SMALL ANIMALS

Antitumor effects of deracoxib treatment in 26 dogs with transitional cell carcinoma of the urinary bladder

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Objective—To evaluate the antitumor activity and toxic effects of deracoxib, a selective cyclooxygenase-2 inhibitor, in dogs with transitional cell carcinoma (TCC) of the urinary bladder.

Design—Clinical trial.

Animals—26 client-owned dogs with naturally occurring, histologically confirmed, measurable TCC of the urinary bladder.

Procedures—Dogs were treated PO with deracoxib at a dosage of 3 mg/kg/d (1.36 mg/lb/d) as a single-agent treatment for TCC. Tumor response was assessed via radiography, abdominal ultrasonography, and ultrasonographic mapping of urinary bladder masses. Toxic effects of deracoxib administration in dogs were assessed through clinical observations and hematologic and biochemical analyses.

Results—Of 24 dogs for which tumor response was assessed, 4 (17%) had partial remission, 17 (71%) had stable disease, and 3 (13%) had progressive disease; initial response could not be assessed in 2 of 26 dogs. The median survival time was 323 days. Median time to progressive disease was 133 days. Renal, hepatic, and gastrointestinal abnormalities attributed to deracoxib administration were noted in 4% (1/26), 4% (1/26), and 19% (5/26) of dogs, respectively.

Conclusions and Clinical Relevance—Results indicated that deracoxib was generally well tolerated by dogs and had antitumor activity against TCC. (*J Am Vet Med Assoc* 2011;239:1084–1089)

Transitional cell carcinoma is the most commonly diagnosed tumor of the canine urinary tract and represents approximately 2% of all cancers in dogs.[1] A variety of therapeutic options have been evaluated for treating TCC, including surgery, radiation therapy, and chemotherapy.[1–9] Complete surgical resection of TCC is difficult and typically unsuccessful because of the trigonal tumor location and propensity for recurrence and metastasis.[1] Intraoperative and full-course radiation therapy have been effective at controlling local disease. Clinically important adverse effects of treatment, however, including urinary bladder fibrosis, colitis, incontinence, cystitis, and stranguria, make radiation a less appealing therapeutic option.[3,4] Multiple chemotherapeutic drugs have been evaluated for use against TCC, including single-agent cisplatin, carboplatin, and doxorubicin as well as the combination of mitoxantrone and piroxicam.[5–8] Single-agent treatments were associated with remission rates of ≤ 25% and median survival times of 130 to 180 days.[6–8] Mitoxantrone combined with piroxicam resulted in remission in 35% of dogs and a median survival time of 291 days.[5]

Abbreviations

COX	Cyclooxygenase
TCC	Transitional cell carcinoma

Nonsteroidal anti-inflammatory drugs, specifically piroxicam, have been evaluated alone and in combination with chemotherapy in the treatment of dogs with TCC.[4,5,9,10] Piroxicam given as a single agent has induced remission in 18% of dogs; the median survival of 62 dogs receiving piroxicam was 195 days.[11] Piroxicam is a nonselective COX inhibitor that inhibits both isoforms of the COX enzyme, COX-1 and COX-2. Cyclooxygenase normally catalyzes the conversion of arachidonic acid to prostaglandins and thromboxanes.[12] Cyclooxygenase-1 is thought to be physiologically important in the protection of the gastrointestinal tract and in renal and platelet function, whereas COX-2 is an inducible enzyme that is upregulated in development, cell growth, and inflammation.[12] Cyclooxygenase-2 is preferentially overexpressed in TCC, compared with normal urothelium, in both dogs and humans, whereas COX-1 is expressed at low amounts in normal and neoplastic urinary bladder tissues.[13–15] The use of a drug that inhibits COX-2, but spares COX-1, is expected to offer an advantage over a nonselective COX inhibitor in

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causing fewer adverse effects, but this has not yet been reported for dogs with TCC. Deracoxib has been shown to selectively inhibit COX-2 in dogs.[16,17] The purpose of the study reported here was to evaluate the antineoplastic activity and toxic effects of deracoxib in dogs with TCC.

Materials and Methods

The study was performed at the Purdue University Veterinary Teaching Hospital following the guidelines and approval of the Purdue Animal Care and Use Committee. The work included a phase II clinical trial of a COX-2 inhibitor in dogs with TCC.

