

Case Report

Volume 7 Issue 5 - September 2024
DOI: 10.19080/IJCSMB.2024.07.555725

Int J cell Sci & mol biol

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Computed Tomography for Diagnosing Canine Adrenal Gland Pheochromocytoma



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Submission: August 08, 2024; **Published:** September 24, 2024

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Abstract

Computed tomography (CT) is a useful, and sensitive technique to plan surgical and pharmacological interventions for the management of an adrenal mass in canines. In the current study, we reported the incidence of canine Pheochromocytoma in a black, spayed female, miniature, Pinscher aged 11 years and 4 months utilizing ultrasonography, computed tomography, as well as, confirmation of the case with histopathology. CT findings displayed distinct hyperplasia with an increased diameter of the cranial pole on the transverse plane. The dog showed no symptoms of adrenal disease; however, we suspected an adrenal mass without vascular invasion based on the CT images. The mass was surgically removed, further diagnosed as pheochromocytoma using histopathology, and treated with 0.5 mg, 0.3 mg, and 0.15 mg/kg prednisolone. This study aimed to clinically characterize the pathological findings through CT examination of the adrenal glands to make a preoperative diagnosis followed by confirmation through histopathological examination. This comprehensive approach is crucial for developing effective protocols for the surgical and pharmacological management of canine adrenal neoplasms that may otherwise go undetected.

Keywords: Adrenal glands; Canine; Computed tomography (CT) evaluation; Pheochromocytoma.

Introduction

Primary neoplasms of adrenal glands are not common in dogs, representing 0.17% - 0.76% of all tumors in dogs [1]. Adenoma and adenocarcinoma are the most common types among adrenal gland primary neoplasia, followed by pheochromocytoma [2], myelolipoma [3], aldosteronoma [4] and deoxycorticosterone-secreting [5] and sex hormone-secreting adrenal tumors [6]. Tumors that arise from chromaffin cells of adrenal medulla are called pheochromocytomas which are often found incidentally in dogs, and they result in excessive releasing of catecholamines

[7,8]. Excessive production of epinephrine or nor-epinephrine causes unspecific potentially fatal symptoms [9]. More than 50% of canine pheochromocytomas are identified during the investigation of concurrent comorbidities or during necropsy examination. Treatment is primarily surgical, followed by adjuvant therapy, such as prednisolone (PDS) and anti-cancer agents. Preoperative diagnosis of the adrenal tumors using useful imaging methods, such as ultrasonography and CT, is essential for surgical planning and treatment. CT is highly sensitive and specific in diagnosing adjacent vascular invasion either surgery or not. A previous report

of pheochromocytoma in a rhinoceros documented increased serum epinephrine and norepinephrine and histologic changes in the medullary portion of the adrenal gland, which had symptoms consistent with those of systemic hypertension [10]. The ultimate goal is to contribute to the development of effective protocols for the surgical and pharmacological management of adrenal neoplasms in dogs, ultimately improving patient outcomes and prognosis.

Case Description

A black, spayed female, miniature, Pinscher aged 11 years and 4 months was presented to a local animal hospital with a history of respiratory distress and anorexia. Initially, we recorded the temperature, pulse, and respiration (TPR), and conducted a general examination of the patient.

The first tentative diagnosis was recurrent pulmonary pneumonia following which the animal was immediately admitted into the intensive care unit and treated with fluids; hepatoprotective agents, such as glutathione (Tathion Inj., DongA ST, Korea) and hepamelz (Hepa-Merz Inj., Hanwha Pharmacy, Korea); amino acids (Saeronamin Inj., Daehan Drug Industry, Korea); vitamin B and C complex (Pan-B-Comp Inj., Daehan Drug Industry, Korea); antibiotics (amoxicillin clavulanate (Clamoxin Inj., Shinpoong Pharmacy, Korea); Metronidazole (Metrynal Inj., Daehan Drug Industry, Korea)), vitamin K (Jaeil Bio, Korea), Tranexamic acid (Tranexamic Acid Inj., Shinpoong Pharmacy, Korea), dihydrocodeine as a pain killer (Codening Tab., Jongkeun Dang, Korea).

