

1 **Comparison of computed tomographic and pathologic findings in 17 dogs with**
2 **primary adrenal neoplasia**

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13 Key words: adrenal gland, computed tomography, dog, neoplasia

14 Running head: CT and histology of adrenal neoplasia

15 Abstract:

16 The CT appearance of canine adrenal masses has been reported, but associations
17 between imaging features and pathologic features of these lesions have not been
18 investigated in detail. In order to test the associations between different types of adrenal
19 neoplasia and their CT and pathologic features, a retrospective study was performed.
20 Seventeen dogs that had histologic diagnosis of primary adrenal neoplasia following a CT
21 contrast of the abdomen and surgical resection of the mass or necropsy examination were
22 included in the study. CT images and histopathologic specimens were reviewed
23 independently by two radiologists and a pathologist, respectively. Diagnoses were
24 adenocarcinoma in 9 (53%) dogs, pheochromocytoma in 5 (29%) dogs, and adenoma in
25 3 (18%) dogs. Pheochromocytoma was associated with CT signs of vascular invasion
26 (likelihood ratio=4.8, 95% CI=1.3-18.3, $P=0.03$) and macroscopic vascular invasion
27 (likelihood ratio=9.6, 95% CI=1.4-65.9, $P=0.02$). There was excellent agreement between
28 signs of vascular invasion in CT images and vascular invasion at surgery or necropsy
29 ($\kappa=0.86$, $P=0.001$). A peripheral contrast-enhancing rim in delayed post-contrast CT
30 images was associated with fibrous encapsulation of the tumor ($\kappa=0.53$, $P=0.05$),
31 and a heterogeneous pattern of contrast distribution in delayed post-contrast CT images
32 was associated with adrenal hemorrhage or infarction on histological examination
33 ($\kappa=0.45$, $P=0.05$). Although CT enabled assessment of features that reflect their
34 biological behavior of adrenal neoplasms with good agreement with pathological
35 findings, the overlap in pathologic features between tumor types will limit the potential
36 for those tumor types to be distinguished by CT.

37 **Introduction:**

38 Primary adrenal neoplasia is an uncommon, but well recognized condition in dogs¹.

39 Adrenal adenoma, adenocarcinoma and pheochromocytoma are considered the most

40 common tumors affecting the canine adrenal gland^{1,2,3,4}. Adrenal myelolipoma, a benign

41 tumor composed of adipose tissue and hematopoietic cells, has also been reported in

42 dogs^{5,6}. Adrenal neoplasms may cause a range of clinical signs, depending primarily on

43 their endocrinological activity. Adrenocortical neoplasms producing cortisol cause signs

44 of canine Cushing's syndrome, including polyuria/polydipsia, polyphagia, hair loss,

45 hepatomegaly and pendulous abdomen. Epinephrine or norepinephrine-secreting

46 pheochromocytomas are associated with signs such as weakness, collapse, cardiac

47 dysrhythmia or hypertension. Endocrinologically inactive adrenal neoplasms usually

48 cause non-specific clinical signs, including weight loss. Adrenal gland masses, both

49 neoplastic and hyperplastic, are recognized frequently during abdominal imaging in

50 older dogs, and in many instances are thought to be clinically silent 'incidentalomas'⁴.

51 Imaging of suspected adrenal neoplasia in dogs is performed with the intention of

52 determining the anatomical origin of the tumor, its morphologic features, which may

53 reflect biological behavior, and to look for signs of metastasis. Of the various adrenal

54 neoplasms, malignant pheochromocytomas are considered the most aggressive, with

55 direct invasion of adjacent vasculature reported in up to 85% dogs and distant metastasis

56 in up to 40% dogs^{1,7,8}.

57 In humans computed tomography (CT) plays an important role in characterizing adrenal

58 neoplasms^{9,10}. The majority of adrenal adenomas and myelolipomas in humans contain a

59 significant amount of intracellular fat, hence these benign tumors usually have lower x-

60 ray attenuation than malignant adrenal neoplasms⁹ and the combination of low density

61 values (<10 HU) in non-enhanced CT images and early contrast wash-in/wash-out
62 through the mass seen in benign tumors, enables correct classification of benign versus
63 malignant adrenal lesions in up to 96% of affected humans¹¹. CT also enables detection
64 of tumor- or blood clot-thrombus in vessels adjacent to the adrenal glands, which occurs
65 as a result of invasion by malignant neoplasms¹².

