Primary Renal Neoplasia of Dogs

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Background: Primary renal tumors are diagnosed uncommonly in dogs.

Hypothesis: Signs and survival will differ among different categories of primary renal tumors.

Animals: Data were collected from the medical records of 82 dogs with primary renal tumors diagnosed by examination of tissue obtained by ultrasound-guided biopsy, needle aspiration, surgery, or at postmortem examination.

Methods: This was a multi-institutional, retrospective study.

Results: Forty-nine dogs had carcinomas, 28 had sarcomas, and 5 had nephroblastomas. The dogs were geriatric (mean 8.1 years; range: 1–17) with a weight of 24.9 kg (range: 4.5–80). Tumors occurred with equal frequency in each kidney with 4% occurring bilaterally. Initial signs included one or more of hematuria, inappetance, lethargy, weight loss, or a palpable abdominal mass. Pain was reported more frequently in dogs with sarcomas (5/28). The most common hematologic abnormalities were neutrophilia (22/63), anemia (21/64), and thrombocytopenia (6/68). Polycythemia was present in 3 dogs and resolved with treatment. Hematuria (28/49), pyuria (26/49), proteinuria (24/50), and isosthenuria (20/56) were the most frequently observed abnormalities on urinalysis. Pulmonary metastases were noted on thoracic radiographs in 16% of dogs at diagnosis. Seventy-seven percent of dogs had metastatic disease at the time of death. Median survival for dogs with carcinomas was 16 months (range 0–59 months), for dogs with sarcomas 9 months (range 0–70 months), and for dogs with nephroblastomas 6 months (range 0–6 months).

Conclusions and Clinical Importance: Primary renal tumors in dogs are generally highly malignant with surgery being the only treatment that improves survival.

Key words: Canine; Carcinoma; Kidney; Nephroblastoma; Sarcoma.

Primary renal tumors are diagnosed uncommonly in dogs. Tumors can arise from the renal epithelium, renal mesenchyme, or from embryonal tissue of mixed origin. Previous published case series have examined primarily carcinomas with very few dogs with sarcomas or nephroblastomas reported. Renal lymphoma has been reported, but it is difficult to determine whether these represent primary or multicentric disease. Affect ed animals are typically middle-aged or older at diagnosis with mean ages of 7.1–8.8 years reported for carcinomas and 8.8 and 8.0 years for sarcomas and nephroblastomas, respectively. Male-to-female ratios of 1.8:1 and 1.6:1 have been reported for dogs with primary renal carcinomas. This is similar to the 1.5:1 ratio reported for humans. Although no breed predispositions have been identified for renal neoplasia, a syndrome of nodular dermatofibrosis associated with renal cystadenocarcinoma has been identified in German Shepherd dogs. No previous article has examined the effect of adjuvant chemotherapy on renal tumors, and surgery is the only reported therapeutic option. Response of human renal cell carcinoma to chemotherapy has been disappointing, with the combinations of gemcitabine and 5-fluorouracil or tamoxifen and vinblastine showing the most promise. Immunotherapy using interleukin-2 and interferon- remains the mainstay of treatment for this disease in people. The purpose of this study was to further characterize the clinical signs, laboratory findings, diagnostic imaging results, histopathologic diagnoses, and the effect of treatment on survival in dogs with primary renal tumors.

Materials and Methods

The medical databases of the veterinary teaching hospitals at the University of Missouri-Columbia, Animal Cancer Center at Colorado State University, Auburn University, the University of Pennsylvania, the Donaldson-Atwood Cancer Clinic of the Animal Medical Center, Florida Veterinary Specialists, Rowley Memorial Animal Hospital, Pacific Veterinary Specialists, as well as the databases of the Veterinary Medical Diagnostic Laboratory of the University of Missouri-Columbia and the Vet Cancer Registry were searched for cases of canine primary renal neoplasia. Cases were included if they were diagnosed by examination of tissue obtained by biopsy, needle aspiration, or postmortem examination, and did not have evidence of an alternative primary site. Cases with the diagnosis of lymphoma were excluded as it is very difficult to definitively demonstrate that the disease has arisen primarily in the kidney. Data regarding the breed, sex, age, weight, diagnosis, presenting complaint, results of complete blood count (CBC), serum chemistry profile, urinalysis, thoracic and abdominal radiographs, and ultrasound, method of diagnosis, location and laterality of tumor, type of treatment, survival time, outcome, and the presence or absence of metastasis at diagnosis or death was collected. Survival time was defined as the time from presentation...
for treatment until death because of the tumor or euthanasia. Histopathology review was performed by one pathologist (SET) in all cases for which samples were available (n = 29). Cases without complete information were included for descriptive purposes, but excluded from categorical variable and survival analysis.

