Clinical signs, treatments, and outcome in cats with transitional cell carcinoma of the urinary bladder: 20 cases (1990–2004)

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Objective — To characterize demographics and clinical signs and evaluate outcomes of treatments in cats with transitional cell carcinoma (TCC) of the urinary bladder.

Design — Retrospective case series.

Animals — 20 cats with TCC.

Procedures — Medical records of 20 cats with a bladder mass identified as a TCC that were examined at 2 veterinary institutions between 1990 and 2004 were evaluated. Signalment, treatments, and outcome were assessed.

Results — Breeds included domestic short hair (n = 14), long hair (2), and medium hair (2) cats; Siamese (1), and Abyssinian (1). All cats had been neutered at an early age (<1 year old; 13 neutered males and 7 spayed females). The median age at diagnosis of TCC was 15.2 years. The trigone region was affected in 9 cats. Treatments included piroxicam administration, chemotherapy, or surgery as single interventions or in combination; 6 cats were not treated. At the time of diagnosis, 3 cats had pulmonary metastasis and 1 cat had metastasis to local lymph nodes. Median survival time for all 20 cats was 261 days. Nearly all deaths were attributable to progressive disease in the urinary tract. Five cats were lost to follow-up.

Conclusions and Clinical Relevance — In cats, TCC of the urinary bladder appears to be a rare and aggressive disease that is more prevalent in male cats and frequently develops at sites distant from the trigone (unlike TCC in dogs). Nevertheless, initial clinical signs of TCC in cats in this study were similar to those reported for affected dogs. (J Am Vet Med Assoc 2007;231:101–106)

Tumors of the urinary bladder comprise approximately 1.5% to 2% of all neoplasms in dogs.1–5 The most common urinary bladder tumor is TCC, which develops most commonly in the trigone region of the bladder.2–5 The incidence of TCC in dogs has increased considerably over the past 25 years.2,4 In dogs, risk factors for TCC include female sex, exposure to marshes sprayed with insecticides, overall industrial activity within dogs’ home region, obesity, neutering, and breed (Scottish, West Highland White, and Fox Terriers; Shetland Sheepdogs; and Beagles are at greater risk than other breeds).2,6 In humans, risk factors for TCC include male sex, cigarette smoking, and exposure to environmental toxins.2

For dogs with TCC, treatment is often limited to chemotherapy because most tumors are not amendable to surgical removal.2 The intensity of adverse effects following radiation therapy applied to the urinary bladder in dogs and humans varies depending on the protocol used, but those effects can be considerable.6–8 Chemotherapy drugs that are commonly used to treat TCC in dogs include mitoxantrone, doxorubicin, carboplatin, cisplatin, and cyclophosphamide. The response rates to single-agent chemotherapy are generally low (<20%), and most dogs are euthanized because of progressive local disease within 4 to 9 months.2,3,9 Treatment with nonsteroidal anti-inflammatory agents has been shown to increase overall survival time and alleviate clinical signs associated with TCC in dogs.10 In dogs treated with administration of piroxicam alone, the objective response rate was reported to be <20% and median survival time was 181 days.10 This is similar to the response rates reported for TCC-affected dogs receiving chemotherapy. Combinations of doxorubicin and cyclophosphamide11 as well as doxorubicin or mitoxantrone combined with a platinum agent have been some of the most effective treatments in dogs with TCC of the urinary bladder.9 Combination treatment with piroxicam and mitoxantrone has been associated with improved survival time;9 the median survival time in that study was 291 days, compared with 181 days with administration of piroxicam alone.12 Overall response rate in the study12 of piroxicam as a single-agent treatment was 81%; 39 of 48 dogs achieved complete or partial responses or stabilization of their disease. Treatment in

Abbreviation

TCC Transitional cell carcinoma

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humans with invasive TCC typically consists of radical surgical removal of the urinary bladder followed by chemotherapy or radiation therapy.\textsuperscript{12,13}

In dogs with TCC of the urinary bladder, positive prognostic indicators include female sex, absence of urethral or prostatic involvement, and anatomic location of the tumor that is amenable to surgery.\textsuperscript{9,14}