The dog underwent clinical chemistry examination, ultrasonography of abdominal organs, and a CT scan to evaluate the adrenal gland's tumor mass. Subsequently, the tumor mass was surgically removed, and histopathology was performed to determine the type of neoplasm. The animal owner provided consent for utilization of scientific data yielded by study of the case and publication of the data. Initially, a complete blood count (CBC) was performed including measurement of mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), hematocrit (HCT), hemoglobin, mean platelet volume (MPV), total red blood cell (RBC) count, and total white blood cell (WBC) count. Additionally, bicarbonate (CHCO_3), which is an indicator of blood pH, was measured in blood along with potassium (K^+), and chloride (Cl^-). Moreover, Inflammatory biomarkers such as total neutrophil and monocyte counts, as well as c-reactive protein (cCRP-P) levels, were also assessed. Total protein, blood urea nitrogen (BUN), globulin, alkaline phosphatase (ALP), and alanine transaminase (ALT) were also measured. Skeletal muscle oxygen saturation StO_2 and procalcitonin were further measured in blood. Both basal and stimulated blood cortisol concentrations were measured to exclude adrenal cortex abnormality because of immediate surgery. However, further analysis of catecholamines, which is the first-line assessment for adrenal medulla neoplasia,

was not performed in this case [11].

Ultrasound images measured the left adrenal gland of the patient in ventral dorsal recumbency [12]. Electronic calipers measuring the length and thickness of the cranial and caudal poles of the adrenal gland were displayed in the sagittal plane. Electronic calipers measuring the thickness and width of the caudal pole of the adrenal gland were displayed in the transverse plane. Furthermore, staging of the rest of the abdomen was performed on the same occasion, including a portion of the uterine horn, a remnant of the left ovary, adrenal gland mass, liver, spleen, and other peritoneal cavity organs. This staging was conducted to check for primary and secondary metastasis and determine the next steps in treatment. CT imaging was referred to for further evaluation and planning of the treatment.

Triple-phase abdominal CT scans were performed on ventral recumbency. General anesthesia was induced with propofol (Provide 1 % w/v, Lot #, AOD0558, Baxter pharmaceuticals, India), which was intravenously infused at around 7 mg/kg and maintained with isoflurane (1.5 %–2 %) in 100 % oxygen (2 L/min). The scanning parameters were as follows: 2.0-mm thick slices, 120 kVp, 150 mAs, 0.688 collimator pitch, and 0.75 s/rotation. Thoracic and abdominal reconstructions with a dorsal and sagittal reconstruction interval of 0.5–1 mm was performed. The contrast medium (X-ray contrast medium concentration, Ominipaque, 300 mgI/mL, GE Healthcare, Sanghai, Co., LTD, Sanghai, 201203, China) was administered at a dose of 900 mgI/kg by cephalic vein with power injector. The injection speed was 3 mL/s. Precontrast (before the injection of contrast medium) and postcontrast (arterial phase, ~20s; portal phase, ~40s; delayed phase, ~120s after the start of injecting the contrast medium) were performed. The CT attenuation values were recorded in Hounsfield unit (HU), and circular regions of interest (ROI) 30 mm² in size were transversely placed on the adrenal mass. The same ROI was copied and placed in the same area of images obtained, before contrast administration, and phased CT images were collected. The enhancement wash (AP-PRE) and washout measurements (AP-VP, AP-DP, and VP-DP) were also calculated. Contrast enhancement was classified into slight (< 60 HU), moderate (> 60 HU), and marked (> 100 HU). Few cases of pheochromocytoma did not show micro- and macrovascular invasions and very low tumor grade. Some cases of pheochromocytoma have been reported to exhibit no micro- or macrovascular invasions and demonstrate a very low tumor grade [8].

We observed a single enlarged adrenal gland on the right side without metastasis into other organs or caudal vena cava (CVC) invasion and attempted to remove it. Before surgical removal and induction of anesthesia, ketamine was infused into the cephalic vein as a pain reliever, and the preanesthetic and anesthetic drugs included propofol and isoflurane, respectively. Cefazoline was used as the antibiotic. The left ovary, a uterine horn remnant ~5 cm in size posterior to the bladder were also removed during the

surgery. The right adrenal gland was surgically removed after ligating the caudal vena cava [13]. For histopathological evaluation, 4-10µm-thick sections of formalin-fixed paraffin-embedded specimens of canine pheochromocytoma were obtained, stained with hematoxylin and eosin, and evaluated using light microscopy [14]. Based on blood chemistry, blood inflammatory markers (cCRP-P), mean platelet value [MPV], and procalcitonin (PCT) were initially and consistently elevated, reaching as high as 93.8.