Statistical analyses were performed using Chi-squared test or the Fisher’s exact test for categorical variables and the Wilcoxon log-rank test for survival analysis using commercial software. One-way analysis of variance or Kruskal-Wallis one-way analysis of variance on ranks was used to compare nonparametric integral data. Comparisons were made between presenting complaint, CBC, serum chemistry, or urinalysis results and diagnosis or category of neoplasia to assess for significant association. Comparisons were also made between survival and diagnosis, category of disease, and whether or not the animal was treated with surgery or received chemotherapy. Animals were censored for survival analysis at the point of last contact if they died or were euthanized because of other causes or were lost to follow-up. Differences were considered to be of statistical significance at \( P \leq .05 \).

## Results

Eighty-two dogs with primary renal neoplasia between 1986 and 2002 were identified. Forty-nine dogs had carcinoma including renal carcinoma (n = 16), transitional cell carcinoma (n = 9), tubular adenocarcinoma (n = 7), tubular and papillary adenocarcinoma (n = 6), renal adenocarcinoma (n = 5), renal tubular carcinoma (n = 4), clear cell renal carcinoma (n = 1), and papillary cystadenocarcinoma (n = 1) (Table 1).

Two-eight dogs had sarcoma including hemangiosarcoma (n = 12), renal sarcoma (n = 7), leiomyosarcoma (n = 4), malignant fibrous histiocytoma (n = 3), spindle cell sarcoma (n = 1), and fibroleiomyosarcoma (n = 1).

Five dogs had nephroblastoma. Histologic examination of archival tissue was performed in 29 cases including 13 carcinomas, 13 sarcomas, and 3 nephroblastomas. Cases that had not been examined by immunohistochemistry were stained with smooth muscle actin for leiomyosarcomas, cytokeratin to rule out carcinoma for undifferentiated sarcomas, Factor VIII for hemangiosarcoma, and vimentin in the mesenchymal population and cytokeratin in the epithelial populations of nephroblas-

### Table 1. Demographic and clinical characteristics of dogs with renal cancer.

<table>
<thead>
<tr>
<th></th>
<th>Carcinoma</th>
<th>Sarcoma</th>
<th>Nephroblastoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases in series</td>
<td>49</td>
<td>28</td>
<td>5</td>
</tr>
<tr>
<td>Age (mean, range)</td>
<td>8.4 (2–15)</td>
<td>8.2 (1–17)</td>
<td>5.2 (1–12)</td>
</tr>
<tr>
<td>Sexa</td>
<td>MI: 7</td>
<td>MI: 0</td>
<td>MI: 2</td>
</tr>
<tr>
<td></td>
<td>MC: 19</td>
<td>MC: 9</td>
<td>MC: 1</td>
</tr>
<tr>
<td></td>
<td>FI: 5</td>
<td>FI: 1</td>
<td>FI: 0</td>
</tr>
<tr>
<td></td>
<td>FS: 17</td>
<td>FS: 18</td>
<td>FS: 2</td>
</tr>
<tr>
<td>Weight (kg) (mean, range)</td>
<td>25.2 (4.5–80)</td>
<td>23.6 (5–80)</td>
<td>40.4 (9.3–53)</td>
</tr>
<tr>
<td>Laterality</td>
<td>Right: 23</td>
<td>Right:11</td>
<td>Right: 1</td>
</tr>
<tr>
<td></td>
<td>Left: 23</td>
<td>Left: 17</td>
<td>Left: 4</td>
</tr>
<tr>
<td></td>
<td>Bilateral: 3</td>
<td>Bilateral: 0</td>
<td>Bilateral: 0</td>
</tr>
<tr>
<td>Metastasis at diagnosis</td>
<td>6/34</td>
<td>3/21</td>
<td>1/5</td>
</tr>
<tr>
<td>Metastasis at death</td>
<td>20/29</td>
<td>14/16</td>
<td>3/4</td>
</tr>
<tr>
<td>Survival (median, range)</td>
<td>16 months (0–59 months)</td>
<td>9 months (0–70 months)</td>
<td>6 months (0–6 months)</td>
</tr>
</tbody>
</table>