To our knowledge, there are few published studies in which urinary bladder carcinomas in cats were characterized. In 1 report\textsuperscript{6} of 27 cats with bladder tumors, carcinoma was diagnosed in 15, benign mesenchymal tumor was diagnosed in 5, sarcoma was diagnosed in 5, and lymphoma was diagnosed in 2. Nine of those cats underwent partial cystectomy. Four cats survived longer than 6 months; however, none of those cats had carcinomas.\textsuperscript{7} Treatment of another cat with TCC of the urinary bladder via surgery and radiation therapy has also been reported.\textsuperscript{15} That cat survived 386 days after surgery. The purpose of the retrospective study reported here was to characterize demographics and clinical signs and evaluate outcomes of treatments in cats with TCC of the urinary bladder.

**Criteria for Selection of Cases**

Medical records of cats that were examined at the University of Minnesota Veterinary Medical Center and the University of Wisconsin Veterinary Medical Teaching Hospital between 1990 and 2004 were searched for the key words feline, cat, bladder, mass, and tumor. Medical records were reviewed, and entry criteria included a bladder mass identified via diagnostic imaging and a diagnosis of TCC based on cytologic or histopathologic findings.

**Procedures**

Information collected from the medical records included sex, breed, age at diagnosis, clinicopathologic data at initial evaluation, results of histologic examination of biopsy specimens obtained from bladder masses, results of radiographic evaluations of the urinary tract (with and without administration of contrast medium), type and date of treatment, date of recurrence of TCC, other concurrent diseases, and date of death. Not all information was available for all cats. Follow-up information was obtained from medical records and telephone calls to the referring veterinarians.

**Statistical analysis**—Survival time was defined as the interval from diagnosis to death that was attributable to TCC. Time to recurrence of TCC was defined as the interval from surgical removal of the tumor to identification of recurrence. The period of progression-free survival was defined as the time from surgical removal of the tumor to recurrence. Survival curves were generated by use of the Kaplan-Meier method, which accounts for cats that were alive, lost to follow-up, or had died from unrelated causes at the time of analysis. Cats were censored if they were still alive at the end of the data collection period or if they had died from a cause unrelated to TCC of the urinary bladder. Information regarding cause of death was collected from the medical record or via telephone conversations with the referring veterinarians.

Overall survival rate for cats without urinary obstruction at initial evaluation was compared with the rate among cats that had urinary obstruction at initial evaluation. Urinary obstruction was defined as an inability to void urine combined with high BUN and serum creatinine concentrations. These groups were compared by use of the Breslow and Mantel-Cox tests of significance to determine differences between survival curves. A value of $P < 0.05$ was considered significant.

**Results**

Medical records for 25 cats were evaluated. Three cats were not included in the study because they were determined to have bladder masses other than TCC (2 undifferentiated carcinomas and 1 lymphoma). Two cats were not included because their medical records were incomplete. Among the 20 cats included in the present study, breeds included 14 domestic short hair, 2 domestic long hair, and 2 domestic medium hair cats; there was also 1 Abyssinian and 1 Siamese. Thirteen (65\%) cats were male, and 7 (35\%) were female. All cats were neutered and had been neutered at an early age (< 1 year old). Most cats in the study population were geriatric (median age at diagnosis, 15.2 years [range, 6.5 to 18.5 years]; mean, 12.5 years). At initial evaluation, clinical signs included hematuria ($n = 16$ [76\%]), stranguria (8 [40\%]), pollakiuria (7 [35\%]), urinary tract obstruction (3 [14.3\%]), and inappropriate urination (3 [14.3\%]). One (4.7\%) cat had no clinical signs attributable to TCC of the urinary bladder. Generally, TCC-affected cats had lower urinary tract signs.