66 CT has also been found to be a useful method for imaging the adrenal glands in dogs. The
67 CT appearance of adrenal glands has been described in healthy dogs^{13,14}, dogs with
68 pituitary-dependent hyperadrenocorticism^{15,16,17}, and dogs with primary adrenal
69 neoplasia^{5,18,19,20}. As in humans, CT is an accurate method for detection of vascular
70 invasion by malignant adrenal neoplasms, with 92% sensitivity and 100% specificity in
71 one study¹⁹. The histologic composition of adrenal neoplasms is somewhat
72 heterogeneous in both humans and dogs with variable amounts of hemorrhage, necrosis
73 and/or mineralization occurring in benign and malignant neoplasms^{10, 21, 22}. As a result,
74 different tumor types may appear similar in CT images^{5,19}; however, previous studies of
75 the CT appearance of canine adrenal tumors have not investigated in detail their imaging-
76 pathologic correlations.

77 The aims of the present study were to: (1) test the associations between different types
78 of adrenal neoplasia and histopathologic and CT imaging features (2) assess the
79 agreement between CT imaging findings and analogous histopathologic features of
80 adrenal neoplasms.

81

82 **Methods:**

83 **Patient selection-** The electronic patient record system at the Queen Mother Hospital
84 for Animals (QMHA) was searched using the terms *adrenalectomy*, *adrenal mass*,

85 *computed tomography*, and *dog*. Pathological data for patients retrieved by this search
86 was then sought in the QMHA's clinical pathology database. Dogs that had abdominal CT,
87 surgical resection of an adrenal mass or necropsy, and histological diagnosis of adrenal
88 neoplasia were included in this study. The breed, age and gender of these dogs were
89 recorded.

90 **CT imaging-** All CT exams were performed using the same 16-slice scanner (Mx8000 IDT,
91 Philips, Best, The Netherlands) with dogs in sternal recumbency under general
92 anesthesia or sedation. All CT studies included one pre-contrast acquisition and at least
93 one post-contrast acquisition of the abdomen. Non-ionic iodinated contrast medium,
94 Iohexol (Omnipaque 350 mg/mL, Nycomed, Oslo) was administered as a bolus injection
95 at a dose of 2 mL/kg using, when available, a pressure injector (Stellant, Medrad,
96 Indianola, PA.) at a rate of 2 mL/s. Post contrast scans were obtained at 30s (early phase)
97 or at 120s (delayed phase) after the start of contrast injection. When contrast was
98 administered by hand injection, a first scan was typically acquired within 60s of the start
99 of injection, followed by another scan at 120s. CT machine settings for image acquisition
100 varied depending on the size of the patient. Typical settings were: helical mode, 2-3 mm
101 slice thickness, 1 s rotation time, 1.25 pitch, 90 or 120 kVp, 100-150 mA, 500 mm
102 acquisition field of view, standard reconstruction algorithm and 512x512 matrix.

103 Two board-certified radiologists (LB, PM) unaware of the surgical and pathological
104 results reviewed the images from the CT studies together and reached a consensus. CT
105 images were displayed in an abdominal window (window level= 40 HU, window width=
106 400 HU) on a workstation using commercially available DICOM image viewing software
107 (OsiriX 64-bit, version 5.2.2, Pixmeo, Switzerland). CT images were reviewed with
108 respect to a set of pre-considered criteria as follows: maximum diameter (mm) of the

109 mass in any reformatted plane (transverse, sagittal or dorsal); adrenal mass outline (well
110 demarcated VS irregularly demarcated); shape (rounded VS lobulated); pattern of pre-
111 contrast attenuation (homogeneous VS heterogeneous); pattern of post-contrast
112 enhancement (homogeneous VS heterogeneous) on early and delayed phases; presence
113 of contrast enhancing peripheral rim on early and delayed phases; and irregular vessel
114 lumen or intraluminal thrombus compatible with tumor invasion or blood clot within the
115 ipsilateral phrenico-abdominal vein, renal vein or caudal vena cava. Average attenuation
116 and standard deviation (SD) in Hounsfield Units (HU) of each adrenal mass was measured
117 on pre-contrast, early- and delayed-phase post-contrast images by manually drawing a
118 region of interest to fit the mass in each image in each plane in which the mass appeared
119 largest. Attenuation data were regrouped into categories of contrast enhancement: slight
120 (< 60HU), moderate (≥ 60 , <110) and marked (≥ 110).