MI, intact male; MC, castrated male; FI, intact female; FS, spayed female.

aSex of one dog was not recorded.

### Common Songs

- Hematuria in 32% (26/82) of dogs; a palpable abdominal mass in

- Malamute
- Labrador Retriever (n = 7), Golden Retriever (n = 1),
- Rottweiler (n = 5), Golden Retriever (n = 5), German Shepherd (n = 3), Miniature Poodle (n = 3), Malamute (n = 2), Springer Spaniel (n = 2), Shetland Sheepdog (n = 2), Boxer (n = 2), and 1 each of Great Dane, Collie, Bernese Mountain Dog, Greyhound, Blue-Tick Hound, Siberian Husky, Standard Poodle, Belgian Sheepdog, Puli, Chow Chow, Border Collie, Pointer, Old English Sheepdog, Beagle, Shih Tzu, Jack Russell Terrier, Lhasa Apso, West Highland White Terrier, Cavalier King Charles Spaniel, Miniature Schnauzer, Chesapeake Bay Terrier, Airedale Terrier, Boston Terrier, Basset Hound, Pomeranian, and Standard Schnauzer.

Common signs reported by the owners were: hematuria in 32% (26/82) of dogs; a palpable abdominal mass in the abdomen.
20% (16/82); polydipsia or polyuria in 10% (8/82); inappetance (27%; 22/82); lethargy (26%; 21/82); weight loss (20%; 16/82); vomiting (13%; 11/82); pain (7%; 6/82); and behavior changes (5%; 4/82). Pain was recorded as the presenting complaint for 6 dogs, and was significantly associated with a diagnosis of sarcoma (P = .016).

Changes recorded in hematologic examinations were nonspecific. Abnormalities were noted in 51 of 70 dogs (73%). Differential white cell counts, platelet count, or red cell parameters were not recorded for all evaluations. Neutrophilia was the most common change and was present in 22 of 63 (35%) ranging from 13,000 cells/µL to 266,500 cells/µL. Four dogs had neutrophil counts >30,000 cells/µL (46,800–266,500 cells/µL). Hematologic abnormalities included: anemia in 21 of 64 dogs (33%); leukocytosis (20%; 13/64); lymphopenia (9%; 6/63); thrombocytopenia (9%; 6/68); and monocytosis (6%; 4/63). Polycythemia was present in 3 dogs, all with carcinomas and which survived 7.5–32 months.

Abnormalities in serum chemistry values were minor and nonspecific. Serum chemistry results were normal in 16 of 65 (25%) recorded results. High serum alkaline phosphatase (ALP) was present in 21 of 65 dogs (22%). Blood urea nitrogen (BUN) was high in 14 of 65 dogs (22%), and serum creatinine was high in 13 of 65 (20%). Serum alanine aminotransferase (15%; 10/65), aspartate aminotransferase (9%; 6/65), cholesterol (6%; 4/65), phosphorous (10%; 6/64), γ-glutaryl transferase (9%; 6/64), and globulins (5% 3/62) were also high. Serum albumin concentration was decreased in 12 of 63 dogs (19%) with a statistically significant association with a diagnosis of sarcoma compared to carcinoma or nephroblastoma (P = .043).