Among the 20 cats, 17 were reported to have concurrent diseases. Ten (50\%) cats had chronic renal failure characterized by high BUN and serum creatinine concentrations, urine specific gravity $\leq 1.035$, and anemia. Renal failure secondary to ureteral obstruction was ruled out on the basis of results of diagnostic imaging. Seven (35\%) cats (2 of which had hyperthyroidism) had a heart murmur identified during physical examination. Although all cats with murmurs underwent thoracic radiography, only 1 (a cat with concurrent hyperthyroidism) had evidence of cardiomegaly. No further characterization of heart disease was performed in any of the cats. Other concurrent diseases included hyperthyroidism (4 [20\%] cats), allergy-related dermatologic disease (2 [10\%] cats), liver disease (3 [15\%] cats), and small cell gastrointestinal lymphoma (1 [5\%] cat). In 4 (20\%) cats, a diagnosis of TCC was made via cytologic examination of percutaneous fine-needle aspirates of the bladder mass. For 1 cat, a diagnosis of TCC was made on the basis of results of a urinary sediment examination. Reports of histologic evaluations of tissue samples were available for 12 (60\%) cats. Ten cats underwent biopsy during surgery, and 1 cat underwent fluoroscopy-guided biopsy by use of a spring-activated core biopsy needle; a sample was obtained via traumatic catheterization in 1 cat. The diagnosis was confirmed at necropsy for the remaining 3 cats.

At the time of diagnosis, a CBC and serum biochemical analyses were performed for all cats; however, among the 20 cats, no consistent abnormalities were identified. Ten of the 20 (50\%) cats had renal failure.
A complete urinalysis was performed in 19 (95%) cats. In 8 cats, microbial culture of urine was performed and yielded positive results for 6 cats. Thoracic radiography was performed for 11 (55%) cats; cardiomegaly was evident in 1 cat with concurrent hyperthyroidism, and 3 cats had pulmonary metastasis at the time of diagnosis of TCC.

Abdominal ultrasonography or radiography was performed in all 20 cats. Abdominal ultrasonography was performed in 15 (75%) cats, and radiography was performed in 14 (70%) cats. Ten (50%) cats underwent both abdominal radiography and ultrasonography. In 7 (35%) cats, radiography of the urinary tract was performed after administration of contrast agent.

On the basis of the results of the imaging procedures, tumor location was recorded for all 20 cats. Eleven (55%) cats had tumors that involved the bladder wall (distant from the trigone), and 9 (45%) cats had tumors that involved the trigone. Transitional cell carcinoma affected the trigonal and urethral regions of the urinary bladders in 2 cats. At initial evaluation, 3 cats had complete urinary obstruction.

In some cats, the TCC was staged at the initial evaluation according to the World Health Organization TNM staging system that is available for dogs. At the time of the study, there was no validated staging system for use in cats; thus, the canine staging system was applied. Complete tumor staging was not performed in all cats. The TCC in 1 cat was staged as T1N0M0 (T1 representing superficial papillary tumor). Sixteen (80%) cats had TCCs that were staged as T2N0M0 tumors (T2 representing tumor invading the bladder wall with induration). Among the 20 cats, metastasis was detected during the initial examination in 4 (20%). One cat had metastasis to the mediastinal lymph nodes, and the TCC was thus classified as T2N0M0. Three cats had distant metastasis to the lungs at the time of diagnosis with no regional lymph node involvement (T2NxN0M0). One cat with distant metastasis also had a ventral abdominal wall mass that was determined to be TCC that may have occurred as a result of needle transplantation.

Four cats were treated medically. One cat received doxorubicin and cyclophosphamide; at initial evaluation, the cat had urethral obstruction, which was relieved with placement of a urinary catheter. Neutropenia and vomiting were reported as complications following chemotherapy with doxorubicin and cyclophosphamide; survival time for this cat was 38 days. The other 3 cats were treated with piroxicam alone; survival times were 1, 23, and 208 days. Adverse effects associated with piroxicam administration were reported for only 1 cat. That cat had melena and anemia, which were alleviated with administration of misoprostol. No other cats required misoprostol or other gastrointestinal tract protectants.

