLOGY

Grossly, pheochromocytomas are light brown to yellow and compress the adrenal cortex into a thin surrounding rim of tissue[8] (Fig. 6). Histologically, these tumors are composed of round to polygonal cells with eosinophilic and granular cytoplasm arranged in nests and separated by a fine fibrovascular stroma. Differentiating pheochromocytoma from adrenal cortical neoplasms can be difficult but immunohistochemical staining procedures can be useful. Chromogranin A has been used in dogs as an immunohistochemical marker for pheochromocytoma.[10, 11] Chromogranin A is a protein of unknown function that is stored and released with catecholamines from storage vesicles in the adrenal medulla. Differentiation of benign from malignant tumors on the basis of histopathology is difficult.[4, 8, 13, 22, 25] This distinction is usually based on the clinical stage of disease.

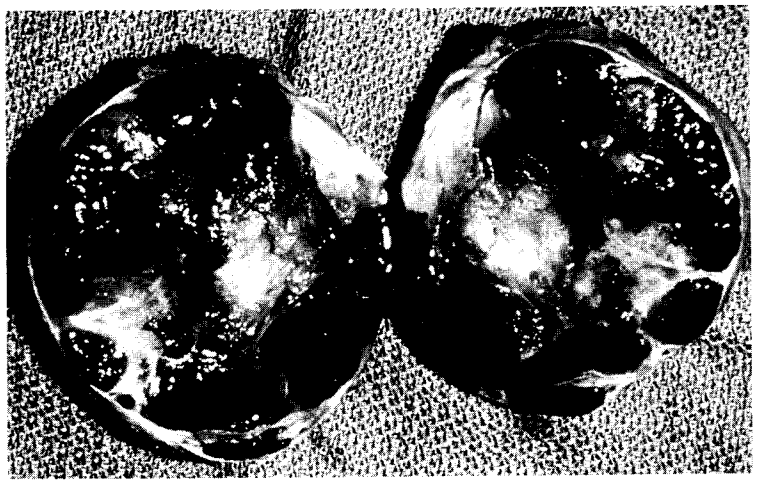

Figure 6. Photograph of a pheochromocytoma. This tumor ablates normal adrenal architecture but is well circumscribed.

Cytology of pheochromocytoma in dogs has been infrequently described. These tumors have a cytologic appearance consistent with neuroendocrine neoplasia.[1] Features include polygonal cells with foamy cytoplasm arranged in groups and, occasionally, individually. Nuclei are round to oval without prominent nucleoli. The cells are uniform overall, but giant nuclei may be observed rarely. Naked nuclei are frequently seen. The cytology of abdominal effusion was interpreted as consistent with that of lymphoma in three dogs of one report.[15] This suggests that cytologic evaluation may be misleading.

PROGNOSIS

The prognosis is difficult to define precisely because pheochromocytomas are rare and a limited number of treated cases have been reported. Unfortunately, dogs and cats with pheochromocytomas have not been evaluated to determine prognostic factors that would assist with the prediction of biologic behavior in individual cases. Gilson et al[15] have speculated that neurologic signs, abdominal distention, and weight loss are clinical signs that may indicate a more advanced stage of disease. The TNM staging classification recommended by the World Health Organization is shown in Table 3.[28] The value of this classification in predicting postoperative prognosis in dogs or cats with pheochromocytomas has not, as yet, been evaluated.

Prognostic factors in humans suggesting a future malignant course

Table 3. CLINICAL STAGES OF CANINE ADRENAL TUMORS AS RECOMMENDED BY THE WORLD HEALTH ORGANIZATION

T:	Primary tumor
	T0: No evidence of tumor
	T1: Well-defined tumor
	T2: Tumor invading neighborhood structures
	T3: Tumor invading blood vessels
N:	Regional lymph nodes
	N0: No metastasis to regional lymph nodes
	N1: Regional lymph node metastasis
M:	Distant metastasis
	M0: No distant metastasis
	M1: Distant metastasis

Adapted from Owen LN: World Health Organization classification of tumors in domestic animals, ed 1. Geneva, Switzerland, World Health Organization, 1980; reproduced from document VPH/CMO/80.20 by permission of the World Health Organization, which retains the copyright.

include large tumor size, local tumor extension at the time of surgery, and DNA ploidy pattern.[43] The DNA ploidy pattern appears to be an important variable associated with the course of disease in humans. A DNA diploidy pattern is associated with a more benign course whereas tumors with DNA aneuploidy and tetraploidy patterns have a more aggressive nature with regard to morbidity and mortality.[24] The association between DNA ploidy pattern and biologic behavior and metastatic potential in the dog and cat has not been reported.

As in humans, the diagnosis of benign versus malignant pheochromocytoma cannot be accurately determined by histologic appearance and is instead dependent on the presence or absence of metastases or invasion. Clinical evidence of invasion and metastasis defines malignancy.[3, 15, 25] Metastatic sites reported in the dog include the lung, liver, spleen, kidney, bone, heart, pancreas, and lymph nodes.[15] About 50% of pheochromocytomas reported in dogs may be considered malignant. Although the long-term prognosis for animals with metastatic or invasive pheochromocytoma is poor, many dogs with noninvasive tumors may live normal lifespans. Extended survivals of 18 months to 2 years have been reported in dogs with successful surgical resection.[14, 15, 39]

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ADRENAL INCIDENTALOMAS

Diagnostic Workup of the Incidentally Discovered Adrenal Mass

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In human medicine, the introduction of high-resolution abdominal imaging, computed tomography (CT), and magnetic resonance imaging (MRI) has led to the identification of clinically silent adrenal masses in 1% to 10% of patients imaged for reasons other than suspected adrenal disease.[13, 27, 37, 56] With an estimated discovery rate of 2 to 3 unsuspected tumors for every 100 abdominal CT procedures, the incidentally discovered adrenal mass or "adrenal incidentaloma" poses a diagnostic dilemma for human physicians.[13, 27, 29, 37, 48, 54, 56] Recent studies have accentuated the growing value of diagnostic imaging with CT, MRI, and abdominal ultrasonography in evaluating veterinary patients.*

Experience with the ultrasonographic localization of the adrenal glands in dogs and cats has improved with recent technologic advances in ultrasound equipment. Current ultrasound machines have axial (depth) resolution capacities of 0.2 to 0.4 mm and lateral resolution capacities of 0.5 to 1.0 mm within the focal zone of standard 5.0 to 7.5 MHz transducers.[41] An adrenal gland identification rate of 85% was found for 50 consecutive dogs evaluated ultrasonographically.[25] The identification rate for the left adrenal gland ranged from 90% to 100% (average rate 96%) for three different sonographers with differing clinical experience. The identification rate for the right gland ranged from 60% to 83%, with 37 of 50 (74%) glands successfully imaged. Deep-chested

*References 3, 9, 11, 18, 24–26, 35, 51, 57, 67, 68, 71.

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