121 **Pathology**- The method of examining each adrenal mass (i.e. surgical adrenalectomy VS
122 necropsy), laterality of the adrenal mass and the presence or absence of macroscopic
123 vascular invasion were recorded. A board-certified pathologist (SP) reviewed archived
124 histopathology samples from the adrenal lesions, being unaware of imaging findings.
125 Variables evaluated based on review of ten x400 high power fields were: mitotic index,
126 cellular differentiation (well-differentiated; moderately well-differentiated; poorly
127 differentiated), percentage of necrosis (N0<10%; N1= 10%-25%; N2= 26%-50%; N3=
128 >50%), presence of hemorrhage or infarction, presence of peripheral capsular invasion,
129 microscopic vascularity (slight, moderate, marked) and presence of microscopic vascular
130 invasion. Classification of tumor grade (high or low) was based on these results: tumor
131 was considered of high grade if for 3 or more results were positive or classified in the
132 higher category group. The pathologist formulated a final diagnosis (i.e. adrenocortical
133 adenoma, adrenocortical adenocarcinoma or pheochromocytoma) for each adrenal mass.

134 Because low-grade adrenocortical adenocarcinomas and adenomas are often difficult to
135 differentiate ⁷, the classification of benign VS malignant was based on combined criteria
136 including mitotic index, tumor grade, capsular invasion and presence of microscopic
137 vascular invasion.

138 **Statistical analysis-** Statistical calculations were performed using commercially
139 available software (SPSS® Software, Version 20.0.0, IBM Corp, Armonk, NY). Fisher's
140 exact test was used to test the association between diagnosis (i.e. adrenocortical
141 adenoma, adrenocortical adenocarcinoma or pheochromocytoma) and each of the
142 following categorical variables: breed, gender, mitotic index, cellular differentiation,
143 percentage of necrosis, presence of areas of hemorrhage or infarction, presence of
144 peripheral capsular invasion, microscopic vascularity, presence of microscopic vascular
145 invasion, macroscopic vascular invasion, tumor grade, outline, shape, pattern of pre-
146 contrast attenuation, pattern of post-contrast enhancement on early and delayed phases,
147 presence of contrast enhancing peripheral rim on early and delayed phases, presence of
148 tumor invasion within the adjacent vasculature and degree of contrast enhancement on
149 early and delayed phases. Monte Carlo estimation for Fisher's exact test was used when
150 a count less than 5 elements per cell was expected in a variable including more than two
151 categories. Likelihood ratios (and 95% confidence intervals, CI) were calculated for
152 results with $P < 0.05$. Continuous data (e.g. age, maximum diameter of the mass on CT,
153 average HU on pre-contrast, early and delayed phases, difference of average HU between
154 early or delayed post-contrast and pre-contrast phases) was tested for normality using
155 the Shapiro-Wilk test, and relationships between these variables and diagnosis were
156 tested using analysis of variance. For all statistical tests, results with $P < 0.05$ were
157 considered to be significant.

158 Certain CT features and pathological features were considered analogous. Agreement
159 between the following binomial CT and histopathology features was tested using the
160 kappa statistic: presence of areas of hemorrhage or infarction VS pattern of contrast
161 enhancement on early and delayed phases, presence of peripheral capsular invasion VS
162 mass outline, presence of peripheral capsular invasion VS contrast enhancing rim on
163 early and delayed phase, presence of macroscopic vascular invasion VS presence of
164 vascular invasion on CT post contrast images. Rank correlation between the following
165 ordinal CT and histopathology features was tested using Kendall's Tau b or c tests:
166 percentage of necrosis VS pattern of contrast enhancement on early and delayed phases,
167 microscopic vascularity VS degree of contrast enhancement on early and delayed phase.
168 Statistical tests were performed by two authors (TG, CRL).

