P rimary adrenal gland tumors are relatively infrequent in dogs, representing 0.17% to 0.76% of all neoplasias in dogs."Among these, adenoma and adenocarcinoma are the most common, followed by pheochromocytoma, myelolipoma, aldosteronoma, and deoxycorticosterone-secreting and sex hormone-secreting adrenal tumors. Once a diagnosis of an adrenal gland tumor has been established, the choice between medical and surgical treatment must be made. In dogs, medical treatment for cortisol-secreting adrenal gland tumors includes mitotane and trilostane. In patients with pheochromocytoma, medical treatment is suggested in the presence of clinical signs related to excess catecholamine activity, such as tachycardia, arrhythmia, or hypertension, and the use of α- or β-adrenergic receptor antagonists may be considered in these patients. Treatment choices are affected by whether adrenal gland tumors invade adjacent structures, have distant metastases, or both, and adrenalectomy is the treatment of choice when the tumor appears resectable.

Adrenalectomy is associated with a high perioperative mortality rate in dogs, but patients surviving to discharge achieve good long-term outcome with a median survival time > 10 months. Few studies have specifically addressed predictors of outcome in dogs undergoing adrenalectomy. In 1 investigation, it was reported that age, histologic type, and tumor size at diagnosis were not associated with survival time. In another study, the presence of abdominal metastases identified at surgery did not influence outcome, and adrenalectomy with caval thrombectomy did not increase the mortality rate. In 1 study, concurrent nephrectomy was associated with a poor prognosis; thrombocytopenia, high BUN concentration and aspartate transaminase activity, and hypokalemia were associated with poorer outcome.

In humans with primary adrenal adenocarcinoma, the size and weight of the tumor are well documented as negative prognostic factors. In addition, tumor invasion of adjacent organs as well as particularly distant metastases at diagnosis are strongly associated with decreased survival time, and ≤ 12% of patients having adrenal adenocarcinoma with distant metastasis survive > 5 years. Compared with partial resection of the adrenal gland tumor, complete excision leads to a more favorable outcome. With regard to pheochromocytoma in humans, the presence of distant metastases is associated with poor survival time. Surgical excision of the affected gland in patients without metastasis is associated with a 60% survival rate at 5 years.
The purpose of the study reported here was to identify factors predictive of outcome in dogs with a primary adrenal gland tumor undergoing adrenalectomy. The variables evaluated were adrenal gland tumor-related factors including tumor type and size, metastasis, and vein thrombosis as well as surgical factors such as excision of the right or left adrenal gland, additional abdominal surgery, type of surgical access, complications, and duration of surgery. In addition, risk factors associated with metastasis and vein thrombosis were investigated.

Materials and Methods

Dogs—Records from dogs with a primary adrenal gland tumor that was surgically removed between May 2002 and November 2008 at the Clinica Veterinaria Nerviano, Clinica Veterinaria Pirani, and University of Turin Veterinary School Surgical Section were reviewed.

A diagnosis of adrenal-dependent hyperadrenocorticism was made on the basis of identification of nonsuppressed serum cortisol concentration by use of an LDDS test or an appropriately high serum cortisol concentration after ACTH stimulation, together with evidence of a mass at the adrenal gland site on ultrasonography or CT. Results of diagnostic imaging to detect possible abdominal metastasis and thrombosis of abdominal vessels were retrieved. Dogs with an adrenal mass and for which results of LDDS and ACTH tests were within reference limits were suspected to have pheochromocytoma; the results of ECGs and noninvasive determination of systemic blood pressure by means of oscillometry were obtained in these patients. Routine thoracic radiography for tumor staging was performed in each dog. To be included in the study, histologic examination had to confirm the adrenal gland origin of the tumor in all dogs and information regarding follow-up had to be available until death or for at least 90 days after adrenalectomy. Dogs that underwent bilateral adrenalectomy and that had pituitary-dependent hyperadrenocorticism were excluded.

Adrenalectomy—Surgical excision of the adrenal gland was performed by 1 of 3 surgeons (GR, SN, and PB). During induction of general anesthesia, all dogs received a single injection of cefazolin sodium (22 mg/kg [10 mg/lb], IV) as antimicrobial prophylaxis. In dogs with adrenal-dependent hyperadrenocorticism, an injection of dexamethasone (1 mg/kg [0.45 mg/lb], IV) was given to prevent postoperative hyperadrenocorticism. Dogs with suspected pheochromocytoma received the α-adrenergic receptor antagonist drug phenoxybenzamine (0.5 mg/kg [0.23 mg/lb], PO, q 12 h) for 1 to 4 weeks prior to surgery if systolic or diastolic blood pressure was increased, as determined on a preoperative visit.