Entry requirements—Entry requirements included dogs with measurable, histologically confirmed TCC of the urinary bladder and informed pet owner consent. The only exclusion factor was expected survival of < 6 weeks. Previous treatment, including chemotherapy and piroxicam administration, was not an exclusion criterion. For this study, a phase II clinical trial design by Gehan[18] was used to select a sample size to estimate drug activity. This design required that remission be seen in ≥ 1 of the first 14 patients enrolled to justify continued enrollment. In the first stage, 14 dogs were entered. If no remissions were observed in this cohort of dogs, the study was discontinued. According to this design, ≥ 1 dog of the first 14 enrolled should have a remission (thereby confirming with 95% confidence that the drug induces remission in ≥ 20% of treated subjects); thereafter, additional dogs were enrolled. After the first 14 dogs, a minimum of 9 additional dogs were enrolled on the basis of the design by Gehan.[18]

Treatment—The COX-2 inhibitor deracoxib[a] was given as a single agent with a planned dosage of 3 mg/kg/d (1.36 mg/lb/d) orally once daily on the basis of the recommended dosage at the time of initiation of the study and was rounded to the nearest available one-half tablet size (25-, 75-, 100-mg tablets). Dogs continued to receive deracoxib until evidence of progressive disease was found.

Assessment of dogs—Dogs were evaluated prior to and during treatment with abdominal ultrasonography, thoracic radiography (3 views), CBC, serum biochemistry analysis, and urinalysis. Primary tumor response was evaluated with ultrasonographic mapping of masses in the urinary bladder following a procedure similar to that described by Chun et al.[6] Two modifications were made to the previous ultrasonographic procedure. First, the amount of saline (0.9% NaCl) solution infused into the urinary bladder for ultrasonography was 4 to 6 mL/kg (1.8 to 2.7 mL/lb), rather than 1.5 to 2.3 mL/kg (0.68 to 1 mL/lb) as in the previous report.[6] Second, in small female dogs with extensive urethral involvement, a urinary catheter was not passed because of the risk of urethral perforation. In these cases, the dogs were placed in a cage for a few hours to allow their urinary bladders to fill. The degree of urinary bladder distention was estimated by urinary bladder size during ultrasonography in order to perform the urinary bladder mapping with a consistent degree of urinary bladder distention.

Initial follow-up evaluations including urinary bladder mapping were scheduled for 4 to 6 weeks into treatment, and then additional follow-up evaluations were scheduled at 8-week and then 12-week intervals. Tumor stage was determined according to the World Health Organization criteria established for canine urinary bladder tumors (**Appendix**).[19] Tumor response was determined by measurement of the primary tumor and metastases observed with ultrasonography and radiography and by measurement of any external TCC masses present such as abdominal wall lesions. Clinical signs were not used in categorizing tumor response because urinary tract infection can cause marked changes in clinical signs. Tumor responses were defined as follows: complete remission, no evidence of cancer detected; partial remission, ≥ 50% reduction in tumor volume; stable disease, < 50% change in tumor volume; or progressive disease, ≥ 50% increase in tumor volume or the development of new tumor lesions. Evidence of toxic effects of deracoxib was evaluated through physical examination, CBC, serum biochemical analysis, and owner observations and was categorized by the Veterinary Cooperative Oncology Group criteria.[20] In relationship to deracoxib toxicosis, azotemia was defined as serum creatinine concentration > 1.5 mg/dL. High liver enzyme activities were based on reference ranges for the Clinical Pathology Laboratory at the Purdue University Veterinary Teaching Hospital and were defined as any increase in alanine aminotransferase > 69 IU/L, alkaline phosphatase > 157 IU/L, or γ-glutamyltransferase > 16 IU/L. The main study end points were initial tumor response and time to progressive disease. Time to progressive disease was defined as the time from the beginning of deracoxib treatment until documentation of progressive disease. Survival time was defined as the time from initiation of deracoxib until death. Information was collected regarding other treatments given prior to or following deracoxib.