Abnormalities were commonly identified by urinalysis. Twenty-eight of 49 dogs (57%) had hematuria and 26 of 49 dogs (53%) had pyuria. Proteinuria was reported in 24 of 50 dogs (48%). Isosthenuria was present in 20 of 63 dogs (32%). Thirty-three of 82 dogs (36%) did not have a urinalysis recorded.

Results of thoracic radiographs were recorded for 61 dogs with 10 dogs (16%) having evidence of metastasis at diagnosis. Of these dogs, 6 had carcinomas, 3 had sarcomas, and 1 had a nephroblastoma. A further 37 dogs (61%) had metastasis identified at the time of death. Twenty of these dogs had carcinomas, 14 had sarcomas, and 3 had nephroblastomas. Data were available documenting metastatic status at death for 49 dogs, yielding an overall metastatic rate of 69% (21/30) for carcinomas, 88% (13/15) for sarcomas, and 75% (3/4) for nephroblastomas. Abdominal radiograph results were recorded for 37 dogs. A mass was identified on radiographs in 33 of these dogs (89%). Abdominal ultrasound results were recorded for 55 dogs with a renal mass identified in 51 of these dogs (93%). Suspected metastatic lesions were identified by ultrasound in the contralateral kidney (n = 1), spleen (n = 1), and liver (n = 2) in 4 dogs.

Of 73 dogs for which the information was available, 7 had other neoplastic diseases in addition to the renal tumor. These included a soft-tissue sarcoma (grade I), insulinoma, plasma cell tumor, adrenocortical carcino-

ma, mammary carcinoma, anaplastic sarcoma, and 1 dog with renal hemangiosarcoma had concurrent leiomyosarcoma, leiomyoma, melanoma, ameloblastoma, and interstitial carcinoma.

There was no statistical difference among survival times by diagnosis (P = .788) (Table 1, Fig 1). Sixty-eight of 82 dogs underwent surgery. Median survival for all dogs undergoing surgery, regardless of tumor type, was 16 months (range, 0–70 months), compared to <1 month (range, 0–32 months) for dogs not undergoing surgery (P < .001). Chemotherapy was administered to 23 dogs, 21 of which had a previous nephrectomy. In dogs with renal carcinoma, 13 received a doxorubicin-based protocol, alone or in combination with cyclophosphamide, carboplatin, mitoxantrone, paclitaxel, or prednisone. An additional 3 dogs with renal carcinoma received protocols of carboplatin, mitoxantrone and piroxicam, or carprofen alone. In dogs with renal sarcoma, 3 dogs received a doxorubicin-based protocol, alone or with doxycycline, vincristine, or cyclophosphamide. In the same group, 1 dog each received mitoxantrone and carboplatin. For dogs with an antemortem diagnosis, median survival time without chemotherapy was 7.5 months (range, 0–70 months) compared to 12.0 months (range, 0–32 months) with chemotherapy (Fig 2). These were not statistically different (P = .39).

Discussion

Primary renal tumors are uncommon in dogs. Previous reports have examined primarily carcinomas with only a series of 6 sarcomas and case reports of a spindle cell sarcoma, osteosarcoma, leiomyosarcoma, hemangio-

oma, hemangiosarcoma, giant cell tumor, oncocytoma, and mixed mesenchymal tumor in the literature. 24-16 Twenty-seven of the dogs presented here were renal cell
carcinomas or a tubular, tubular and papillary, or clear cell variant of renal carcinoma. Twelve had more differentiated tumors classified as adenocarcinomas. Nine dogs had tumors arising from the transitional epithelium. One dog had bilateral papillary cystadenocarcinomas. No survival difference could be identified among these tumor groups, making the epithelial cell of origin a poor predictor of outcome. The sarcomas were more varied in tissue of origin, and could not be grouped for analysis. No survival difference was observed based on histologic tumor type in sarcomas. All groups of tumors exhibited malignant behavior in this series, regardless of their histologic diagnosis.