169

170 **Results:**

171 Seventeen dogs with a total of 17 adrenal masses were included in this study. Tumors
172 were diagnosed as adrenocortical adenocarcinoma (n=9, 53%), pheochromocytoma
173 (n=5, 29%), and adrenocortical adenoma (n=3, 18%). These masses were analyzed either
174 after they were removed by surgical adrenalectomy (n=15, 88%) or on post-mortem
175 examination (n=2, 12%). More tumors affected the left adrenal gland (n=11, 65%) than
176 the right (n=6, 35%). Median age of the patients was 10 years (range: 5-15 years). Breeds
177 were German shepherd (n=2), Golden retriever (n=2) and Lurcher (n=2), Boxer (n=1),
178 Cocker Spaniel (n=1), Collie (n=1), Fox Terrier (n=1), Jack Russell Terrier (n=1), Labrador
179 (n=1), Miniature Poodle (n=1), Rottweiler (n=1), Shih Tzu (n=1), West Highland White
180 terrier (n=1) and cross breed (n=1).

181 Relationships between tumor type and pathological findings are summarized in Table 1.
182 The only significant association found was between pheochromocytoma and presence of
183 macroscopic vascular invasion (likelihood ratio=9.6, 95% CI 1.4-65.9).

184 Relationships between tumor type and CT features are summarized in Table 2. In three
185 dogs, only the early post-contrast CT images were available for review. There was a
186 significant association between pheochromocytoma and CT signs of vascular invasion or
187 thrombus formation (likelihood ratio=4.8, 95% CI 1.3-18.3). The higher mean HU pre-
188 contrast for pheochromocytoma compared to other neoplasms was of borderline
189 significance ($P=0.06$). No other significant associations were found.

190 Results of the agreement or correlation between analogous histopathological and CT
191 findings are summarized in Table 3. There was moderate agreement between absence of
192 peripheral capsular invasion by neoplastic cells on histopathology and the presence of an
193 enhancing rim on post-contrast late phase CT images ($\kappa=0.53$, $P=0.05$). There was
194 excellent agreement with respect to presence of vascular invasion ($\kappa=0.86$,
195 $P=0.001$). In one dog the adrenal mass was considered to be invasive because of marked
196 impingement on the caudal vena cava and focal irregularity in intraluminal contrast
197 observed in CT images; however, no evidence of vascular invasion by this mass was
198 identified during surgery or on histopathologic examination. There was moderate
199 agreement between hemorrhage or infarction seen histologically and a heterogeneous
200 pattern of post contrast enhancement in late phase CT images ($\kappa=0.45$, $P=0.05$).

201

202 **Discussion:**

203 CT is now routinely used in referral practices for the preoperative assessment of dogs
204 with an adrenal mass because it is considered more accurate than abdominal

205 ultrasonography for the detection of the vascular invasion¹⁹. In the present study there
206 was excellent agreement between signs of vascular invasion in CT images and finding
207 vascular invasion at surgery or necropsy. A discrepancy (false positive) was identified in
208 only one dog; hence sensitivity, specificity and accuracy of CT for vascular invasion in this
209 study were respectively 92%, 89% and 94%. The single erroneous CT interpretation of
210 vascular invasion probably occurred because of the marked compression of the caudal
211 vena cava by the adrenal mass, which caused narrowing of the vessel lumen. Such
212 impingement may alter the blood flow and disrupt the pattern of post-contrast
213 enhancement of these vessels, mimicking a thrombus, which is the principal imaging sign
214 of vascular invasion. The presence of vascular invasion influences the choice of surgical
215 approach for tumor resection²⁴, although there appear to be no significant differences in
216 perioperative morbidity and mortality rates between patients with or without a tumor-
217 associated thrombus.

218 Pheochromocytoma appears more likely to invade adjacent vessels than adrenocortical
219 adenoma or adenocarcinoma (Fig. 1), as has been reported previously²⁵; however, this
220 finding at surgery or necropsy result was not associated with microscopic vascularity or
221 histological signs of vascular invasion within this tumor. In two dogs, one with a high-
222 grade pheochromocytoma and one with a high-grade adenocarcinoma, there was
223 evidence of peripheral capsular invasion by the tumor, with additional focal infiltration
224 of neoplastic cells in the adipose tissue surrounding the gland in the dog with
225 pheochromocytoma. Pheochromocytoma invading the hypaxial and epaxial musculature
226 has been reported in dogs^{18,19}, but this feature was not observed in dogs in the present
227 study.