Ten cats were treated surgically. Two cats died during the immediate postoperative period at 2 and 5 days after surgery. The cat that died 2 days after surgery had complete urethral obstruction at the initial evaluation and had undergone removal of a urinary bladder polyp 976 days earlier. A partial cystectomy (performed with curative intent) was attempted in 7 cats, and 1 cat underwent debulking surgery. Surgical margins were reported as complete for 2 cats and incomplete for 3 cats; reports for the remaining 5 cats did not contain comments regarding completeness of excision. Six of the 8 cats that survived the immediate postoperative period had tumor recurrence. The median progression-free interval in those 8 cats was 89 days (range, 61 to 1,545 days for those cats surviving the immediate postoperative period; Figure 1). Of the 2 cats with complete surgical margins, 1 was lost to follow-up immediately after surgery and the other was euthanized 5 days after surgery because of urinary incontinence.

Eight of the 10 cats that underwent surgery were treated with adjunctive therapies. Four cats received piroxicam alone. Of those 4 cats, 2 were lost to follow-up; 1 had no sign of tumor recurrence during its last visit to the hospital at 1,545 days, and the other was lost to follow-up at 49 days after tumor recurrence was detected. For the other 2 cats, 1 had survived 269 days after surgery and the other had survived 84 days after surgery, as determined at the end of the data collection period. The 3 cats with incomplete surgical margins all received adjunctive treatments and were still alive at the end of the data collection period. One cat, as mentioned, received piroxicam alone (alive at 84 days after surgery); another received piroxicam and carboplatin (alive 103 days after surgery with tumor recurrence detected at 89 days). The third cat received meloxicam and doxorubicin after a debulking surgery and was alive at 61 days after surgery with tumor recurrence detected at 55 days. Treatment with doxorubicin was discontinued in this cat, and carboplatin administration was initiated. The eighth cat was treated with chlorambucil and prednisone for small cell gastrointestinal lymphoma before and after diagnosis of TCC. Tumor recurrence was detected at 79 days after surgery in that cat, and it had an overall survival time of 261 days.

Piroxicam (0.3 mg/kg [0.14 mg/lb]) was administered orally 2 to 3 times/wk in all 8 cats receiving the drug. For the 2 cats that received carboplatin, the drug was administered IV (240 to 260 mg/m²) every 3 to 4 weeks. Doxorubicin was administered IV (25 mg/m²)

Figure 1—Kaplan-Meier survival curve depicting the progression-free interval in 8 cats with TCC of the urinary bladder that were treated surgically and that survived the immediate postoperative period. Two additional cats that died within 2 days of surgery were not included in the progression-free interval analysis. Median progression-free interval was 89 days. Censored cats are indicated by vertical marks on the trace.
every 3 to 4 weeks to the 2 cats receiving that treatment. The cat that was treated with cyclophosphamide received a dose of 200 mg/m², IV, which was alternated with doxorubicin treatment every 2 to 3 weeks.

Six cats received no treatment. Five of those cats were euthanized within 24 hours of diagnosis. One lived 276 days with no treatment. Three of those cats were euthanized at time of diagnosis, after which necropsies were performed. At necropsy, lung metastasis was detected in 1 cat. None of the cats that were treated and for which some follow-up information was available developed new or additional metastatic lesions. However, this number may be falsely low because necropsies were not performed on any of those cats. Deaths attributable to TCC were a result of clinical signs of local disease.

Overall, the median survival time for all cats was 261 days (Figure 2). The survival times of the cats with urethral obstruction were 0, 2, and 38 days. A median survival time for those cats receiving surgery, with or without other therapies, and surviving the immediate postoperative period had not been reached by the conclusion of the study period.

Discussion

In the population of cats included in the present study, neutered males were most commonly affected with TCC and their tumors were typically classified as T2 or higher according to the canine staging system. That system was adopted from the human staging system, and the authors elected to adopt it for application to the cats in the present study. Further evaluation of cats with this disease is necessary to determine whether this staging system is truly appropriate for cats. Although TCC more commonly affects males than females among humans,3-6 neutered female dogs appear to be at greater risk than male dogs in general for development of this tumor.1-3 In humans, muscle-invasive TCC is uncommon (developing in approx 20% of TCC-affected people) but carries a worse prognosis than more superficial forms. In dogs and cats, TCC has often invaded the muscle of the bladder wall at the time of diagnosis.2,10 In humans with TCC classified as stage 2 or higher, radical cystectomy is the treatment of choice.1,17 Because radical cystectomies have not been well tolerated in veterinary patients, other treatments have become more commonly used.

