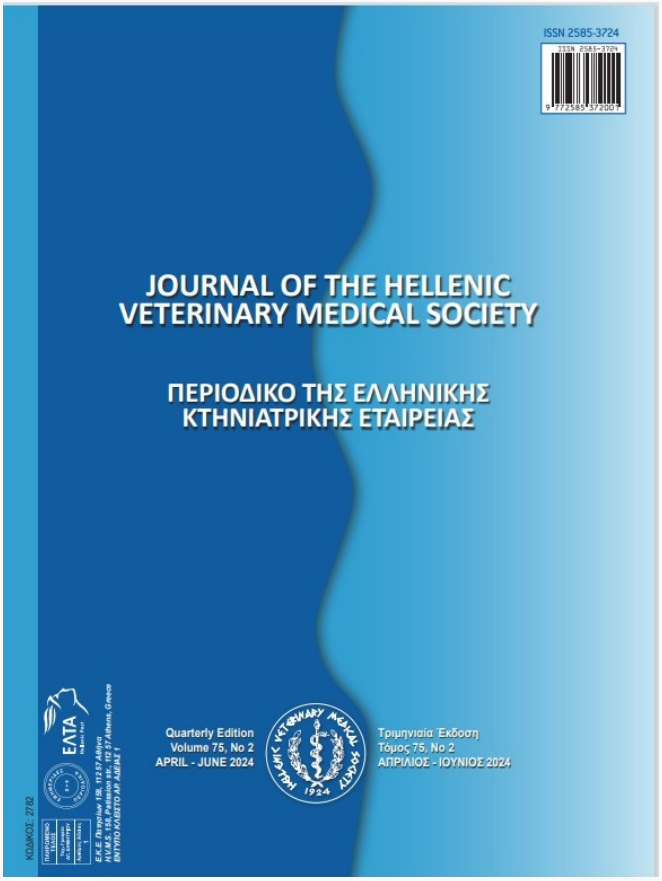
Journal of the Hellenic Veterinary Medical Society

Vol 75, No 2 (2024)



A Case of Canine Renal Cell Carcinoma: an Immunohistochemical Approach

M Usta, A Ayaz, F İlhan, M Karaman, H Özen

doi: 10.12681/jhvms.32370

To cite this article:

Usta, M., Ayaz, A., İlhan, F., Karaman, M., & Özen, H. (2024). A Case of Canine Renal Cell Carcinoma: an Immunohistochemical Approach. *Journal of the Hellenic Veterinary Medical Society*, *75*(2), 7267–7272. https://doi.org/10.12681/jhvms.32370 (Original work published July 10, 2024)

J HELLENIC VET MED SOC 2024, 75 (2): 7621-7626
ΠΕΚΕ 2024, 75 (2): 7621-7626

Case report
Κλινικό περιστατικό

A Case of Canine Renal Cell Carcinoma: An Immunohistochemical Approach

M. Usta[1], A. Ayaz[2], F. İlhan[3], M. Karaman[4], H. Özen[5]*

[1]*Department of Pathology, Faculty of Veterinary Medicine, Balıkesir University, Balıkesir, Türkiye*

[2]*Institute of Medical Sciences, Balıkesir University, Balıkesir, Türkiye*

[3]*Department of Pathology, Faculty of Veterinary Medicine, Balıkesir University, Balıkesir, Türkiye*

[4]*Department of Pathology, Faculty of Veterinary Medicine, Balıkesir University, Balıkesir, Türkiye*

[5]*Department of Pathology, Faculty of Veterinary Medicine, Balıkesir University, Balıkesir, Türkiye*

ABSTRACT: Canine Renal Cell Carcinoma (Canine RCC) is a primary renal tumor in dogs. No definitive immunohistochemical marker for this tumor is yet defined in veterinary medicine. In this case presentation, a Canine RCC detected in an 8-year-old intact male Golden Retriever was described and suitability of RCC-PN15 mouse monoclonal antibody as a diagnostic marker for this tumor was investigated. The primary tumor mass was in the right kidney and there were metastases in liver, spleen, lung, and the left kidney. Solid, tubular, and papillary subtypes of Canine RCC were noted in the primary tumor mass. In immunohistochemical staining for RCC-PN15, weak to strong immunoreactivities were observed in the primary and metastatic nodules. In this case report, RCC-PN15 was shown to be successfully used in diagnosis of Canine RCC.