Statistical and risk factor analysis—Summary statistics for continuous variables were reported as mean ± SD. A multinomial logistic regression was completed to evaluate the effect of age, body weight, sex, neuter status, T stage, N stage, M stage, dose of deracoxib received, and administration of chemotherapy prior to starting deracoxib (yes or no) on initial response to deracoxib, with partial remission, stable disease, and progressive disease as outcome levels. A Cox proportional hazard model was performed to evaluate the effects of the same variables and receiving chemotherapy with deracoxib (yes or no) after detecting progressive disease on survival time. Multivariate analysis for both the multinomial regression and Cox hazard model was performed in a forward stepwise selection by removing individual variables at $P > 0.2$, where $P < 0.05$ was considered significant. All analyses were performed with commercial software.[b]

Results

Animals—Twenty-six dogs were enrolled in the study. There were 16 spayed females, 1 sexually intact female, 8 neutered males, and 1 sexually intact male. The dogs' breeds included mixed breed (n = 7), Scot-

tish Terrier (4), Shetland Sheepdog (4), Beagle (4), and 1 each of the following breeds: West Highland White Terrier, German Shepherd Dog, Jack Russell Terrier, Dachshund, Lhasa Apso, Greyhound, and Shih Tzu. The mean body weight of dogs at the start of deracoxib administration was 15.5 ± 7.6 kg (34.1 ± 16.7 lb). The mean age at diagnosis was 11.3 ± 2.2 years. At the time of instituting deracoxib treatment, the tumor stage was classified as T2N0M0 in 21 dogs, T3N0M0 in 1 dog, T2N1M0 in 1 dog, and T2N0M1 in 3 dogs. Eight dogs had received prior treatments including piroxicam (n = 4), cisplatin and piroxicam (3), and mitoxantrone and piroxicam (2). One dog had previously been treated with the combination of cyclophosphamide, vincristine, and prednisone for multicentric lymphoma that was in complete remission. One dog had marked bilateral hydronephrosis because of partial obstruction of both ureters. In this dog, bilateral ureteral stents were placed surgically just before the dog was enrolled in the deracoxib study.

Treatment—Deracoxib was given at a mean dosage of 2.85 ± 1.07 mg/kg/d (1.3 ± 0.49 mg/lb/d), with a range 1.54 to 4.08 mg/kg/d (0.7 to 1.85 mg/lb/d). Five owners elected to continue giving deracoxib to their dogs after progressive disease was detected on the basis of their dogs' improved quality of life while receiving deracoxib. Ten dogs went on to receive ≥ 1 additional chemotherapy protocol after detection of progressive disease, including chlorambucil (n = 5), mitoxantrone (4), mitomycin-C (1), vinblastine (1), cyclophosphamide (1), and carboplatin (1).

Tumor response—In the first 14 dogs treated, partial remission was observed in 3 dogs. A total of 26 dogs were enrolled, and tumor response was assessed in 24 dogs. In 2 dogs, initial tumor response was not available. In the first of these dogs, the owner could not return for follow-up evaluation of the pet, although some follow-up assessments were performed by the referring veterinarian. Similarly, in the second dog, images were not available for comparison of tumor size. These 2 dogs received deracoxib until death and lived for 74 and 515 days, respectively. Initial responses in 24 dogs with scheduled follow-up included partial remission in 4 (17%) dogs, stable disease in 17 (71%) dogs, and progressive disease in 3 (13%) dogs. Median time to detection of progressive disease (n = 20) was 133 days (range, 36 to 482 days). Dogs that did not receive additional treatment after deracoxib treatment failed (n = 16) had a median survival time of 312 days. Dogs that did receive additional chemotherapy after deracoxib treatment failed (n = 10) had a longer median survival time of 371 days from the start of deracoxib treatment until death (**Figure 1**). Overall median survival time for all 26 dogs was 323 days.

Statistical and risk factor analyses—In a univariate analysis, age, sex, prior chemotherapy administration, T stage, N stage, M stage, and dose of deracoxib received were not significantly associated with initial response to deracoxib. Heavier dogs (mean body weight, 26.9 kg [59.2 lb]) were found to have a significantly ($P = 0.031$) poorer response to deracoxib treatment, compared with that of dogs of lighter body weight. Because of the lack of additional significant variables, a multivariate analysis was not indicated or performed.