No breed group was apparently overrepresented among these 82 dogs. Previous reports have generally found no breed predilection for renal tumors.\(^7\)\(^,\)\(^8\)\(^,\)\(^17\) The one exception to this is the occurrence of hereditary multifocal renal cystadenocarcinomas in German Shepherd dogs in association with nodular dermatofibrosis.\(^6\)

Dogs in this report were geriatric with ages of 8.4 +/- 3.4 years and 8.2 +/- 3.7 years, respectively, for dogs with carcinomas and sarcomas. This is similar to previous reports.\(^3\)\(^,\)\(^4\) This is also similar to the geriatric presentation of renal carcinomas and sarcomas in humans.\(^5\)\(^,\)\(^20\) In humans, nephroblastomas typically affect children and have been reported to affect dogs younger than 2 years of age.\(^5\)\(^,\)\(^21\) In this series, although 3 of the 5 dogs with nephroblastoma were <=2 years, the mean and median ages did not differ statistically from the ages of dogs with carcinoma or sarcomas. Of the 3 nephroblastomas in this study that were available for histopathologic confirmation, the two that were confirmed by the presence of vimentin staining in the mesenchymal population and cytokeratin staining of the epithelial population were from the two oldest dogs with nephroblastoma, aged 9 and 12 years.\(^22\) This finding corroborates the previous reports of nephroblastomas in dogs up to 8 years of age.\(^4\)\(^,\)\(^17\)\(^,\)\(^23\)

As in previous reports, presenting complaints and clinical signs were nonspecific and included polyuria/polydipsia, vomiting, and behavior changes.\(^4\) It has been previously reported that an abdominal mass could be palpated in as many as 43% of cases of renal tumors.\(^4\) In this series, only 20% presented with a palpable abdominal mass. An equal proportion of dogs presented for weight loss with a higher proportion presenting for inappetance (27%) and lethargy (26%). Similar complaints were reported in another case series of renal carcinomas.\(^1\) Hematuria was the most common presenting complaint, occurring in 32% of the cases. This is similar to the frequency previously reported.\(^4\) Pain was recorded as the presenting complaint for 6 dogs. There was a significant association between this complaint and the diagnosis of sarcoma. A similar phenomenon has been observed in 81% of humans presenting with angiosarcoma.\(^24\) Arising from mesenchymal structures, thus avoiding intraluminal urinary obstruction or bleeding, these tumors may cause fewer clinical signs than carcinomas or nephroblastomas before growing large enough to cause pain.

Recorded CBC abnormalities in these dogs were nonspecific, as no abnormality had a statistical association with any type of renal tumors. Neutrophilia was the most commonly reported abnormality. This was likely associated with a stress response, corticosteroid administration, or a response to infection in most of the dogs. However, for dogs with neutrophilia greater than 40,000 cells/µL, paraneoplastic syndrome was a possible explanation. In a previous report, paraneoplastic neutrophilia resolved after nephrectomy for a renal carcinoma.\(^25\) Two dogs (1 with hemangiosarcoma and 1 with carcinoma) died in the early diagnostic period, 1 lived 2 months with hemangiosarcoma and 1 lived 4 months with carcinoma. Both short-term survivors died with metastasis. Neither dog had a recorded re-evaluation of the CBC. Paraneoplastic polycythemia was present in 3 dogs, and resolved in each case after nephrectomy.\(^5\) Polycythemia was not associated with a shorter survival time.

Serum chemistry profile changes were also nonspecific. Azotemia was the most common abnormality, and was not statistically significantly associated with any tumor type. The only statistically significant association was a decreased likelihood for dogs with sarcoma to have hypoalbuminemia compared to carcinoma or nephroblastoma patients. There was not, however, a concomitant significant increase in the proteinuria of dogs with carcinomas or nephroblastomas.

Proteinuria and hematuria were detected with nearly equal frequency. Both were present in approximately half of the urinalyses recorded. Virchow’s triad of hematuria, flank pain, and flank mass, however, was not described for any dog in this study.\(^26\) Pyuria was detected in as many dogs as was hematuria, raising the possibility that secondary infection is common in dogs with renal tumors. This must be identified and addressed.
if surgery is planned or cytotoxic chemotherapy is to be instituted.