Keywords: *Canine RCC; RCC-PN15; PAX-8; CD10; histopathology.*

Corresponding Author:
Hasan Özen Department of Pathology, Faculty of Veterinary Medicine, Balıkesir University, Balıkesir, Türkiye
E-mail address: hasanozen@hotmail.com

Date of initial submission: 14-12-2022
Date of acceptance: 19-11-2023

INTRODUCTION

Canine renal cell carcinoma (Canine RCC) is the most common primary renal neoplasm arising from epithelial cells of the nephron in dogs (Peat et al., 2017). Primary renal neoplasms are reported to consist of 0.3 to 1.5% of all canine neoplasms, and 49-65% of these neoplasms are estimated to be Canine RCC (Carvalho et al., 2017; Edmondson et al., 2015). Canine RCC are classified according to histologic (papillary, tubular, solid, and cystic type) or cytologic (chromophobic, eosinophilic, and clear cell type) subtypes. Although these tumors can be subdivided into histologic and cytologic subtypes, different subtypes can coexist in some cases (Meuten & Meuten, 2016; Nielsen et al., 1976). This case report aims to describe the gross and histopathologic characteristics of Canine RCC detected in an 8-year-old dog as well as immunohistochemical features giving special emphasis to RCC-PN15, which was previously not described in Canine RCC.

CASE HISTORY

An 8-year-old intact male Golden Retriever with no previous clinical sings was presented for necropsy purposes to the Department of Pathology, Faculty of Veterinary Medicine, Balıkesir University. On necropsy, the dog was in normal body condition. A gray-white firm mass sizing 10x12x15 cm in diameters located at the cranial pole of right kidney was seen (Figure 1A). The cut surface of the tumor mass included a necrotic center surrounded by irregularly shaped reddish to dark brown foci (Figure 1B). There were also multiple soft gray-white nodules 1-2 cm in diameter on the liver (Figure 1C) and the spleen (Figure 1D) and gray-white miliary nodules on the caudal lobes of the lungs (Figure 1E) and the left kidney. There was no macroscopic finding in the other abdominal and thoracic organs and regional lymph nodes. Based on the macroscopic features, it was considered that the primary mass originated from the renal tissue, and the nodules in the lung, liver, and spleen were metastatic lesions.

Tissue samples from the mass and the organs were collected and fixed in 10% neutral buffered formalin. After the fixation, the samples were routinely processed and stained with Hematoxylin and Eosin (HE) for histopathological evaluation. Immunohistochemistry was performed using BenchMark Ultra Stainer (Roche). Primary antibodies used against the following antigens were Renal Cell Carcinoma (clone PN15, prediluted; Cell Marquer, Roche), PAX8 (clone MRQ-50, prediluted; Cell Marquer, Roche) and CD10 (clone SP67, prediluted; Ventane, Roche). The sections were evaluated under a light microscope.

Histopathologic patterns of the primary renal mass and metastatic nodules were indicated in Table 1. The primary renal mass was partially demarcated and showed infiltrative growth to the adjacent normal renal tissue. All three forms of the primary tumor mass had poor stroma. Neoplastic cells in the solid subtype of the primary tumor mass were mostly not organized in a specific pattern or occasionally showed loosely formed short sheets. Approximately 70-80% of the solid areas of the primary renal mass were composed of cuboidal to columnar cells with granular, lightly

