Canine Transitional Cell Carcinoma

Anthony J. Mutsaers, William R. Widmer, and Deborah W. Knapp

Transitional cell carcinoma (TCC) of the urinary bladder, the most common malignancy of the urinary tract in dogs, is challenging to both diagnose and treat effectively. The prevalence of this disease may be increasing. The etiology of canine TCC is likely multifactorial. Epidemiological studies of TCC in the dog have revealed a number of risk factors, including breed and female gender, as well as environmental factors, such as insecticide exposure. This tumor is difficult to remove surgically and responds poorly to chemotherapy. The efficacy of radiotherapy and other treatment modalities needs further investigation. Cyclooxygenase-inhibiting drugs have some activity against TCC, and studies to further define these effects are ongoing. Use of the tumor/node/metastasis (TNM) classification scheme for bladder cancer has allowed for the identification of prognostic factors. Urinary tract obstruction and metastatic disease remain challenges to treat. Work with canine TCC has demonstrated how closely this disease resembles human invasive urinary bladder cancer. Therefore, future research has the potential to benefit both dogs and humans with TCC.

Key words: Animal models; Bladder cancer; Chemotherapy; Cyclooxygenase; Piroxicam; Risk factors.

Urinary bladder cancer in dogs is a challenging disease to diagnose, stage, and treat. Fortunately, urinary bladder cancer is uncommon in the dog, comprising <2% of all reported canine malignancies.1 Transitional cell carcinoma (TCC) is the most common neoplasm affecting the urinary bladder of dogs. In this article, we review current knowledge of canine TCC with regard to frequency, etiology, histopathological characteristics, cellular and molecular features, response to therapy, and prognostic factors. We also discuss why canine TCC is a good model of human invasive bladder cancer.

Frequency

Although the true prevalence of canine TCC is not known, it is the most common form of urinary tract cancer in the dog and comprises 1.5–2% of all canine cancers.2,3 The hospital prevalence, or proportionate morbidity, of bladder cancer at university-based veterinary hospitals appears to be increasing.4 A search of the Veterinary Medical Data Base (VMDB) from 1975 to 1995 showed a continuous increase in the prevalence of bladder cancer, with prevalence defined as the number of dogs with bladder cancer divided by the total number of individual dogs seen for any reason at the same participating university veterinary hospitals.4

Etiology and Risk Factors

The etiology of canine TCC is most likely multifactorial. Risk factors that have been identified include exposure to topical insecticides for flea and tick control, exposure to marshes that have been sprayed for mosquito control, and industrial activity in the host county of the veterinary hospital.9 Bladder cancer mortality in Caucasian men and women in the same counties showed a similar correlation with industrial pollution.10

In a case-control study, 59 pet dogs with TCC and 71 age- and breed size–matched control pet dogs with other chronic disease or tumors were studied to determine if an association existed between bladder cancer and exposure to sidestream cigarette smoke and chemical use in the home, use of topical insecticides, and obesity.11 Bladder cancer risk was not related to sidestream cigarette smoke and household chemical exposure. There was, however, a significant, dose-related association between topical application of flea and tick dip and TCC. This risk was increased in overweight or obese dogs. In addition, risk of TCC was higher in dogs living near marshland sprayed with insecticide(s). The authors speculated that the “inert” ingredients, accounting for >95% of the total product, were the probable carcinogens in these products.

Multiple studies have confirmed the increased risk of bladder cancer in female dogs. The female: male ratio in a series of 102 dogs with TCC treated at the Purdue Univer-
Cyclophosphamide Exposure

Cyclophosphamide causes sterile hemorrhagic cystitis in humans and pet dogs. In humans, cyclophosphamide treatment (for cancer or immune mediate disease) increases the risk of bladder cancer 9-fold. TCC has been reported in a small number of pet dogs following cyclophosphamide treatment for other malignancies, although cause and effect has not been proven in dogs. It is likely that the possible bladder carcinogenic properties of cyclophosphamide treatment are related to chronic irritation because of cystitis from exposure to the acrolein metabolite. If this is true, TCC development could be more common with chronic oral dosing versus intravenous bolus dosing, which would be more carcinogenic if peak metabolite concentrations in the bladder are more important in the development of TCC.