Because of the retrospective nature of the present study, it has inherent weaknesses. We were unable to assess the role of reproductive status (neutered vs sexually intact), obesity, or toxin exposure (all of which are risk factors for the development of TCC in dogs)1-3,5 in the study population. Transitional cell carcinoma often develops in the trigone region of the urinary bladder in dogs; approximately 56% of those tumors concurrently involve the urethra, and in male dogs, approximately 29% of those tumors concurrently involve the prostate.3,4 In humans and dogs, the trigone is theorized as a commonly affected location because of its anatomic positioning and the effect of gravity that allow for urine pooling in this area. This leads to chronic exposure of the urothelium to toxins that are excreted in the urine. Unlike dogs, approximately half of the cats in the present study had developed tumors that did not affect the trigone region; however, the trigone was still a common site of disease. Anatomic features in cats may be slightly different from those in dogs, resulting in pooling of urine in other areas of the bladder.18

Clinical signs, predominately lower urinary tract signs, among the cats in our study were similar to those reported in TCC-affected dogs.1-3 Feline lower urinary tract disease is common and is typically associated with chronic lower urinary tract signs and negative results of microbial cultures of urine. Abdominal radiography to rule out vesicular calculi is often performed, but urinary bladder tumors are rarely detected by use of this technique. For cats with TCC, abdominal ultrasonography is an essential diagnostic procedure because it is a sensitive imaging tool for detection of neoplasia and other diseases.19

In the present study, various specimens were collected from the cats and examined, and diagnosis was made on the basis of histologic or cytologic findings. Cytologic evaluation of specimens is generally not an acceptable diagnostic tool by itself. In dogs with TCC, concurrent cystitis is common; diagnosis of TCC via examination of urine sediment is diagnostic in only approximately 30% of dogs because it can be difficult to differentiate tumor cells from nonneoplastic transitional cells in an inflammatory environment.11 However, cytologic findings suggestive of neoplasia with detection of a bladder mass can lead to a high suspicion of TCC. Because of the small size of the urethra in cats, most tissue samples were obtained via biopsy procedures instead of via traumatic catheterization or cystoscopy in the present study. Traumatic catheterization was possible in 1 cat, and examination of the collected specimen yielded a diagnosis; however, this procedure is unlikely to be a commonly used diagnostic tool in cats. Laparotomy with surgical removal of the mass was the most common approach used in the cats of the present study. None of the cats that underwent surgery had evidence of seeding of the abdomen or implantation of the incision with neoplastic cells. Fluoroscopically
guided biopsy was also performed to obtain tissue from 1 cat; that cat did not develop seeding of neoplastic cells through the biopsy tract.

Fine-needle aspiration of the bladder mass was performed in several cats. One of the cats that had distant metastasis at the time of diagnosis also developed TCC on the ventral body wall; this was likely attributable to seeding of neoplastic cells from the site of cystocentesis (undertaken without ultrasound guidance), which had been performed in an attempt to obtain a urine sample for microbial culture. This phenomenon has been reported in dogs and humans after fine-needle aspiration of a TCC; thus, patients with urinary bladder masses should not have cystocentesis performed until TCC of the urinary bladder has been definitively ruled out as a differential diagnosis. Among tumors in humans, implantation after aspiration is most likely to develop with prostatic carcinoma. However, implantation after aspiration has also been reported for humans with TCC. The incidence of implantation of neoplastic cells following needle biopsy procedures in humans is reported to be <0.01%. Not all cats underwent complete staging of their tumor, and serial clinicopathologic tests were not performed for most cats in the present study. From the data collected, there were no consistent hematoologic or serum biochemical abnormalities associated with TCC in the study cats. A complete urinalysis was performed in 18 cats. Although TCC was diagnosed from findings of urine sediment examination for 1 cat, the definitive diagnosis was made on the basis of those findings in combination with detection of a urinary bladder mass via intravenous urography. Microbial culture of urine samples was performed for only <0.01% of the 20 cats. Six of those cats had a urinary tract infection. Disease involving the bladder mucosa and potential incomplete micturition may support the development of secondary bacterial infections in cats with TCC. The incidence of secondary urinary tract infections may be higher than results of the present study have indicated. The authors suggest that microbial culture of urine samples should be performed routinely in cats with TCC and that urinary tract infections should be treated appropriately on the basis of results of antimicrobial susceptibility testing.