228 The presence of a peripheral contrast-enhancing rim in late phase CT images was
229 associated with fibrous encapsulation of the tumor on histological examination (Fig. 2).
230 A fibrous pseudocapsule (composed of compressed adjacent soft tissues), free of
231 neoplastic cell infiltration is recognized more frequently in well-differentiated and low-
232 grade tumors. All adrenal adenomas in the present study had both CT and
233 histopathological features compatible with a pseudo-capsule around the tumor. Finding
234 a peripheral contrast-enhancing rim and absence of signs of vascular invasion in CT
235 images of an adrenal mass suggests benign behavior. In contrast, the capsular infiltration
236 identified in two dogs with high-grade adenocarcinoma and pheochromocytoma,
237 respectively, was indicative of the malignant biological behavior of these tumors.

238 Necrosis and hemorrhage are common in adrenal tumors^{18,23}, and these features were
239 considered responsible for the variable echogenicity of adrenal tumors in one study²¹.
240 Similarly, in the present study, the presence of hemorrhage or infarction within an
241 adrenal mass was associated with a heterogeneous pattern of contrast enhancement on
242 late phase CT images (Fig.3). Masses with a homogeneous post contrast enhancement
243 were less likely to contain foci of hemorrhage or infarction. In a report of four dogs with
244 pheochromocytoma, the adrenal masses also had variable appearance in CT images, with
245 multiple foci of low attenuation interspersed with hyperattenuating, highly vascularized
246 areas¹⁸. It may not be possible to distinguish types of adrenal tumor based on CT features
247 such as pre-contrast pattern of attenuation or degree or pattern of post-contrast
248 enhancement because hemorrhage or necrosis are liable to occur when any tumor
249 reaches a certain size.

250 In humans, adrenal adenomas may be recognized by CT because of their characteristic
251 low x-ray attenuation that occurs due to the presence of fat-laden cells in up to 70% of

252 these tumors^{9,26}. Intracellular lipid-rich substances such as cholesterol and fatty acids
253 have also been reported in canine patients with adrenal hyperplasia and adenomas². A
254 report of CT findings in a dog with bilateral adrenal adenomas and myelolipomas
255 described one enlarged gland with a hypoattenuating center (-56HU) compatible with fat,
256 while the contralateral adrenal gland was more homogeneous with a higher attenuation
257 (39HU)⁵. The latter value is similar to the mean HU value (40.8HU) found for adenomas
258 in pre-contrast CT images in the present study. These values are also similar to the HU
259 values of 31.8 and 33.1 reported for hyperplastic adrenal glands in dogs with pituitary
260 microadenoma or macroadenoma¹⁵. A recent study found that pheochromocytomas had
261 higher mean attenuation (44.5HU) than adrenal adenocarcinomas (28.2HU)²⁷.
262 Interestingly, we also found evidence that the mean pre-contrast HU value for
263 pheochromocytomas may be higher than for other adrenal neoplasms, although this
264 result was of borderline significance.

265 Another criterion used in humans to differentiate adrenal adenomas from malignant
266 tumors is the early contrast wash-out associated with adenomas that is observed in
267 delayed (typically at 15 minutes) post-contrast images^{11,28}. We found no significant
268 differences in the degree of enhancement or HU values measured in post-contrast CT
269 images of different tumor types. Similarly no significant differences were found in their
270 microscopic vascularization. These results differ from results presented in two recent
271 studies in which pheochromocytoma was found to have more marked contrast
272 enhancement than adenocarcinoma^{27,29}; however, it is uncertain if this difference in
273 results occurred because of differences in the timing of post-contrast acquisitions as this
274 information was not included.

275 The present study has several limitations. The relatively small number of adrenal tumors
276 included limits the power of the statistical tests. Inclusion criteria (e.g. final histologic
277 diagnosis after adrenalectomy or post mortem examination) may have caused a patient
278 selection bias in favor of dogs with more marked clinical signs and more
279 endocrinologically active or malignant tumors, such as some adenocarcinomas and
280 malignant pheochromocytomas, at the expense of dogs with adenomas^{7,25}. There are also
281 limitations in the comparison of CT and pathological findings. Histologic sections reveal
282 microscopic structures below the resolution of CT scanners, and usually cover only a
283 small part of a lesion observed by CT, hence discrepancies in the presence and extent of
284 reported abnormalities are inevitable. The retrospective nature of the study limited the
285 amount of information available, particularly about other macroscopic pathologic
286 features, which may have helped distinguish tumor types of strengthened imaging-
287 pathological correlations.