In all dogs, anesthesia was induced with slow IV injections of fentanyl (2 µg/kg [0.91 µg/lb]) and propofol (4 mg/kg [1.82 mg/lb]) via an IV catheter, followed by maintenance with isoflurane in oxygen after endotracheal intubation. Intraoperative hypotension, if present, was managed by administering IV crystalloid fluids (lactated Ringer’s solution or saline [0.9% NaCl] solution), plasma volume expanders (ie, colloids), or dopamine hydrochloride, according to individual needs.

To expose the adrenal gland tumor, a midline laparotomy was performed, which was combined with a paracostal laparotomy if a right adrenal gland tumor was deeply located or particular complications occurred during surgery (eg, hemorrhage). In dogs with a thrombus confined to the phrenicoadominal vein, adrenalectomy was performed in combination with the removal of the phrenicoadominal vein, which was ligated and divided at its junction with the caudal vena cava. In the instance of tumors associated with caval thrombosis, a Rumel tourniquet was placed around the caudal vena cava just caudal to the liver and proximal to the renal veins and tightened. The thrombus was removed by means of traction after lateral phlebotomy. The vein was sutured closed with 5-0 polypropylene in a continuous pattern before release of the tourniquet. In all patients, the neoplastic adrenal gland was removed via gentle dissection; hemostasis was achieved via manual vessel ligation or application of vascular clips. If the tumor had invaded the kidney or a thrombus had obstructed the renal vein, concurrent nephrectomy was performed. The size of the tumor was measured with caliper on the 3-D axis after adrenalectomy and before fixation for histologic processing. The major axis length (cm) of the tumor was recorded for all patients.

After surgery, as standard care, all dogs were given IV crystalloid fluids, cefazolin (22 mg/kg, IV, q 12 h, 5 to 10 days), and analgesic drugs (fentanyl [4 µg/kg/h, IV] or buprenorphine [10 µg/kg [4.55 µg/lb], IV, q 4 h], progressively tapered and discontinued when dogs did not have signs of abdominal pain on gentle palpation). In the case of adrenal-dependent hyperadrenocorticism, corticosteroids were given. Administration of prednisone (1 mg/kg, PO, q 24 h) was started after the dog began to eat and drink (ie, usually within 24 to 36 hours after surgery). The dosage of prednisone was decreased during the following 4 weeks and administration was then discontinued. In dogs with suspected pheochromocytoma and hypertension, systemic blood pressure was monitored and administration of phenoxycbenzamine was suspended if pressure normalized. In the case of caval thrombectomy, heparin was administered (200 U/kg, 90.9 U/lb, SC, q 8 h for 1 week) to prevent further thrombus formation. Following surgery, owners were advised to have their dog evaluated via thoracic radiography and abdominal ultrasonography every 3 to 4 months in the first year and every 6 to 8 months thereafter. Additional evaluations were performed if clinical condition worsened.

Statistical analysis—Median overall survival time of all dogs undergoing adrenalectomy was calculated with Kaplan-Meier product limit estimates. The following factors were investigated to determine their influence on overall survival time, which was defined as time of surgery to death: sex (male or female), age (<10 or ≥10 years), breed (crossbred or purebred), body weight (≤15 or >15 kg [33 lb]), tumor type (adenoma, adenocarcinoma, pheochromocytoma, or myelolipoma), tumor size defined as major axis length (<5 or ≥5 cm), presence of metastasis (confirmed at histologic analysis), thrombosis of the caudal vena cava or renal vein, right or left adrenalectomy only, adrenalectomy with or without additional abdominal surgery (ie, partial pancreactectomy, hepatic lobectomy, thrombectomy, or nephrectomy), type of surgical access (midline or combined midline and paracostal approach), complications during surgery (ie, bleeding or hypotension), duration of surgery (<90 or ≥90 minutes), and institution where the surgery was performed (Clinica Veterinaria Nerviano, Clinica Veterinaria Pirani, or University of Turin Veterinary School Surgical Section). The influence of these factors was assessed by use of the Kaplan-Meier product limit estimates followed by the log rank test.