The basal and stimulated cortisol levels were within the normal limits before (2.3–4.5 units ug/dL) and after (2.7–17 units ug/dL) surgery excluding adrenocortical neoplasia.

On ultrasonography, the patient showed a remnant of the right uterine horn and left ovary, along with the presence of nodules in the left 4th mammary gland and the right 5th mammary gland (data not shown). The diameter of the right side of the adrenal gland measured 1.02 x 0.9 cm (Figure 1).

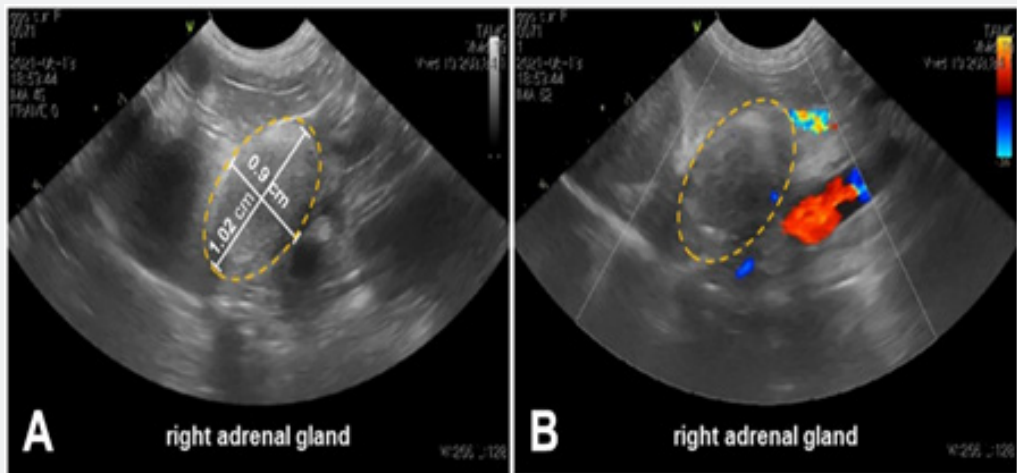


Figure 1: Ultrasonography of the canine right adrenal gland. (A) Ultrasonography of the canine right adrenal gland visualized for right-side mass (Dotted Oval Circle) and (B) Doppler for blood flow in this case.

Transverse, dorsal, and sagittal postcontrast CT images showed a heterogenous dense nodule on the right adrenal gland in the central portion of the tumor without invasion of the CVC and abdominal organs (Figure 2). Nodules in the right 4th and right 5th mammary gland were found without significant reaction of lymph nodes and metastasis. Hepatic and splenic low dense nodules were also observed. Bronchial dilatation and impaction with mucus were also observed. Aorta and CVC diameters were (4.88 × 5.14 mm) and (5.91 × 6.17) respectively. CVC/aorta ratio was around 1.2 (Figure 2). The (CVC/Ao ratio) is a measurement utilized to

assess fluid responsiveness in dogs, particularly in cases of heart failure. It also serves as a predictor of anemia and hypertension. The HU value was 18 HU/0.30 cm² for pheochromocytoma based on precontract CT images in the present study. The enhancement washin (AP-PRE, 13 HU) and washout measurement (AP-VP [54 HU], AP-DP [68 HU], and VP-DP [14 HU]) were also calculated. The mean arterial, portal, and delayed phases were 52.3 HU, 103 HU, and 93.4 HU, respectively. The CT attenuation values were shown in Table 1.

Table 1: Attenuation values for soft tissue window. (HU, Hounsfield Unit).

Canine organs	BEFORE PHASE	ARTERIAL PHASE	PORTAL PHASE	DELAYED PHASE (HU)/0.30cm ²
	(HU)/0.30cm ²	(HU)/0.30cm ²	(HU)/0.30cm ²	
Adrenal gland	18	31	85	99
Liver	74	66	84	114
Kidney	51	267	271	224
Spleen	78	69	87	96
Lung	-898	-925	-900	-900
Mammary gland	15	18	61	104
Urinary bladder	22	25	33	27
Muscle	47	56	45	70