288 Another possible limitation might be the method used to evaluate the microscopic
289 vascularity of adrenal tumors, which was based on partially subjective criteria
290 (pathologist's judgment, based on review of ten x400 high power fields for each slide).
291 Quantitative methods of assessment of tumoral microvasculature (e.g. microscopic
292 vascular density) have been reported as a method to evaluate the response of a tumor to
293 antiangiogenic therapy.³⁰ It is unclear if this method offers advantages over the subjective
294 method used because it is also susceptible to variability because of heterogeneity within
295 a mass.

296 In conclusion, although CT enabled assessment of features that reflect the biological
297 behavior of adrenal neoplasms with good agreement with pathological findings, the
298 overlap in pathologic features between tumor types will limit the potential for those

299 tumor types to be distinguished by CT. Further studies of a larger number of dogs are
300 needed to support our results.

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Table 1. Relationships between tumor type and histopathological findings

	Adenoma n=3	Adenocarcinoma n=9	Pheochromocytoma n=5	P-value
Mitotic index	MI0=2, MI2=1	MI0=3, MI1=1, MI2=4, MI4=1	MI0=2, MI1=2, MI3=1,	0.48
Cellular differentiation	Well differentiated=3	Well differentiated=4 Moderately differentiated=3 Poorly differentiated=2	Well differentiated=4 Moderately differentiated=1	0.38
% of necrosis	N0=3	N0=6; N1=1; N2=1; N3=1	N0=3; N1=2	0.81
Hemorrhage/infarction	No=2;Yes=1	No=7;Yes=2	No=2;Yes=3	0.54
Capsular invasion	No=3	No=6;Yes=3	No=4;Yes=1	0.66
Microscopic vascularity	Mild=2;Moderate=1	Mild=4;Moderate=2;Marked=3	Mild=1;Moderate=1;Marked=3	0.61
Microscopic vascular invasion	No=2;Yes=1	No=5;Yes=4	No=1;Yes=4	0.43
Macroscopic vascular invasion	No=3	No=8;Yes=1	No=1;Yes=4	0.02
Tumor grade	Low=3	Low=4;High=5	Low=1;High=4	0.1

Table 2. Relationships between tumor type and CT features

	Adenoma n=3	Adenocarcinoma n=9	Pheochromocytoma n=5	P-value
Maximum diameter (mm)	Mean= 25.3 +/- 4.6 SD	Mean= 29.5 +/- 14.1 SD	Mean= 41.4 +/- 18.4 SD	0.26
Outline	Irregular demarcation=1 Well demarcated=2	Irregular demarcation =1 Well demarcated=8	Irregular demarcation =2 Well demarcated=3	0.77
Shape	Rounded=3	Rounded=8;Lobulated=1	Rounded=2;Lobulated=3	0.12
Pattern pre-contrast attenuation	Heterogeneous=2;Homogeneous=1	Heterogeneous=4;Homogeneous=5	Heterogeneous=4;Homogeneous=1	0.54
Pattern post-contrast enhancement (early)	Heterogeneous=3	Heterogeneous=3;Homogeneous=6	Heterogeneous=4;Homogeneous=1	0.14
Pattern post-contrast enhancement (late)	Heterogeneous=2;Homogeneous=1	Heterogeneous=1;Homogeneous=6	Heterogeneous=3;Homogeneous=1	0.22
Contrast-enhancing rim (early)	Yes=3	No=6;Yes=3	No=3;Yes=2	0.17
Contrast-enhancing rim (late)	Yes=3	No=5;Yes=2	No=3;Yes=1	0.12
Vascular invasion	No=2;Yes=1	No=8;Yes=1	No=1;Yes=4	0.03
Mean HU pre-contrast	Mean= 40.8 +/- 14.3 SD	Mean= 36.7 +/- 11.8 SD	Mean= 52.3 +/- 5 SD	0.06
Mean HU post-contrast (early)	Mean= 66.7 +/- 8.3 SD	Mean= 83.9 +/- 52.7 SD	Mean= 103 +/- 21.7 SD	0.49
Mean HU post-contrast (late)	Mean= 55.5 +/- 22.4 SD	Mean= 76.9 +/- 28.4 SD	Mean= 93.4 +/- 14.3 SD	0.16
Degree of contrast enhancement (early)	Mild=1;Moderate=2	Mild=5;Moderate=3; Marked=1	Moderate=4; Marked=1	0.227
Degree of contrast enhancement (late)	Moderate=3	Mild=4;Moderate=3	Moderate=3; Marked=1	0.09
HU difference pre-post (early)	Mean= 25.9 +/- 21.3 SD	Mean= 47.2 +/- 46.5 SD	Mean= 50.6 +/- 23.6 SD	0.65
HU difference pre-post (late)	Mean= 14.7 +/- 21.7 SD	Mean= 41.8 +/- 17.7 SD	Mean= 42.8 +/- 14.2 SD	0.09