Breed Predisposition

There is considerable variation in the risk of canine TCC between different breeds, with the Scottish Terrier having an 18-fold increased risk compared to mixed breeds. Similarly the Beagle, Shetland Sheepdog, Wire Hair Fox Terrier, and West Highland White Terriers have been at increased risk. An association has not been found between breed and the biological behavior of the tumor or its response to therapy. The cause of this breed-associated risk is not known, but in all likelihood, it represents genetic predisposition to bladder cancer, such as differences in the biochemical pathways that activate and detoxify carcinogens.

Histopathologic Characteristics

Tumor tissue samples from 74 dogs with TCC were classified using a system developed by Mostofi and modified by Valli and DeNicola. The majority of tumors were papillary infiltrative TCC of intermediate to high grade. Eighty-one percent of tumors were histologic grade 2 and 16% were grade 3. These findings were similar to those reported by Valli et al, except Valli reported a slightly higher percentage of dogs with carcinoma in situ. Similarly, low grade TCC is rare in dogs and is less well characterized.

Other Cellular and Molecular Features

Excluding histopathologic studies, limited work has been performed to characterize canine TCC at the cellular and molecular level. Clemo et al reported that 34 (79%) of 43 canine TCCs were aneuploid. The immunoreactivity of canine TCC (n = 51 dogs) to monoclonal antibodies (B72.3, CC49, CC83) for tumor-associated glycoprotein 72 (TAG-72) has also been reported. As is the case with human TCC, however, immunoreactivity to B72.3 was not specific for canine TCC.

Clinical Signs, Diagnosis, Staging, and Biologic Behavior

Canine TCC is typically a disease of older dogs. The mean age at diagnosis of 102 dogs with TCC was 11.1 years. The mean body weight in this series of dogs was 15.7 ± 10.3 kg (range 3.0–51.0 kg), and the female to male ratio was 1.7 : 1. Common presenting signs included hematuria, stranguria, and other forms of dysuria and, less commonly, lameness, lethargy, and weight loss. Similarly, Norris reported dysuria (84%), grossly visible hematuria (50%), and pollakiuria (37%) as the most frequent clinical signs in 115 dogs with bladder or urethral tumors.

Recently, a urine bladder tumor antigen screening test...
(Bard BTA test) has become commercially available. This test had an overall sensitivity of 90% and a specificity of 78% in a study of 20 dogs with TCC, 19 healthy controls, and 26 nonneoplastic, urologic disease controls. False positive results were seen with hematuria, proteinuria, and glucosuria. Similar results were found in a more recent study for the veterinary version (V-BTA) of this test. This emphasizes the need to evaluate the entire clinical picture and follow a positive screening test with appropriate methods to make a definitive diagnosis.

The definitive diagnosis of canine bladder cancer requires histopathologic examination of tissues obtained by cystotomy, cystoscopy, or catheter biopsy. Transplantation of tumor cells has been suspected to occur following surgical manipulation of the tumor. Therefore, care must be taken during diagnostic and therapeutic procedures to prevent the possible seeding of tumor cells.

Clinical staging of canine bladder cancer is performed with complete physical examination, radiography of the thorax and abdomen, and imaging of the bladder (pneumocystography and double-contrast cystography, ultrasonography, or computed tomography). Contrast cystography demonstrated a mass or filling defect in 96% of 91 dogs in one study. Widmer and Chun have described a technique for imaging bladder tumors using ultrasonography. To measure response to therapy, it is important to reproduce the same imaging technique at each staging visit. In our experience, ultrasonography, when performed in a systematic fashion, is superior to contrast cystography for imaging bladder masses. Exceptions to this include mineralized lesions that scatter or attenuate the sound waves, producing a poor image, and lesions caudal in the pelvic canal (urethral lesions), where a good window for the study cannot be obtained. Ultrasonography also has the added benefit of improved staging of lymph nodes and abdominal organs. Contrast cystography has the advantages of not requiring expensive ultrasound equipment and, perhaps, of having a more reproducible technique when multiple staff members are involved in the imaging on different visits. In both ultrasonography and cystography, the bladder must be fully distended for accurate assessment of the location and size of the mass. In most cases, this requires general anesthesia to carefully place a urinary catheter near friable tumor tissue, which can easily rupture if traumatized by the catheterization. Assessment of urethral lesions is best accomplished by a contrast urethrogram and careful rectal palpation.