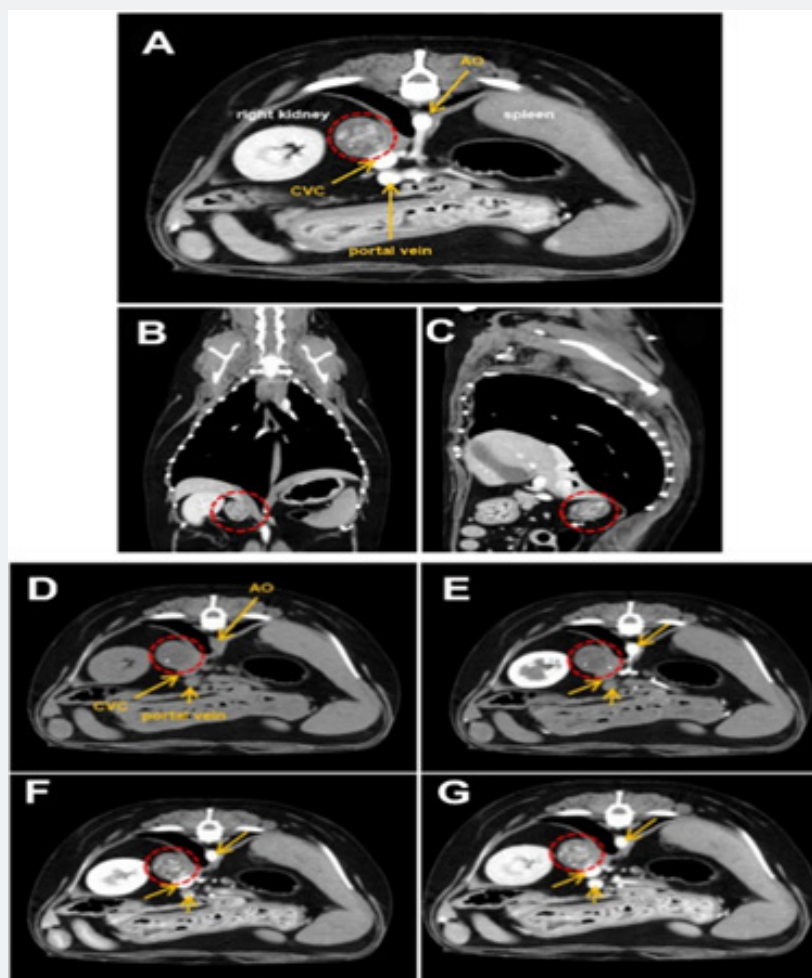


Figure 2: Portal phase of soft tissue window for transverse (A), dorsal (B) and sagittal (C) computed tomography. * Triple-phase thoracic abdominal computed tomography. (D) Prephase, (E) Arterial phase, (F) Portal Phase, (G) Delayed Phase, displaying right side adrenal gland highlighted with Dotted Circle at the soft tissues window; Bronchial dilation with mucous impaction at the delayed phase of lung window.

Before right adrenalectomy, phenoxybenzamine (0.2–1.5 mg/kg twice daily) was administered to minimize catecholamine release. Before anesthesia, ketamine was infused into the cephalic vein as a pain reliever, and paraneesthesia included propofol while anesthesia included isoflurane. The antibiotic used was cefazoline. The left ovary was removed, and a remnant of uterine horn ~5 cm in size was found posterior to the bladder and removed. The right-side adrenal gland was surgically removed after the ligation of blood vessels. After inpatient care, the dog was given basic antibiotics, fluids, antiemetics, hepatic protection agents, and prednisolone. Histopathological examination revealed hyper vasculitis and myxoid degeneration in the cytoplasm, finely granular eosinophilic cytoplasm, round-to-oval nuclei with prominent nucleoli, cytologic pleomorphism of tumor cells, nesting, elongated and prominent nucleoli, neoplastic cells' palisading arrangement around the necrotic tissue, hemorrhages around blood vessels and pocketing patterns surrounded by

an adjacent layer of sustentacular cells and a thin layer of fibrovascular stroma. No mitotic figures were identified. Minimal anisocytosis and anisokaryosis were present (Figure 3).

Postoperative care included the administration of prednisolone as adjuvant treatment. Follow-up of the animal's health status showed a normal life without any signs of adrenal gland-derived neoplasm.