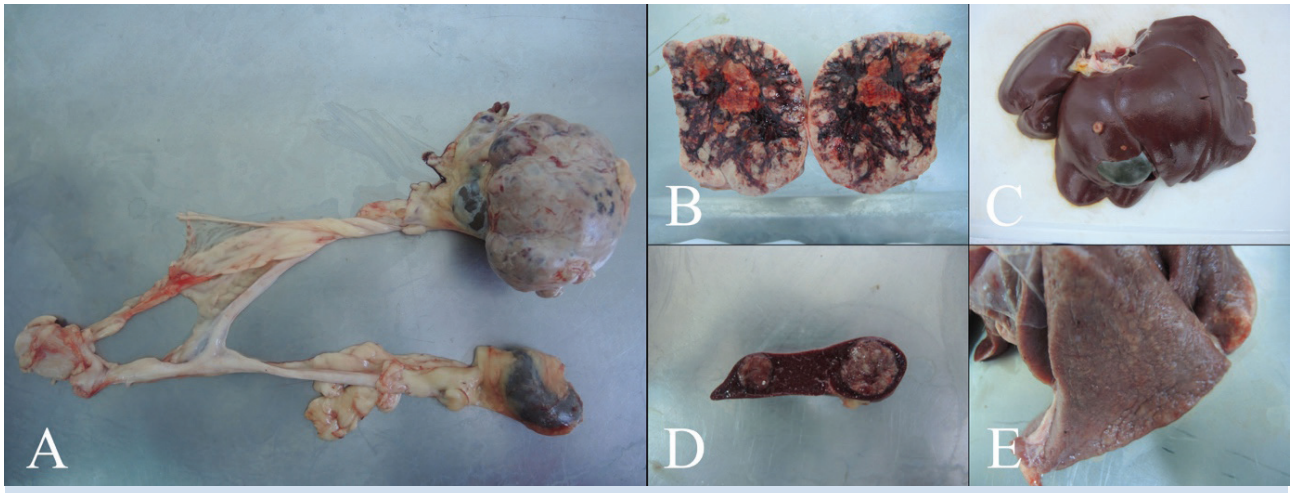


Figure 1. (A) A gray-white mass sizing 10x12x15 cm in diameters located at the cranial pole of the right kidney, (B) cut surface of the primary tumor; a necrotic center surrounded by irregularly shaped reddish to dark brown foci, (C) the liver; gray to white nodules on the right medial lobe, (D) the spleen; irregularly shaped reddish to dark brown nodules, (E) the lung; gray to white miliary nodules on the caudal lobes.

Table 1. Histologic subtypes of the tumor tissues.

Tissue	Histologic subtypes
Primary tumor mass	Papillary - Tubular - Solid
Liver nodule	Solid
Spleen nodule	Papillary - Tubular
Pulmonary nodule	Solid
Left kidney nodule	Solid