In dogs, the frequencies of local and distant metastases at the time of diagnosis of TCC are reported as 16% and 14%, respectively. At the time of death, ≥50% of dogs with TCC will have metastases. The most common sites of metastases are the regional lymph nodes, lungs, and bones. The overall metastatic rate at the time of initial evaluation in the present study was 20%. Three of 11 cats that underwent thoracic radiography had metastasis to the lungs. The incidence of pulmonary metastasis in the present study may be artificially low because of the low number of cats that underwent thoracic radiography. On the basis of our data, TCC appears to metastasize to the same sites in cats as it does in dogs; however, the incidence of pulmonary metastasis appears to be higher in the former. Necropsies were performed on only 3 of the 20 cats. One of these cats had lung metastases that were not previously detected; no other metastatic lesions were identified in any of these cats.

As is typical in retrospective studies, the treatments provided for the cats in the present study varied. There were insufficient numbers of cats to associate a significant survival advantage to any 1 treatment. Combination chemotherapy has been reported to be the most successful treatment for unresectable TCC in dogs. Only 1 cat was treated with combination chemotherapy (consisting of doxorubicin and cyclophosphamide) in the present study. That cat received doxorubicin despite having chronic renal failure; the authors suspect that this was the reason for the cat’s poor tolerance of the treatment protocol. A prospective analysis comparing combination and single-agent treatments would be necessary to determine drug efficacy in cats with TCC.

Dogs with TCC of the urinary bladder that are treated with mitoxantrone combined with piroxicam have reported median survival of 291 days. However, none of the cats in our study received that drug combination. Administration of the mitoxantrone–piroxicam combination may have potential usefulness in cats with urinary bladder TCC. Single-agent treatment with piroxicam has been used in many dogs with TCC of the urinary bladder; reported median survival associated with that regimen is 181 days. The value of nonsteroidal anti-inflammatory drugs as an anticancer treatment has not been evaluated in cats, but the pharmacokinetics of multiple doses of piroxicam have been reported. The drug is generally well tolerated in dogs but can cause clinically relevant gastric ulceration; renal and hepatic toxicoses may also develop. Gastric ulceration can be considerably abrogated through the use of histamine (H2) receptor blockers (eg, famotidine) or synthetic prostaglandins (eg, misoprostol). Piroxicam was well tolerated by most of the 8 cats receiving the drug in the study reported here. A diagnosis of chronic renal failure had been made previously for 4 of the cats that were treated with piroxicam. One cat received only 1 dose and was euthanized shortly after diagnosis of TCC. The other 3 cats received piroxicam with no reported adverse effects. One cat received meloxicam in conjunction with other chemotherapy agents with no reported adverse effects. Several cats treated surgically also received either chemotherapy or nonsteroidal anti-inflammatory drugs. A median survival time was not reached for that group. In the present study, there are too few cats to evaluate the effect that surgery may have on survival. However, in dogs, survival is reported to be improved for those with tumors that are resectable, compared with those that are not resectable.

Transitional cell carcinoma of the urinary bladder appears to be a rare but aggressive tumor in cats. Similar to dogs with TCC of the urinary bladder, the diagnosis is often made late in the disease process in affected cats. Neoplasia of the urinary bladder should be considered as a differential diagnosis for a geriatric cat with lower urinary tract signs. Unlike dogs, there was a predilection toward males, bladder wall involvement, and pulmonary metastasis among the cats in the present study. Prospective analyses of treatment options and risk factors are necessary to determine effective treatments for cats with TCC of the urinary bladder.
References