In a univariate analysis, age, sex, T stage, dose of deracoxib received, and prior chemotherapy administration were not found to be significantly associated with survival time. Receiving chemotherapy after detection of progressive disease, neuter status, body weight, and N stage had values of $P < 0.20$ on univariate analysis and were therefore included in multivariate analysis. Multivariate analysis revealed that administration of chemotherapy after dogs with progressive disease had been treated with deracoxib was significantly ($P = 0.039$) associated with longer survival time (hazard ratio, 0.33; 95% confidence interval, 0.13 to 0.91; Figure 1). Nodal metastasis at the start of deracoxib treatment was not significantly ($P = 0.078$) associated with survival time in multivariate analysis (hazard ratio, 8.72; 95% confidence interval, 0.78 to 97.0).

Toxic effects of deracoxib—Clinical signs of a gastrointestinal disorder occurred in 10 dogs. In 5 of the 10 dogs, the signs were not attributed to deracoxib administration; these dogs had evidence of pancreatitis, gastrointestinal infection, or progressive azotemia leading to gastrointestinal signs. Gastrointestinal signs were considered potentially deracoxib related in 5 dogs. These included 2 dogs with grade 2 vomiting, 1 dog with grade 1 anorexia, 1 dog with grade 1 vomiting and grade 2 colitis, and 1 dog with grade 1 diarrhea and grade 2 colitis. No grade 3 toxicities occurred, and no dogs discontinued deracoxib treatment because of gastrointestinal signs.

Hematologic and serum biochemical analyses revealed that 13 dogs had azotemia and 11 dogs had high serum liver enzyme activities. Of the 13 dogs that had

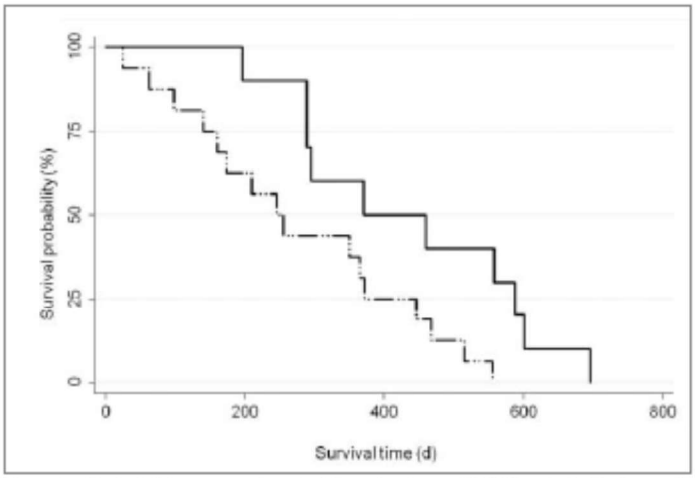

Figure 1—Kaplan-Meier curves of survival times for dogs with TCC treated with deracoxib that did (solid line; n = 10) and did not (dashed line; 16) receive additional chemotherapy after the detection of progressive disease during deracoxib treatment. Administration of chemotherapy was significantly ($P = 0.039$) associated with a longer survival time.

azotemia during treatment, 7 dogs had azotemia prior to deracoxib treatment. Three of these 7 dogs had worsening of their azotemia, which was attributed to pyelonephritis (n = 1) or tumor progression (2). Six dogs developed azotemia during deracoxib treatment. In 5 of these 6 dogs, evidence of hydronephrosis (n = 2), nephroliths (2), and tumor progression (1) was detected and thought to be causing progressive azotemia. In 1 dog receiving 2.2 mg/kg/d (1 mg/lb/d) of deracoxib, an underlying cause for azotemia other than deracoxib treatment was not detected.

High serum liver enzyme activities were observed in 11 dogs and included an increase or a combination of increases in serum alanine aminotransferase, alkaline phosphatase, and γ-glutamyltransferase activities. Five of the dogs with high serum liver enzyme activities had concurrent evidence of hyperadrenocorticism, and 1 dog was on long-term phenobarbital treatment for suspected epilepsy. Of the 5 remaining dogs, 4 had high serum liver enzyme activities prior to beginning deracoxib treatment. One dog developed a high serum alanine aminotransferase activity of 278 IU/L during deracoxib treatment. This dog continued receiving deracoxib without any clinical manifestations of liver disease or further progression of the high serum alanine aminotransferase activity.