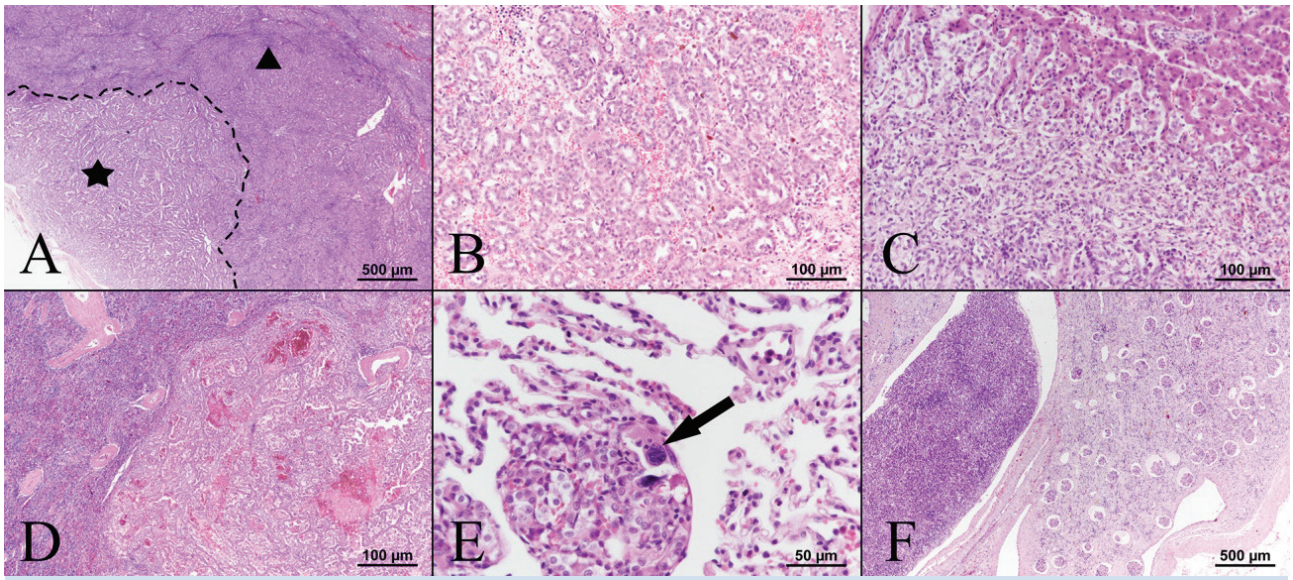


Figure 2. Microscopic view of the primary tumor and the metastases. (A) Right kidney; solid (triangle) and papillary (star) subtypes of renal cell carcinoma, (B) tubular subtypes of renal cell carcinoma in the kidney, (C) the liver; center of nodules had areas of sarcomatous differentiation and periphery had light eosinophilic cytoplasm and uniform central nuclei, (D) the spleen; fibrovascular stroma lined up by cuboidal epithelium, (E) the lung; tumor cells clustered in a small nest and a bizarre nucleated giant cell (arrow), (F) the left kidney, intravascular metastasis, glomerular atrophy and interstitial fibrosis. HE

to intensely eosinophilic, having abundant cytoplasm with distinct cell borders. The nuclei of the tumor cells in these solid areas were round to ovoid and the nucleoli were prominent and eosinophilic. Papillary areas of the primary renal mass lined up on a thin stroma and formed finger-like projections (Figure 2A). Tumor cells in the papillary areas were large pleomorphic cuboidal cells with prominent nucleoli. Tumor cells in the tubular areas had also pleomorphic nuclei and eosinophilic cytoplasm and were lined up in a single row around the lumen (Figure 2B). The mitotic index was high according to the scale given by Edmondson et al. (2015). Adjacent to the primary tumor mass in renal tissue were observed glomerular atrophy, interstitial fibrosis, necrosis, and hemorrhages. Metastatic nodules in the liver were finely demarcated and showed invasion into the normal tissue (Figure 2C). The center of the nodules had areas of sarcomatous differentiation and cuboidal cells with pleomorphic nuclei and eosinophilic cytoplasm in irregular pattern. Cells in the periphery of the nodules had light eosinophilic cytoplasm and uniform central nuclei. Metastatic nodules in the spleen had well demarcated fibrous capsule and showed no invasion (Figure 2D). The metastatic nodules were composed of branching fibrovascular stroma lined by cuboidal epithelium. The pulmonary nodules were also composed of tumor cells clustered in small nests. In some of the pulmonary nodules, bizarre nucleated giant cells were seen (Figure 2E). In the left renal sections, intravascular metastasis, glomerular atrophy, interstitial fibrosis, and hemorrhage were noted (Figure 2F). In immunohistochemical staining for PAX8, CD10 and RCC, tumor cells showed positive immunoreactivities for all the antibodies tested. Expression profiles of these antibodies in different histologic subtypes were indicated in Table 2. In the tubular subtype, RCC-PN15 immunoreactivity was intracytoplasmic and strongly observed in neoplastic cells located in where stroma is abundant. In other areas, neoplastic cells also showed immunoreactivity against RCC-PN15 antibody, yet the immunoreactivity was weak (Figure 3A). In the solid subtype, no specific staining pattern was observed for RCC-PN15. Some neoplastic cells

Table 2. Immunohistochemical expression profiles of PAX-8, CD-10 and RCC in different histologic subtypes of the Canine RCC.