The tumor/node/metastasis (TNM) classification scheme for canine urinary bladder cancer has been defined by the World Health Organization (Table 1). Following the WHO classification scheme, the TNM stage at diagnosis of 102 cases of TCC was determined. Staging included 2 dogs with T1 tumors, 80 dogs with T2 tumors, and 20 dogs with T3 tumors. Lymph node (N1 or N2) and distant metastases (M1) were present in 16% and 14% of dogs respectively. Ten percent of dogs had both nodal and distant metastases at the time of diagnosis. Of 102 dogs with TCC, the urethra was involved as well as the bladder in 57 dogs (56%). Of 38 male dogs, the prostate was involved in 11 dogs (29%). The majority of the canine bladder tumors were located in the trigone region of the bladder.

The TNM stage at the time of death was also available for 80 dogs, and 49% of the dogs had distant metastases at death. When the primary tumor is not controlled, death by urinary tract obstruction occurs in many dogs with TCC prior to the development of lethal metastasis. When the primary tumor can be controlled, metastatic disease occurs more frequently. The cause of death, which was known for 85 of the 102 dogs, was the primary tumor in 52 dogs (61%), metastatic disease in 12 dogs (14%), and nontumor-related causes in 21 dogs (25%). Sites of TCC metastases detected at necropsy in 50 dogs included lung (14 dogs, 28%), regional lymph nodes (13 dogs, 26%), liver (9 dogs, 18%), kidney (2 dogs, 4%), spleen (2 dogs, 4%), presacral lymph node (2 dogs, 4%), and uterus (2 dogs, 4%). One case each (2%) had metastases in: mesenteric lymph nodes, cecum, bronchial lymph nodes, vertebrae, ilium, colon, abdominal wall, diaphragm, renal lymph node, and oral mucosa.

### Table 1. Clinical Stage (TNM) of canine TCC

<table>
<thead>
<tr>
<th>T</th>
<th>Primary tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>T1</td>
<td>Superficial papillary tumor</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invading the bladder wall, with induration</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invading neighboring organs (prostate, uterus, vagina, and pelvic canal)</td>
</tr>
<tr>
<td>N</td>
<td>Regional lymph node (internal and external iliac lymph node)</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node involved</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node involved</td>
</tr>
<tr>
<td>N2</td>
<td>Regional lymph node and juxtaglomerular lymph node involved</td>
</tr>
<tr>
<td>M</td>
<td>Distant metastases</td>
</tr>
<tr>
<td>M0</td>
<td>No evidence of metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis present</td>
</tr>
</tbody>
</table>

**Response to Therapy**

**Surgery**

Canine TCC is difficult to remove surgically because of the trigonal location of the tumor, frequency of urethral involvement, and metastases in 20% or more of dogs at the time of diagnosis. Complete cystectomy that may be routine in human bladder cancer patients has not been attempted to any extent in the dog. Conduits with external collection devices and continent reservoirs drained by intermittent catheterization would not be acceptable to many pet owners of dogs. Enterocystoplasty with cystectomy and subtotal in-tracapsular prostatectomy has been described in male non-tumor-bearing dogs, but the hourly micturition frequency observed in dogs undergoing this procedure would be unacceptable for most pet owners of house dogs. Partial cystectomy was reported in dogs with bladder cancer, but local and distant tumor relapse occurred in 8 of 10 dogs. Ileocolonic anastomosis was reported in 10 dogs with TCC, but complications were frequent and included hyperammonemia, hyperchloremic metabolic acidosis, uremia, and pyelonephritis. Vaginourethroplasty of localized canine urethral tumors and ileocecalplasty of canine bladder tumors have been reported, but these procedures are not...
useful for tumors involving the trigone region of the bladder. The trigone is the area most frequently affected by canine TCC. For palliation of urinary obstruction and to allow time for other therapies to work, prepubic cystostomy catheters, which bypass urethral obstruction, have been used in a small number of dogs.\(^4\)