A necropsy was performed on 9 dogs and confirmed TCC within the urinary bladder of these dogs. Metastases were detected in the liver (n = 2), lung (3), regional lymph nodes (2), spleen (1), and abdominal wall (2). One dog also had histiocytic sarcoma in the spleen with metastasis to the liver and a thyroid carcinoma. Lung metastases were present in this dog; however, the tumor of origin could not be determined. One dog had a hepatocholangiocellular carcinoma. All 9 dogs had pathological findings in the kidneys including renal cysts (n = 1), hydronephrosis (2), interstitial nephritis (5), pyelonephritis (2), or another nephropathy (1).

Discussion

Previous studies[9–11] have shown antitumor effects of the nonselective COX inhibitor piroxicam in treating TCC in dogs. Piroxicam, however, can have undesirable and, in some cases, serious adverse effects.[9–11] A selective COX-2 inhibitor should be associated with fewer adverse effects because COX-2 is minimally expressed in normal tissue. This study was performed to determine the effects of deracoxib in dogs with TCC. The basis for this treatment selection was the finding that COX-2 is overexpressed in TCC of dogs, whereas COX-1 expression is minimal and similar to that in normal tissues. Cyclooxygenase inhibition is thought to play a major role in the antitumor effects of COX inhibitors, although effects independent of COX have been reported.[21]

Piroxicam treatment has resulted in 6% complete remission, 12% partial remission, 53% stable disease, and 29% progressive disease in 1 study[9] of dogs with TCC. In the study reported here, administration of deracoxib resulted in partial remission in 17% (4/24) of dogs, stable disease in 71% (17/24) of dogs, and progressive disease in 13% (3/24) of dogs. On the basis of these results, deracoxib appears to have similar activity to piroxicam in controlling TCC. It was noted that no dogs with complete remission were observed in the present study, whereas piroxicam was associated with complete remission in 6% of dogs of the previous study.[9] It is possible that dogs with complete remission may have been observed if larger numbers of dogs were treated with deracoxib. It is also possible that COX-1 inhibition or other effects, such as prolonged half-life of piroxicam, could be involved in the anticancer activity in some cases. Of particular interest was the tumor response seen in dogs receiving deracoxib that had previously received another chemotherapy or piroxicam, including 1 dog that was in partial remission while receiving deracoxib after previously developing progressive disease while being treated with cisplatin and piroxicam.

Nonsteroidal anti-inflammatory medications have been reported to cause gastrointestinal, renal, hepatic, and platelet abnormalities.[12,22,23] No platelet abnormalities were observed in the study population of the present report. Gastrointestinal, renal, and hepatic abnormalities were noted in dogs receiving deracoxib.

Nonselective COX inhibitors result in adverse effects on the gastrointestinal tract that manifest as anorexia, melena, and vomiting and can ultimately cause gastrointestinal ulceration.[9,22,24,25] These effects are thought to be due in large part to the inhibition of COX-1–mediated production of prostaglandins that protect the gastrointestinal mucosa. Deracoxib is thought to be associated with fewer adverse effects because it spares the isoenzyme, COX-1, which is primarily responsible for protection of the gastrointestinal tract and maintenance of renal blood flow. Studies[17,24,25] have shown that deracoxib is well tolerated for the treatment of osteoarthritis in dogs and that deracoxib is associated with fewer gastric lesions in healthy dogs, compared with treatment with aspirin. In dogs with TCC receiving piroxicam as the sole treatment, 17% of dogs had gastrointestinal signs.[9] Six dogs had to discontinue piroxicam for a few days, and 2 dogs were able to resume treatment when gastrointestinal protectants were given concurrently.[9] Even though 38% (10/26) of dogs in the present study receiving deracoxib had gastrointestinal signs, signs in half of these dogs were attributed to causes other than deracoxib administration. In 19% (5/26) of dogs, gastrointestinal signs (ie, anorexia, diarrhea, or vomiting) were thought to be due to deracoxib administrations. The dogs' gastrointestinal signs were mild and were categorized as grade 1 or 2 (out of a maximum of 5). No dogs had to discontinue treatment because of their gastrointestinal signs.