Histologic subtype	PAX-8 (clone MRQ-50)	CD-10 (clone SP67)	RCC (clone PN15)
Solid	+++	+++	+++
Papillary	++	++	+
Tubular	+++	+	+++

(- negative, + weak, ++ moderate, +++ strong)

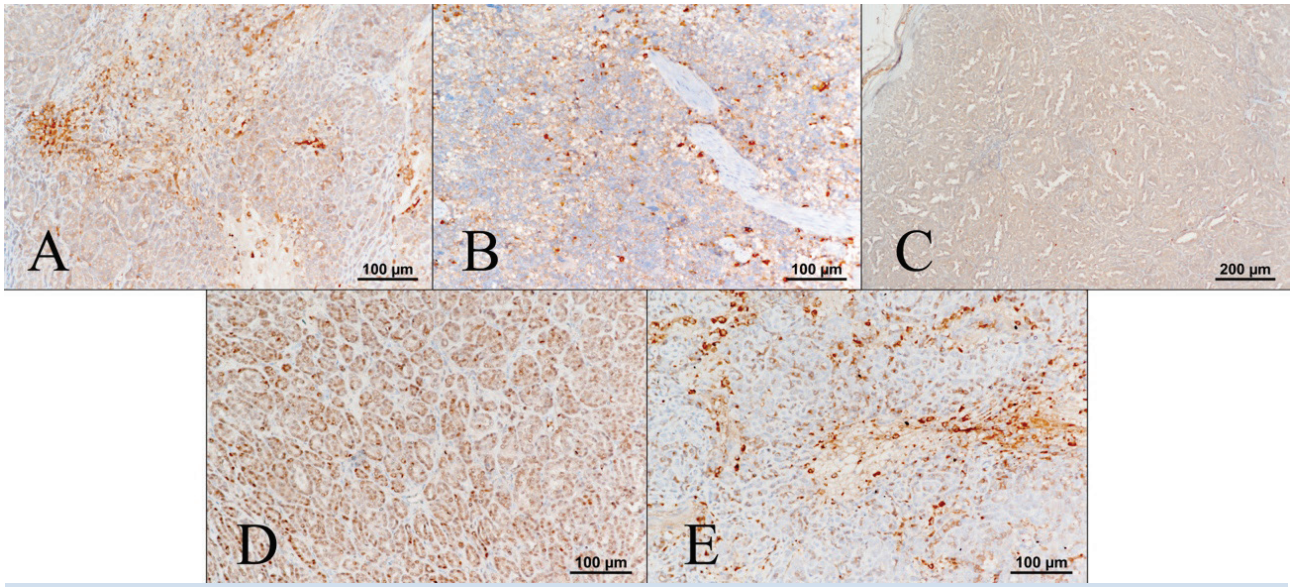


Figure 3. Microscopic view of the immunohistochemistry. (A) RCC-PN15; strong immunoreactivity in the tubular subtype of the primary tumor nodule in the right kidney, (B) RCC-PN15; strong immunoreactivity in the solid subtype of the primary tumor nodule, (C) RCC-PN15; weak immunoreactivity in the papillary subtype of the primary tumor nodule, (D) PAX-8; strong immunoreactivity in the primary tumor nodule, (E) CD-10; strong immunoreactivity in the primary tumor nodule.

in the solid subtype showed strong immunoreactivity while others had weak to moderate immunoreactivity (Figure 3B). In the papillary subtype, all neoplastic cells revealed weak intracytoplasmic RCC-PN15 expression (Figure 3C). PAX8 immunoreactivity was intracytoplasmic and showed moderate to strong immunostaining in neoplastic cells in all subtypes (Figure 3D). CD10 immunoreactivity was also intracytoplasmic and weak to strong in subtypes of the tumor (Figure 3E). Based on the histomorphological patterns and the findings of immunohistochemical investigation, the case was diagnosed as Canine RCC.