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Results

Dogs—Fifty-two dogs satisfied the inclusion criteria and were available for analysis. Sixteen adrenalectomies were performed at the Clinica Veterinaria Pirani, and 13 at the University of Turin Veterinary School Surgical Section. The mean age was 10.6 years (median, 11 years; range, 6 to 17 years). Twenty-six (50%) dogs were < 10 years of age, and 26 (50%) were ≥ 10 years of age. There were 17 (32.7%) sexually intact males, 23 (44.2%) sexually intact females, and 11 (21.2%) spayed females; sex was not recorded for 1 dog. Thirty-eight (73.1%) dogs, was 90 minutes (mean, 84.7 minutes; range, 40 to 180 minutes); in 30 (65.2%) dogs, surgery lasted ≥ 90 minutes, the median time to discharge was 3 days (mean, 3.8 days; range, 2 to 5 days).

Histologic findings—Twenty-five (48.2%) adrenal gland tumors were adenomas, 18 (34.6%) were adenocarcinomas, 7 (13.4%) were pheochromocytomas, and 2 (3.8%) were metastatic nodules.

Figure 1—Kaplan-Meier curve of survival time for 52 dogs with an adrenal gland tumor that underwent adrenalectomy.

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were myelolipomas; 1 dog with an adenoma had results of LDDS and ACTH stimulation tests within reference limits. Of the 6 thrombi removed, 4 were associated with adenocarcinomas and 1 each with a pheochromocytoma or an adenoma of the adrenal gland. The nodules of the excised liver lobe (n = 3), pancreas (2), and kidney (2) were tumoral (6 adenocarcinoma and 1 pheochromocytoma).

Outcome—Median survival time for the 52 dogs undergoing adrenalectomy, calculated with Kaplan-Meier product limit estimates, was 953 days (range, 0 to 1,941 days; Figure 1). At the time of the study, 25 (48.1%) dogs were alive and in good clinical condition (ie, laboratory or ultrasonographic evidence of relapse was absent), without detectable lung or abdominal metastasis, and 27 (51.9%) had died. One dog died intraoperatively because of nonresponsive hypotension, and 7 died during the first 10 days after surgery. Causes of death included pulmonary thromboembolism (n = 3 dogs; 2 with adenocarcinoma with concomitant caval thrombosis and 1 with adenoma) that was confirmed on necropsy; acute pancreatitis (1), cardiac arrest following a hypertensive crisis associated with pheochromocytoma (1), or unknown reasons (2).

Following discharge, 6 additional dogs died of diffuse metastasis in the liver (n = 5) or in the liver and pancreas (1). The 5 dogs with hepatic metastasis had a median survival time of 70 days (mean, 121 days; range, 1 to 365 days), and the dog with hepatic and pancreatic metastasis had a survival time of 192 days. Among the remaining 13 dogs, 2 died of a mammary gland carcinoma and 1 each died of an oral tumor, sepsis, and leishmaniasis; the cause of death was unknown in 8 dogs.

A necropsy was performed in 19 dogs. Metastasis of the excised adrenal gland tumor was documented in 7 dogs: 4 in the liver (in 2 dogs with recurrence at death), 1 in the liver and kidney, 1 in the pancreas and liver (in 1 dog that received liver lobectomy during surgery), and 1 in the pancreas. At necropsy, 6 of the 7 metastatic adrenal gland tumors were adenocarcinomas and 1 was a pheochromocytoma.

Analysis of prognostic factors—Several adrenal gland tumor–related factors were associated with survival time at univariate analysis (P < 0.10). Survival time was shorter for dogs that had an adenocarcinoma (median survival time, 360 days; mean, 200 days; range, 0 to 910 days), tumor major axis length ≥ 5 cm (median survival time, 156 days; mean, 338 days; range, 1 to 1,279 days), metastasis (median survival time, 120 days; mean, 108 days; range, 1 to 192 days), or vein thrombosis (median survival time, 2.5 days; mean, 173 days; range, 1 to 981 days). Among factors related to surgery, a shorter survival time was observed in dogs undergoing adrenalectomy along with an additional abdominal surgical procedure (median survival time, 120 days; mean, 142 days; range, 0 to 910 days). Median survival time of dogs without these factors was not calculated because > 50% of the animals survived or died of another disease by the end of the study. Survival time was not as-
associated with sex, age, breed, body weight, side of adrenalec-
tomy, type of surgical access, duration of surgery, and
institution performing the surgery. The analysis was not
performed for complications during surgery because of the
low number of dogs that developed complications.