Table 3. Agreement or correlation between analogous histopathological and CT features

Histopathological feature	CT feature	Statistic	P-value
Capsular invasion	Outline	0.3 ^a	0.5
Capsular invasion	Contrast-enhancing rim (early)	0.27 ^a	0.29
Capsular invasion	Contrast-enhancing rim (late)	0.53 ^a	0.05
Vascular invasion	Vascular invasion	0.86 ^a	0.001
% necrosis	Post-contrast enhancement (early)	0.069 ^b	0.77
% necrosis	Post-contrast enhancement (late)	-0.02 ^b	1
Hemorrhage or infarction	Pattern of post-contrast enhancement (early)	0.37 ^a	0.3
Hemorrhage or infarction	Pattern of post-contrast enhancement (late)	0.45 ^a	0.05
Microscopic vascularity	Degree of contrast enhancement (early)	-0.03 ^b	0.91
Microscopic vascularity	Degree of contrast enhancement (late)	-0.36 ^b	0.18

^aKappa; ^bKendall's tau

Legends:

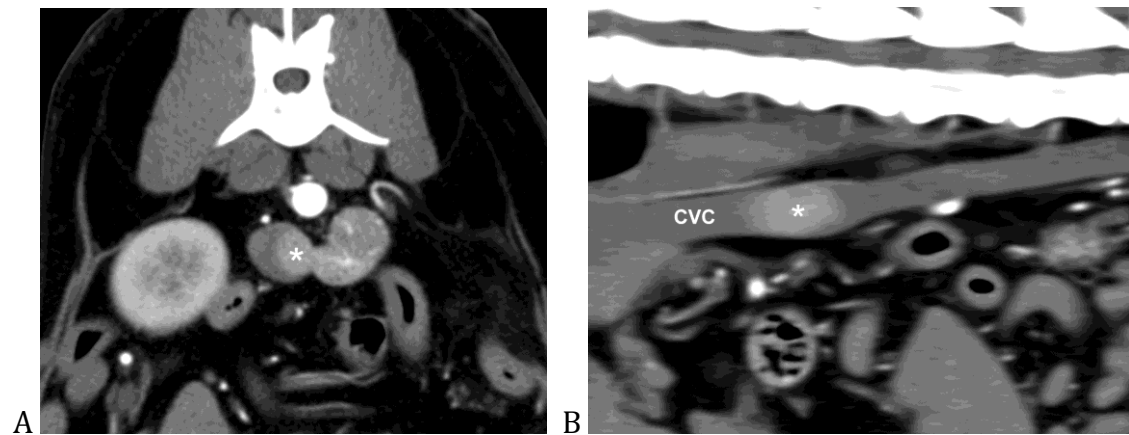


Fig. 1. A) Transverse and B) sagittal post-contrast CT images showing vascular invasion of a left adrenal mass. There is a contrast enhancing mass (*) within the lumen of the caudal vena cava (CVC).