When performing tumor “debulking” with or without partial cystectomy, surgical cure is rarely achieved. In a series of 102 dogs with TCC, “complete resection” of the primary tumor (with histopathologically tumor-free margins) was only accomplished in 2 dogs.\(^4\) For these 2 dogs rendered “tumor free,” extensive local recurrence was noted in 1 dog 8 months postsurgery. In the 2nd dog, tumor regrowth in the bladder was not detected, but distant relapse occurred within 4 months of surgery. It is not surprising that survival after surgery is short. An analysis of data from the PCOP Tumor Registry\(^46\) revealed a median survival time of only 106 days for 42 dogs with TCC that underwent surgical debulking. Similarly, Norris reported postsurgery median survival of 125 days in 23 dogs,\(^1\) and Helfand reported 86 days in 14 dogs with TCC.\(^47\) A point worth noting is that in relapse after surgery, new lesions are frequently observed distant from the original site, raising the question of whether the “field effect”\(^48\) or tumor seeding within the bladder is important in canine bladder cancer.

The role of surgical debulking, however, in combination with other therapies warrants further investigation. In the study of 102 dogs with TCC, the median survival of 25 dogs that had surgical debulking plus medical therapy (piroxicam or chemotherapy) was 272 days. The median survival times for 42 dogs that had surgery for biopsy only plus medical therapy and for 35 dogs that had medical therapy, but no surgery, were 195 and 150 days respectively.

**Radiation Therapy**

Radiation therapy has been used infrequently in canine TCC.\(^49,50\) Walker reported the use of intraoperative radiation therapy in 13 dogs with bladder tumors, including 11 dogs with TCC.\(^49\) The median survival time postsurgery was 15 months for dogs with TCC, and recurrence (local or distant) was noted in 6 dogs. Side effects included: pollakiuria, urinary incontinence, cystitis, stranguria, and hydronephrosis; 4 dogs were euthanized because of the side effects of therapy.

In a pilot study of palliative external beam radiation therapy in combination with mitoxantrone and piroxicam in 10 dogs, stable disease with clinical improvement was noted in 7 cases.\(^51\) Three dogs experienced cancer progression during therapy. Side effects related to radiation were reported to be minimal, and the overall median survival was 240 days. The role of radiation therapy in the control of TCC requires further investigation.

**Chemotherapy**

Table 2 summarizes the response of canine TCC to chemotherapy.\(^3\) This table summarizes results on prospective clinical trials using single-agent chemotherapy where data on response to treatment were available. TCC is considered to have a poor response to chemotherapy. Retrospective studies of combination chemotherapy protocols have also been reported. In these studies response data could not be assessed; however, favorable median survival times were reported with both the combination of doxorubicin\(^52\) and cyclophosphamide\(^5\)\(^3\) treatment in 11 dogs (259 days),\(^47\) as well as anthracycline (either doxorubicin or mitoxantrone) and platinum (either cisplatin\(^5\) or carboplatin) drug combinations in 15 dogs (358 days).\(^52\) Intravesical chemotherapy using thiotepa\(^5\) in 6 dogs has also been reported, with poor results, likely because of the invasive nature of the tumor at diagnosis and the inability of the chemotherapy to reach infiltrated muscularis.\(^47\) The pharmacokinetics of the chemotherapy agents paclitaxel,\(^53\) gemcitabine,\(^54\) and 5-fluorouridine,\(^55\) administered via the intravesical route in dogs, have also been evaluated.