In the multivariate analysis, the size of the tumor and
the presence of metastasis or vein thrombosis were of
prognostic importance (Figure 2). In particular, an adrenal
gland tumor with major axis length ≥ 5 cm was associated
with 85% shorter survival time (HR, 7.57; 95% CI, 1.67
to 34.48; \( P = 0.009 \)), the presence of metastasis with 93%
shorter survival time (HR, 27.78; 95% CI, 2.18 to 166.67;
\( P = 0.010 \)), and vein thrombosis with 90% shorter survival
time (HR, 13.16; 95% CI, 1.97 to 90.91; \( P = 0.008 \)). Tumor
type and adrenalectomy with or without additional abdom-
inal surgeries were not associated with survival time. With
regard to tumor type, the multivariate model was repeated,
including adenoma, pheochromocytoma, and myelolipoma
in a single category, because an effect was observed only for
adenocarcinoma at univariate analysis. Regardless of the
model, adenocarcinoma was not predictive of survival time
in the multivariate analysis.

Analysis of factors associated with metastasis and vein
thrombosis—The presence of metastasis was significantly
(\( P = 0.01 \)) associated with adenocarcinoma but not with tu-
mor size (\( P = 0.60 \)) or origin (\( P = 0.44 \)), the presence of vein
thrombosis was significantly (\( P = 0.02 \)) associated with adre-
nal gland tumors with major axis length ≥ 5 cm, but not with
histologic type (\( P = 0.17 \)) or primary origin (\( P = 0.69 \)).

Discussion

In the present study, dogs with an adrenal gland tumor
with major axis length ≥ 5 cm, documented metastasis, or
vein thrombosis had a poorer prognosis. More frequent
metastasis was noted in dogs with adenocarcinoma and
more frequent vein thrombosis if adrenal gland tumors
were ≥ 5 cm in length. Although adrenalectomy is gen-
erally considered a surgical procedure with an uncertain
prognosis, dogs in the present study had a median survival
time of 953 days (range, 0 to 1,941), with 65% surviving > 1
year following surgery. The intraoperative mortality rate
was very low, with only 1 of 52 (1.9%) dogs dying dur-
ing surgery; perioperative mortality rate was relatively low,
with an additional 7 (13.5%) dogs dying during the first
10 days after surgery. A prior study\(^{15}\) on adrenalectomy
in dogs reported a perioperative mortality rate of approxi-
mately 60%, including 28% of dogs euthanatized during
surgery. Perioperative mortality rate was lower in later in-
vestigations; van Sluijs et al\(^{15}\) and Barthez et al\(^{11}\) reported
perioperative mortality rates of < 30%, and Anderson et al\(^{11}\)
reported a perioperative mortality rate < 20%. A peri-
operative mortality rate of approximately 20% was more
recently reported by Kyles et al\(^{15}\) and Schwartz et al.\(^{16}\)

To date, few studies\(^{14,15}\) have explored the prognos-
tic factors in dogs with adrenal gland tumors. In the pres-
ent study of dogs with primary adrenal neoplasia that
underwent adrenalectomy, size of the excised tumor and
the presence of metastasis or vein thrombosis at diagno-
sis were found to be predictive of outcome. In particular,
dogs with adrenal gland tumors with major axis length
≥ 5 cm had significantly shorter survival times than did
dogs with smaller tumors. Median survival time of dogs
with larger adrenal gland masses was 156 days. These re-
results are in agreement with findings in humans, in which
it has been shown that adrenal gland tumors with major
axis length > 4 cm are more likely to be malignant and
associated with a poor outcome.\(^{20,25,26}\) Previous studies\(^{14,16}\)
in dogs did not identify a prognostic value for adrenal
tumor size. However, in 1 report,\(^{19}\) dogs had relatively
small adrenal gland tumors, with the largest being 2 to 3
cm, whereas in the present study, 10 dogs had tumors ≥ 5
cm. In another study,\(^{16}\) adrenal gland tumors in dogs had
a mean size of 8.5 cm, calculated by adding the 3 spatial
measurements; thus, most of these tumors were likely to
have major axis length < 5 cm.