DISCUSSION

A variety of cells in nephron can cause different tumor types in renal tissue. Canine RCC is a renal tumor arising from the nephron (Gil da Costa et al., 2011). In Canine RCC, histologically papillary, tubular, solid, and cystic subtypes and cytologically chromophobic, eosinophilic, and clear cell types were described. These histologic subtypes may be of uniform pattern, but more than one histologic pattern can be found in different areas of the same tumor (Edmondson et al., 2015b; Meuten & Meuten, 2016). Similarly, in the current case, solid, tubular, and papillary patterns were observed in some areas of the primary tumor. It was also noted papillary and tubular patterns in spleen metastases, solid pattern in lung, liver, and the left kidney metastases. In mix types of Canine RCC, mostly two subtypes were described (Gil da Costa et al., 2011; Peat et al., 2017). In one case three subtypes, solid, tubular, and papillary, were also seen in an 8-years old male terrier dog (Birdane et al., 2004). Similarly, in the present case, three different subtypes were noted. Although Canine RCC are subdivided into histologic and cytologic subtypes, there is no information about their biological behavior in dogs (Woldemeskel, 2013).

Canine RCC is more common in middle-aged dogs. The age range of affected dogs varies from 3 to 15 years, with an average age of 7.1 years (Lucke & Kelly, 1976). Male dogs appear to be affected more frequently than females, but there is no breed predi-

lection (Woldemeskel, 2013). In our case, the dog was an 8-year-old male, which was consistent with the literature. Canine RCC frequently metastases, usually targeting lungs, opposite kidney, regional lymph node, bones, liver, spleen, skin, and serosal surfaces (Carvalho et al., 2011; Carvalho et al., 2017). In this case, the sites of metastases were seen in liver, spleen, lung, and the other kidney.

In the Human RCC, the most significant prognostic factor is the histologic grading (Edmondson et al., 2015). The 4-tiered Fuhrman Grading System for renal cell carcinoma is the most widely used grading method (Delahunt et al., 2019). The Fuhrman Grading System is based on the assessment of the uniformity of nuclear size, nuclear shape, and nucleolar prominence (Fuhrman et al., 1982). However, its scarce interobserver reproducibility, has pushed the International Society of Urological Pathology (ISUP) to propose a new grading system (ISUP grading). Fuhrman Grading System has been replaced by the new ISUP grading which has been implemented in the latest version of the WHO "blue book" on urogenital tumors. ISUP grading is 4-tiered, like The Fuhrman Grading System (Delahunt et al., 2019). According to the Edmondson, The Fuhrman Grading System had similar success in predicting outcome for the dogs which corroborates the notion that human and canine renal cell carcinoma are similar (Edmondson et al., 2015). We used ISUP grading to evaluate Canine RCC. In this case, there were nuclear pleomorphism and giant cells in lung metastasis, and sarcomatoid differentiation in liver metastasis, similar with ISUP Grade-4 definition.

Although Canine RCC is the most common type among primary renal tumors, there is no definitive immunohistochemical marker (Peat et al., 2017). In cases where the primary tumor mass is in the kidney, the diagnosis of Canine RCCs is usually easy on HE stained sections. However, it may be difficult to distinguish kidney metastases originated from other epithelial tissues, to confirm metastatic Canine RCC in other organs, and to find the primary one in the presence of more than one epithelial tumor (Meuten & Meuten, 2016; Peat et al., 2017). In Canine RCC, PAX8 was indicated to be more sensitive than CD10 and Napsin A in immunohistochemical diagnosis (Peat et al., 2017). In addition to these markers, RCC (Clone PN15) is also frequently used in Human RCC (Inamura, 2017; Shen et al., 2012; Truong & Shen, 2011). In this case, diagnosis of Canine RCC was also confirmed by PAX8 and CD10. In addition, RCC (Clone PN15) was investigated in the current case, and positive immune reactivity was seen in all histologic patterns (papillary, tubular, and solid).

In this presentation, a case of Canine RCC was described histopathologically and immunohistochemically. In human, RCC antibody sensitivity and specificity were reported to be 72-79.7% and 79-98%, respectively (Bakshi et al., 2007; McGregor et al., 2001). Since in this preliminary study a single case was evaluated for RCC antibody and there is no previous study present in dogs, the sensitivity and specificity of RCC antibody in dogs further needs to be investigated. Additionally, RCC-PN15 mouse monoclonal antibody is considered as a useful tool to confirm diagnosis of Canine RCC when used in combination with previously used markers.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

Bakshi, N., Kunju, L.P., Giordano, T., Shah, R.B. (2007). Expression of renal cell carcinoma antigen (RCC) in renal epithelial and nonrenal tumors: diagnostic implications. Applied Immunohistochemistry & Molecular Morphology, 15(3), 310-315.