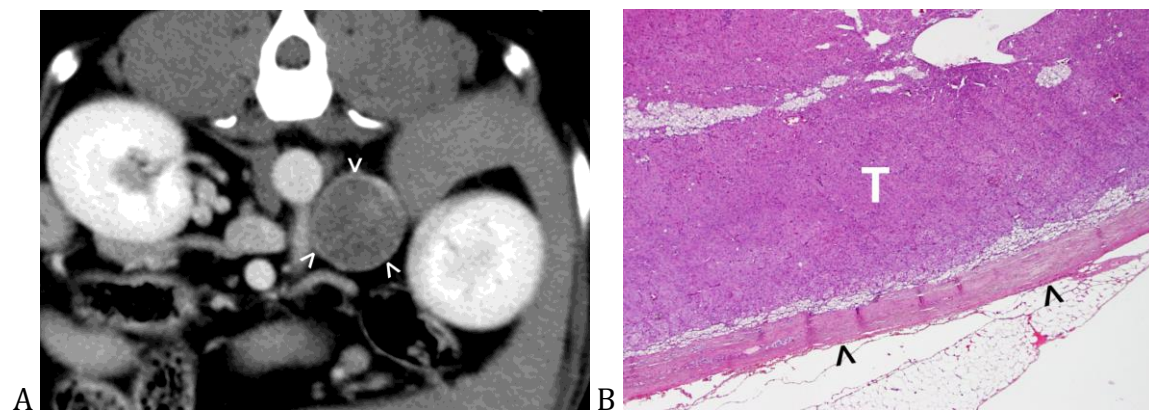


Fig. 2. A) Transverse post-contrast CT image showing thin, peripheral rim of enhancement (arrowheads) in a left adrenal mass. B) Corresponding histologic section showing a layer of fibrous tissue (arrowheads) forming a pseudo-capsule around the tumor (T).

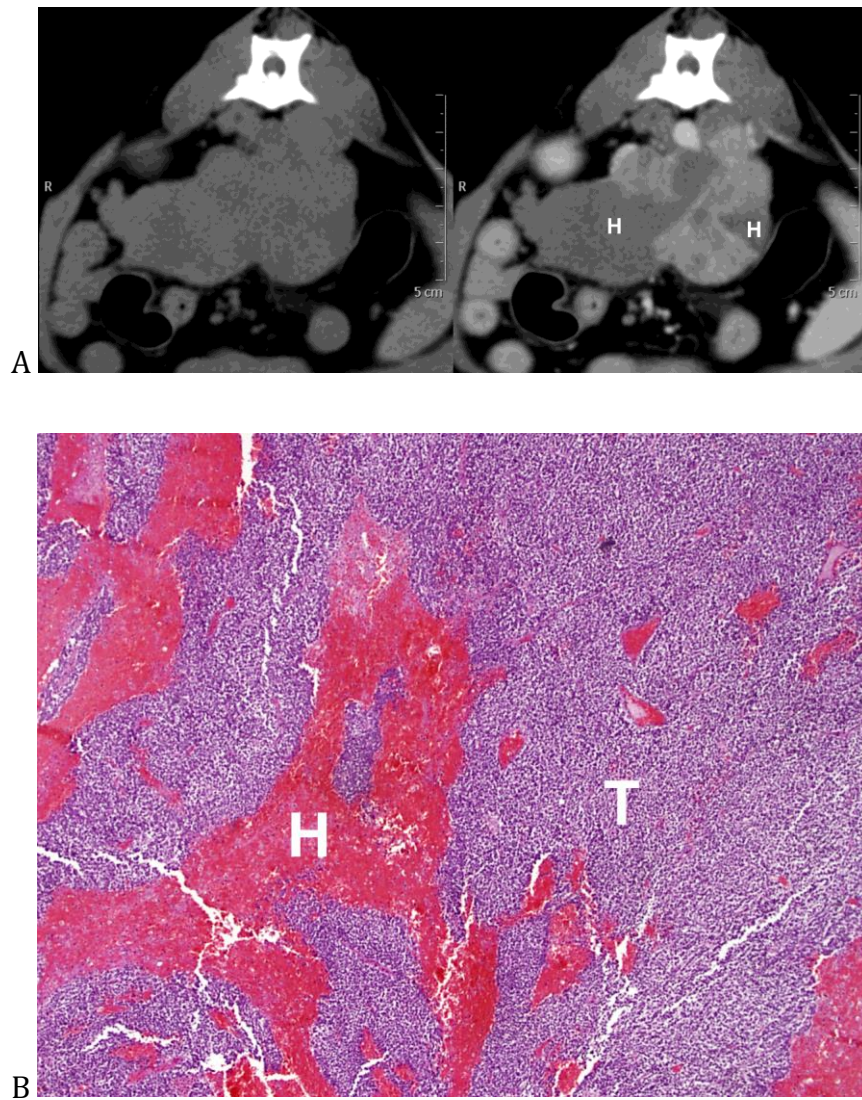


Fig. 3. A) Transverse pre- (left) and post-contrast (right) CT images of a large left adrenal mass. The lesion has faintly heterogeneous attenuation in the pre-contrast image. Several non-contrast enhancing areas representing hemorrhage (H) within the tumor become apparent after contrast administration. B) Corresponding histologic section of the same mass showing irregular areas of hemorrhage (H) within the tumor (T).