As in humans,\(^{19}\) dogs with detectable metastasis at
the time of surgery (7/52 [13.5%]) in the present study
had a poorer outcome. Survival time (median, 120 days;
range 1 to 941 days) in dogs with metastasis was reduced
by > 90%. The role of metastasis has not yet been inves-
tigated in dogs with adrenal gland tumors because of the
low documented rate of metastasis. In 1 study,\(^{16}\) only 2 of
40 dogs had histologically confirmed metastases, located
in the omentum in both patients. In 2 other reports,\(^{14,15}\)
none of 21 dogs with adrenal gland tumors had detectable
metastases at surgery\(^{14}\) and only 4 of 40 dogs had meta-
stasis at diagnosis (3 in the liver and 1 in the ovary).\(^{15}\)
In the series of 40 dogs,\(^{15}\) adrenal gland adenocarcinoma
had the highest rate of metastases at diagnosis. Similarly,
in the present study, 6 of the 7 patients with tumors with
metastasis to abdominal organs had adenocarcinomas at
surgery, and 1 of the 7 tumors was a pheochromocytoma.
These results may suggest a relatively high metastatic
rate for adenocarcinoma, compared with other adrenal
gland tumors, as described in humans.\(^{10,20,27}\)

With regard to localization of detectable metastases,
all dogs with tumor spread in the present study had
involvement of abdominal organs. The liver was most com-
monly affected (n = 3), followed by the pancreas (2) or
kidneys (2). On the basis of results of thoracic radiogra-
phy, lung metastasis was not identified in any dog. These
results reflect previous reports\(^{14,16}\) in dogs with adrenal
gland tumors, in which lung metastasis was not diagnosed
in any of the affected animals on initial examination.

In the present study, multivariate analysis did not pro-
vide evidence of an association between histologic type of
the adrenal gland tumor and survival time. Survival time
of dogs with adenocarcinoma was comparable to that of dogs
with adenoma, pheochromocytoma, and myelolipoma,
despite being more likely to yield metastasis, which was
associated with a poor survival time. However, 12 of the
18 dogs with adenocarcinoma had no evidence of tumor
spread, either to abdominal organs or the lungs. Human
patients with stage 3 or 4 adrenal adenocarcinoma (ie, a pri-
mary tumor with local or distant metastasis) have a poorer
prognosis than do human patients without metastasis.\(^{20}\)

Dogs with thrombosis had significantly shorter sur-

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In the present study, an association was demonstrated between vein thrombosis and large adrenal gland tumors. Vein thrombosis has been identified more often in dogs with pheochromocytomas or right-sided adrenal gland tumors, although the effect of size was not known. Four of 10 tumors with tumor major axis length ≥ 5 cm were associated with caval or phrenicoadominal vein thrombosis in the present study, whereas only 2 of 35 (5.7%) dogs with small tumors had a detectable thrombus. Moreover, of the 6 tumors with concomitant thrombosis, 4 were adenocarcinomas, 1 was a pheochromocytoma, and 1 was an adenoma. No association was found between thrombosis and histologic type or size of tumor origin, likely because of the low number of patients.

In contrast to tumor size and presence of metastasis or vein thrombosis, neither histologic type nor adrenalectomy with or without an additional surgery was associated with survival time in multivariate analysis in the present study. However, performing other surgical procedures at the time of adrenalectomy reduced survival time in dogs in a prior report. There were some limitations to the present study. The retrospective nature of the investigation resulted in incomplete clinical data in some instances. In addition, the group was heterogeneous and consisted of animals with various histologic types of adrenal gland tumors or that were scheduled for additional surgical procedures. Analyzing subgroups of dogs with homogeneous characteristics might have revealed more precise information regarding outcome of specific tumors or surgical techniques. However, by creating more homogeneous subgroups, the number of cases would have been substantially reduced, thereby precluding reliable analysis. Our results are nonetheless reflective of a routine clinical situation.

Measurement of adrenal gland masses was performed with a caliper after removal of the tumor in each patient, which may not closely reflect measurements made on preoperative diagnostic images. Studies need to be performed to address correlations between measurements obtained by these 2 methods. In the present study, to reduce bias attributable to inaccuracy of measurements, size of adrenal gland masses was used in the analysis as a dichotomous variable instead of on a continuous scale. It cannot be excluded that tumors with a size close to the cutoff value of 5 cm for the time of adrenalectomy reduced survival time in dogs in a prior report.

There were some limitations to the present study. The retrospective nature of the investigation resulted in incomplete clinical data in some instances. In addition, the group was heterogeneous and consisted of animals with various histologic types of adrenal gland tumors or that were scheduled for additional surgical procedures. Analyzing subgroups of dogs with homogeneous characteristics might have revealed more precise information regarding outcome of specific tumors or surgical techniques. However, by creating more homogeneous subgroups, the number of cases would have been substantially reduced, thereby precluding reliable analysis. Our results are nonetheless reflective of a routine clinical situation.

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References