Birdane, F.M., Hatipoğlu F., Ortatatlı, M., Koç, Y., Turgut, K. (2004). Renal cell carcinoma in a dog: Pathologic and cytologic findings. Revue de Medecine Veterinaire. 155(4), 212-216.

Carvalho, P.H., Conceicão, L.G., Barros, M.S., Moreira, J.C.L.M., Amorim, R.L., Pinczowski, P. (2011). Renal cell carcinoma with cutaneous metastasis in a dog. Brazilian Journal of Veterinary Pathology. 4(2), 132-137.

Carvalho, S., Stoll, A.L., Priestnall, Ş.L., Suarez-Bonnet, A., Rassnick, K., Lynch, S., Schoepper, I., Romanelli, G., Buracco, P., Atherton, M., De Merlo, E.M., Lara-Garcia, A. (2017). Retrospective evaluation of COX-2 expression, histological and clinical factors as prognostic indicators in dogs with renal cell carcinomas undergoing nephrectomy. Veterinary and Comparative Oncology. 15(4), 1280-1294.

Delahunt, B., Eble, J.N., Egevad, L., Samaratunga, H. (2019). Grading of renal cell carcinoma. Histopathology. 74(1), 4-17.

Edmondson, E.F., Hess, A.M., Powers, B.E. (2015). Prognostic significance of histologic features in canine renal cell carcinomas: 70 nephrectomies. Veterinary Pathology. 52(2), 260-268.

Fuhrman, S.A., Lasky, L.C., Limas, C. (1982). Prognostic significance of morphologic parameters in renal cell carcinoma. The American Journal of Surgical Pathology. 6(7), 655-663.

Gil Da Costa, R.M., Oliveira, J.P., Saraiva, A.L., Seixas, F., Faria, F., Gärtner, F., Pires, M.A., Lopes, C. (2011). Immunohistochemical characterization of 13 canine renal cell carcinomas. Veterinary Pathology. 48(2), 427-432.

Inamura, K. (2017). Renal cell tumors: Understanding their molecular pathological epidemiology and the 2016 WHO classification. International Journal of Molecular Sciences. 18(10), 15-20.

Lucke, V.M. & Kelly, D.F. (1976). Renal carcinoma in the dog. Veterinary Pathology. 13(4), 264-276.

McGregor, D.K., Khurana, K.K., Cao, C., Tsao, C.C., Ayala, G., Krishnan, B., Truong, L.D. (2001). Diagnosing primary and metastatic renal cell carcinoma: The use of the monoclonal antibody renal cell carcinoma marker. The American Journal of Surgical Pathology, 25(12), 1485-1492.

Meuten, D.J. & Meuten, T.L.K. (2016). Tumors of the Urinary System. In D. J. Meuten (Ed.), Tumors in Domestic Animals. 4th ed., John Wiley & Sons, Iowa, p 632-688.

Nielsen, S.W., Mackey, L.J., Misdorp, W. (1976). Tumors of the kidney. Bull. World Health Organ. 53(2-3), 237-245.

Peat, T.J., Edmondson, E.F., Miller, M.A., Dusold, D.M., Ramos-Vara, J.A. (2017). Pax8, Napsin A, and CD10 as immunohistochemical markers of canine renal cell carcinoma. Veterinary Pathology. 54(4), 588-594.

Shen, S.S., Truong, L.D., Scarpelli, M., Lopez-Beltran, A. (2012). Role of immunohistochemistry in diagnosing renal neoplasms when is it really useful? Archives of Pathology & Laboratory Medicine. 136(4), 410-417.

Truong, L.D. & Shen, S.S. (2011). Immunohistochemical diagnosis of renal neoplasms. Archives of Pathology & Laboratory Medicine. 135(1), 92-109.

Woldemeskel, M. (2013). Renal cell carcinoma in humans and animals: A brief literature review. Journal of Clinical & Experimental Pathology 03(02), 1-7.