Another form of treatment for the primary tumor currently being investigated is photodynamic therapy. Photodynamic therapy with 5-aminolevulinic acid (ALA)-induced protoporphyrin IX has undergone preclinical evaluation in nontumor-bearing dogs, with the intent to proceed to the treatment of canine TCC.\(^56\) The protophotosensitizer ALA, given orally, was well tolerated. Within the urinary bladder, fluorescence appeared to be confined to the mucosa and was not damaging to the muscularis or serosa.\(^56\) Early detection of TCC could provide the best opportunity for

**Table 2. Results of chemotherapy for the treatment of canine TCC.**\(^4\)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage (mg/m(^2))</th>
<th>No. Treated</th>
<th>No. CR/PR</th>
<th>% CR + PR</th>
<th>Survival (days)</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>60</td>
<td>25(^a)</td>
<td>0/3</td>
<td>12</td>
<td>130</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>15</td>
<td>0/3</td>
<td>20</td>
<td>132</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>25–50</td>
<td>8</td>
<td>0/1</td>
<td>25</td>
<td>NA</td>
<td>68</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>300</td>
<td>14</td>
<td>0/0</td>
<td>0</td>
<td>132(^b)</td>
<td>36</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>2.5–5</td>
<td>6</td>
<td>0/1</td>
<td>17</td>
<td>NA</td>
<td>69</td>
</tr>
<tr>
<td>Adriamycin</td>
<td>30</td>
<td>5(^a)</td>
<td>0/1</td>
<td>20</td>
<td>NA</td>
<td>70</td>
</tr>
<tr>
<td>Actinomycin D</td>
<td>0.5–1.1</td>
<td>6(^a)</td>
<td>0/1</td>
<td>17</td>
<td>NA</td>
<td>71</td>
</tr>
</tbody>
</table>

CR, complete remission: complete resolution of all radiographic, ultrasonographic, and clinical evidence of TCC; PR, partial remission: ≥50% reduction in tumor volume; TCC, transitional cell carcinoma.

\(^a\) Also includes additional dogs treated by the same protocol at the Purdue University Veterinary Teaching Hospital (part of a series of 102 dogs).

\(^b\) After failing carboplatin therapy, dogs were then treated with piroxicam.
photodynamic therapy, as well as other forms of intravascular therapy, to be effective.

**Nonsteroidal Anti-inflammatory Drug (NSAID) Therapy**

Our interest in NSAID therapy began when dogs with various forms of spontaneous cancer had remission while receiving the NSAID piroxicam, and no other therapy, for pain control. In a phase I study of piroxicam in 62 dogs with various histopathologically confirmed, measurable tumors, gastrointestinal toxicity was dose related and dose limiting, but antitumor activity occurred at the lower, less toxic doses. Partial remission (≥50% reduction in tumor volume) occurred in 8 dogs, including 3 of 10 dogs with TCC. A phase II clinical trial of piroxicam (0.3 mg/kg PO q24h) in dogs with histologically confirmed, measurable, nonresectable TCC was performed. Tumor responses in 34 dogs included 2 complete remissions (CR, complete resolution of all clinical and radiographic evidence of TCC), 4 partial remissions (PR, ≥50% reduction in tumor volume), and 18 stable disease (SD, <50% change in tumor volume) and 10 progressive disease states (PD, ≥50% increase in tumor volume or the development of new tumor lesions). The 2 dogs with complete remission lived 2.1 years and 3.3 years, respectively, and were tumor free on postmortem examination. Piroxicam therapy was generally well tolerated, with gastrointestinal toxicity noted in 6 dogs and renal papillary necrosis in 2 dogs. The median survival was 180 days. Piroxicam has been used in additional dogs with TCC in our hospital, and currently, tumor responses in 62 dogs have included 2 CR, 9 PR, 35 SD, 16 PD, and a median survival of 195 days. The response of canine TCC to piroxicam has led to a phase II clinical trial of piroxicam in humans with carcinoma in situ of the urinary bladder (precursor lesion to invasive bladder cancer). Piroxicam does not work like chemotherapeutic agents. Recent studies have shown close association between TCC remission and induction of apoptosis.