The detection of pulmonary metastasis at presentation was recorded in 16% of cases compared to 48% previously reported. The lower rate of detection may suggest diagnosis earlier in the course of disease in the animals in this study compared to the older study. Earlier stage is supported by the lower rate of palpation of abdominal masses in this study, as well. Abdominal ultrasound studies were performed more frequently than abdominal radiographic studies in this series. With either examination, a renal mass was detected in approximately 90% of cases. However, intra-abdominal metastasis was strongly suspected in 4 dogs based on ultrasound findings and confirmed at surgery in three of these dogs. Abdominal radiographs did not reveal strong evidence for metastasis in any of the dogs. The overall metastatic rate was 77% at death. These were proportionally distributed through the 3 types of tumors. All forms of primary renal neoplasia reported in this study exhibited malignant biologic behavior. Metastatic sites commonly include the lungs or any of the abdominal organs. Metastasis or local extension to the adrenal gland occurs in approximately 4% of human renal cell carcinoma cases. In this series, it was seen in only 1 case. However, extension into the vena cava and the mesentery occurred in other cases. These structures should be evaluated carefully for such extension or metastasis in preoperative imaging studies.

In human patients, the development of one form of neoplasia is a risk factor for further neoplastic events. Seven (9%) of the dogs in this study were diagnosed with neoplasia of other body systems either before, concurrently, or after the diagnosis of renal neoplasia. The most striking of these dogs was one who had five other forms of neoplasia diagnosed over a period of several years before the renal hemangiosarcoma. This raises the possibility of a mutation in a tumor suppressor gene giving rise to multiple neoplastic changes. A retrospective case series of humans with urologic malignancies identified second malignancies in 5 patients with renal tumors. These included colon, thyroid, uterus, and breast cancer. Mutations of genes such as UROC28 have been identified in cancers of multiple organs. Mutations of the p53 tumor suppressor gene have been reported in osteosarcoma, melanoma, and mammary and squamous cell carcinomas in dogs. Occurrences of several forms of aggressive neoplasia, such as the dog in the present case series, raise the likelihood that mutations in genes like p53 may result in syndromes similar to Li-Fraumeni in humans.

Definitive diagnosis in this series of dogs was most often made after nephrectomy. Surgical resection of the renal tumor had the most positive impact on survival compared to other treatment modalities. Dogs that underwent nephrectomy outlived dogs that were untreated (12 dogs) or dogs that received only medical therapy (2 dogs). Nephrectomy has been advocated with both curative- and palliative-intent for managing human renal tumors. This procedure is most beneficial in unilateral disease where a curative procedure is possible. Clinical signs can be relieved by removing the mass causing pain or morbidity when renal lymphoma has been excluded as a diagnosis with aspiration cytology or needle biopsy. It is clear in this series that there is a survival benefit to surgical removal of the primary renal mass. What is less clear is the role of adjuvant chemotherapy in dogs with renal neoplasia.

Dogs treated with chemotherapy in this series did not survive a detectably longer time than dogs not treated with chemotherapy. As this is a retrospective series of many types and classes of renal neoplasia with no uniformity of chemotherapy protocol, this may be because of a lack of power to detect a difference. This retrospective study was not designed to determine a therapeutic outcome, and multiple chemotherapy combinations were used in these patients. What is clear from this series of dogs is that each of the tumor types represented has a high risk of metastasis. Prospective, randomized trials are necessary to elucidate the benefit of adjuvant chemotherapy in treating dogs with these tumors.

Primary renal neoplasia remains an infrequent diagnosis in dogs. Clinical signs and clinicopathologic findings are nonspecific, so careful early evaluation of patients with clinical signs referable to the urinary tract is necessary to detect these tumors at a manageable stage. Successful management is dependent on complete excision of the mass. Adjuvant chemotherapy may play a role in management of a number of these tumors, but that role has not been defined.

Footnotes

* SigmaStat for Windows 3.10. Systat Software Inc., Richmond, CA

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