Although 50% (13/26) of dogs receiving deracoxib in the present study had azotemia, for most dogs this was likely attributed to factors commonly associated with TCC (chronic urinary tract infection, urinary obstruction, and renal damage from cisplatin). There was only 1 dog that developed azotemia while receiving deracoxib in which other conditions did not appear responsible for the decrease in renal function. Necropsy did reveal that 5 dogs had interstitial nephritis, which is consistent with renal hypoxia and has been reported for dogs receiving COX inhibitors. Mechanisms, however, other than COX inhibition may have played a role in the observed renal pathological findings.[26] Of the 5 dogs with interstitial nephritis detected on necropsy, 3 dogs had azotemia before

death, but 2 of these dogs also had hydronephrosis, and 1 dog had unilateral renal hypoplasia. Renal papillary necrosis is a reported histologic consequence of long-term NSAID administration.[26,27] Renal papillary necrosis was reported for dogs with TCC receiving piroxicam[9]; however, this pathological finding was not observed in dogs receiving deracoxib in the present study.

Toxic effects of COX-2 inhibitor administration on the liver in dogs have been reported.[23] These effects have ranged from an increase in serum liver enzyme activities in the absence of clinical signs to dogs that had signs of vomiting, anorexia, and icterus.[22,23] High serum liver enzyme activities were present in 42% (11/26) of dogs in the present study. However, in the 11 dogs with high serum liver enzyme activities, deracoxib administration was thought to be the cause in only 1 dog, whereas hyperadrenocorticism or other preexisting conditions were likely to be the cause in the remaining dogs. None of the dogs receiving deracoxib became clinically ill at the time of high serum liver enzyme activities, although these results warrant monitoring of biochemical profiles of dogs receiving deracoxib for TCC.

The median survival time in the present study was 323 days, which appears longer than the median survival in previous reports.[4–9] However, it may not be accurate to compare the median survival time in this study with that of other studies because the standard of care has improved with the advent of urethral and ureteral stents, superior antimicrobials for the treatment of urinary tract infections, and the use of different protocols to control tumor growth over a course of time. Results of statistical analysis revealed that dogs that received more than 1 treatment protocol had a significant survival advantage over dogs that did not go on to receive additional treatments. The exact reason for this is not known. Any antitumor activity of subsequent treatments could certainly be important in prolonging survival. It is also possible that pet owners who elected to have their dog participate in a clinical trial were also more motivated to continue with additional treatments. No other variables were found to be significantly associated with survival time. In earlier studies, dogs with T3, N1, or M1 stage cancer had shorter survival times than did dogs with less advanced cancer. In this trial of deracoxib, however, the number of dogs with T3, N1, or M1 disease was small, and there was not sufficient statistical power to continue with the multivariate analysis. It is also possible that dogs that survived longer were then able to undergo more treatments, regardless of how effective those treatments were.

In conclusion, the results of the present study demonstrate that deracoxib has antitumor effects in dogs with TCC and that the overall remission rate and median time to detection of progressive disease appear similar to those in previous reports on the administration of nonselective COX inhibitors. Deracoxib was generally well tolerated, with toxic effects of deracoxib limited to mild gastrointestinal signs and mild increases in serum liver enzyme activities. Deracoxib appears to be a safe and effective approach to COX inhibitor treatment in dogs with TCC.

a. Deramaxx, Novartis Animal Health Inc, Greensboro, NC.
b. STATA software, version 10.2, StataCorp, College Station, Tex.

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Appendix

World Health Organization clinical (TNM) staging of TCC of urinary bladder tumors in dogs.[19]

Category	Description
T (primary tumor)	
Tis	Carcinoma in situ
T0	No evidence of tumor
T1	Superficial papillary tumor
T2	Tumor invading the urinary bladder wall with induration
T3	Tumor invading neighboring organs
N (RLN)	
N0	No evidence of RLN involvement
N1	RLN involved
N2	RLN and juxtaregional lymph node involved
M (distant metastasis)	
M0	No evidence of distant metastasis
M1	Distant metastasis detected

RLN = Regional lymph node.

Correction: Extralabel use of cabergoline in the treatment of a pituitary adenoma in a rat

In the article "Extralabel use of cabergoline in the treatment of a pituitary adenoma in a rat" (*JAVMA* 2011;239:656–660), a greater than symbol was inadvertently changed to a less than symbol. The correct sentence on page 659 of the Discussion section (left column, beginning on line 6 of the second full paragraph) should read, "A hemorrhagic appearance of the pituitary gland is frequently seen in rats with large spontaneous tumors that are > 10 mm in diameter.[1,3,7,23]"