Discussion

In the current study, we presented the employment of CT scan in the diagnosis of pheochromocytoma that was discovered incidentally in a dog that has been suffering from respiratory distress and anorexia. The CT findings were correlated with ultrasonography and histopathology findings after resection of the tumor. CT is now routinely used in referral practices for the preoperative assessment of canines with adrenal masses because it is considered more accurate than abdominal ultrasonography

in detecting vascular invasion [15]. Therefore, triple-phase CT values assist in preoperative differential diagnosis and give essential information for surgical planning for treating canine adrenal tumors. In this case, we positioned the animal in the

sternal recumbency posture, then we minimized any influence and achieved better transverse planes, which is more efficient to evaluate right adrenal mass for monitoring.

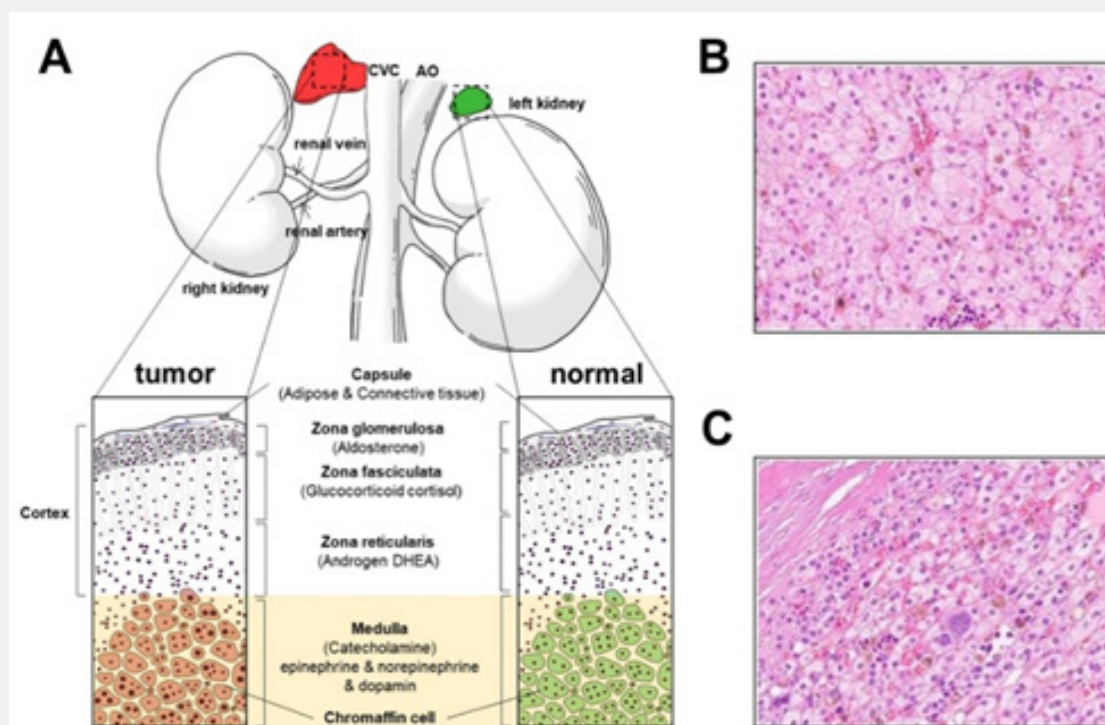


Figure 3: Schematic diagram of the canine adrenal gland with histopathological findings. (A) Schematic anatomic diagram of the patient. (B), and (C) Microscopical description of right adrenal gland medulla-derived tumors, showing hyper-neovascularization, myxoid changes, pleomorphism of tumor cells, and elongated palisading arrangement around the necrotic tissues.

According to CT Test, Aorta and CVC diameters were (4.88×5.14 mm) and (5.91×6.17) respectively. CVC/aorta index was around 1.2 suggesting presence of cardiac muscle dysfunction that may result in hypertension (Figure 3). The clinical use of CVC dilation as an indicator of right heart abnormalities may be limited by individual variability and physiologic factors, including the phase of respiration, pleural pressure, phase of the cardiac cycle, and volume. Click or tap here to enter text [16]. In addition, the CVC/aorta index may be a predictor of body fluid status in emergency departments, especially in patients with heart failure. The mean CVC/Aorta index of healthy dogs (1–6 months) and aged dogs (> 6 months) was between 0.87 and 0.93 [17]. In the current study, the HU value for pheochromocytoma based on precontrast CT images was measured as 18 HU/0.30 cm². The enhancement wash (AP-PRE, 13 HU) and washout measurement (AP-VP [54 HU], AP-DP [68 HU], and VP-DP [14 HU]) were also calculated. The attenuation values of different organs were presented in Table 1.

In our case, the mean HU values of the adrenal mass were found to be compared to those previously reported [18–20]. Along with this, the adrenal mass exhibited heterogeneous enhancement patterns, suggesting the presence of hemorrhage,

necrosis, or infarction within the tumor. Moreover, we observed multiple pathological changes including; mammary adenoma, left remnant ovary, right-side uterine horn, perivaginal lipoma, splenic and hepatic multiple nodules, which were benign as suspected, and lung window, which exhibited bronchiectasis with mucous impaction. The remnant of the uterine horn and left-side remnant ovary may cause recurrence of stump pyometra, requiring removal. The spleen and hepatic nodules were not clinically significant. A severe grade of bronchiectasis was observed, which may contribute to respiratory diseases and necessitate further monitoring. Pheochromocytomas appear to be more likely to invade adjacent vessels than adrenocortical adenoma and adrenal carcinoma. Pheochromocytomas were locally invasive in 39 % of affected dogs and produced metastases in 13 % of the cases [21]. However, in this case, no lymph node reactions or lymphatic and blood vessel invasions were observed. Blood tests may also help in ruling in or out a functional tumor of the adrenal cortex (hyperadrenocorticism) and medulla. Notably, in our case the basal and stimulated cortisol levels were within the normal limits before (2.3–4.5 units ug/dL) and after (2.7–17 units ug/dL) surgery. Unfortunately, one of the limitations of the present

study was the absence of catecholamine blood measurements. Cytological diagnosis of neuroendocrine tumors is difficult to perform and is not reliable in distinguishing benign from malignant neuroendocrine neoplasia. Furthermore, potentially severe and even fatal side effects, such as pain, hemorrhage, and severe hypertensive crisis due to a sudden release of catecholamines, could arise in the event of a catecholamine producing tumor being sampled; Although recently FNA of adrenal gland medulla is safer [22]. Immunohistochemistry including chromogranin A and synaptophysin may help further in the diagnosis of pheochromocytoma when the histopathology is not definitive, however, that was not performed in our case.

Furthermore, CT values for preoperative assessment are critical for surgical planning of canine adrenal tumors. Positive prognostic factors of pheochromocytoma reported for canine are complete resection, absence of metastatic disease, tumor under 3 cm size, absence of comorbidities, phenoxybenzamine administration, and no or limited invasion into adjacent organs [23]. Preoperative management of adrenocortical and adrenomedullary canine tumors usually varies because of the secretion of different hormones from these tumor types. Additionally, in the case of nonfunctional adrenal tumors with normal preoperative catecholamine levels, tachycardia, arrhythmia, hypertension, and cardiac arrest may suddenly occur during the surgery processing. Regardless of tumor origin, adrenalectomy is the treatment of choice for a primary tumor. During the preoperative stage, phenoxybenzamine was administered as an irreversible alpha-blocker and anti-hypertensive agent due to its efficacy in reducing the vasoconstriction caused by epinephrine and norepinephrine by forming a permanent covalent bond with adrenergic receptors, which causes vasodilation [18]. This medication lowers the mortality rate during the surgery.

Toceranib phosphate is a tyrosine kinase (TKI) available in veterinary medicine that is molecularly similar to sunitinib; it blocks the same key receptor associated with angiogenesis [24]. Thus, it may be a good treatment option for animals suffering from advanced inoperable tumors, similar to human pheochromocytomas that cannot be surgically managed. This case has been noted on well recovered patient without any side effects and hormonal changes, so furthermore, we followed regular check without any clinical abnormal signs observed at this point. Therefore, the standard care protocol of adrenal gland abnormality might be surgical resection, which often results in a normal life span; however, 10%–30% of animals will develop distant metastases, and 6.5 %–16 % will develop recurrence [25,26].

In conclusion, these steps can be valuable in preparing patients with pheochromocytoma for surgery. However, further studies with a larger number of cases are required to assess the effectiveness of standardized therapy protocols.

Acknowledgement

This research was funded by the Academic Research Fund of Hoeso University in 2022-2023 (20220341001).

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DOI: [10.19080/IJCSMB.2024.07.555725](https://doi.org/10.19080/IJCSMB.2024.07.555725)

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