Piroxicam has also been evaluated in combination with platinum-based chemotherapy. Responses to treatment have been improved when compared to single-agent chemotherapy with the use of cisplatin and piroxicam (2 CR and 8 PR in 14 dogs); however, an increased risk of nephrotoxicity was observed in 12 of 14 dogs (azotemia; 87%). Carboplatin and piroxicam treatment in 13 dogs resulted in 5 partial responses with no signs of renal toxicity.

**Prognostic Factors**

Using data from the series of 102 dogs with TCC, analyses were performed to look for an association between TNM stage at diagnosis, development of metastasis between diagnosis and death, response to systemic therapy, and survival. The TNM stage at both diagnosis and death was known in 80 of the 102 dogs. Thirty-four of 60 dogs (57%) with stage N0, M0 tumors at diagnosis, progressed to stage N1/2 or M1 at death. Two factors associated with the development of metastasis between diagnosis and death were vascular invasion and urethral involvement of the tumor. The response to chemotherapeutic agents and piroxicam were similar. Two factors, T3 stage at diagnosis and histologic glandular differentiation, were associated with a very poor response to chemotherapy or piroxicam therapy. Shorter survival was significantly associated with more advanced TNM stage at diagnosis. There was a negative association between survival and prostate involvement, and a possible positive association (but not significant) between survival and debulking surgery. This possible association between debulking surgery and survival is currently being investigated further.

A recent retrospective study of 25 cases investigated prognostic factors for urinary bladder carcinoma, including tumor angiogenesis (measured by factor VIII immunohistochemistry), inherent drug resistance (using P-glycoprotein and glutathione-S-transferase π immunohistochemistry) and clinical factors. Immunohistochemical characteristics did not correlate with prognosis, although the statistical power of the study was low.

**Comparison of Canine and Human Invasive TCC**

Canine TCC is also important in that it serves as a model of invasive urinary bladder cancer in humans. The similarities and differences between canine and human invasive TCC are summarized in Table 3. As demonstrated in Table 3, canine and human invasive TCC are extremely similar. One of the few differences between canine and human TCC is the difference in gender predilection, with men being at greater risk than women and female dogs being at greater risk than male dogs. The reason for this difference is not known but could involve several factors. Smoking and occupational exposures are thought to be responsible for much of the increased risk of bladder cancer in men, and these risks would generally not be relevant to canine TCC. Similarly, it is not known why the location of the tumor within the bladder differs between dogs and humans. Although further characterization of canine TCC must continue, especially at the molecular level, current knowledge provides strong support for dogs with TCC being a useful and relevant model of human invasive bladder cancer. In fact, promising results of canine studies have already lead to clinical trials in people with TCC.

**Discussion and Future Research**

Although much progress has been made in the treatment of TCC, most affected dogs still die of this disease, and approximately 12,000 people die with TCC each year in this country. Several key challenges exist with respect to the invasive urinary bladder cancer field. Improved methods of prevention, early detection, and treatment of both primary and metastatic disease are needed.

Advances in prevention will involve gaining an understanding of environmental as well as genetic risk factors and developing strategies to avoid or to compensate for these factors. Certain environmental risk factors have been well documented to contribute to the development of canine TCC. However, genetic risk factors are largely unknown. Studies of breeds at high risk for bladder cancer might help to identify genetic factors important in bladder cancer initiation and development. This work is especially timely given current efforts to map the canine and human genomes...
Table 3. Canine and human invasive TCC: similarities and differences.4

<table>
<thead>
<tr>
<th></th>
<th>Canine TCC</th>
<th>Human TCC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I. Similarities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of all cancers</td>
<td>1.5–2%</td>
<td>2%</td>
</tr>
<tr>
<td>Change in occurrence</td>
<td>Increase in university hospital prevalence (60 equivalent dogs)</td>
<td>0.75 increase in annual incidence52</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>11 years</td>
<td>65 years</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subpopulations at risk</td>
<td>Breeds (eg, Scottish Terrier)</td>
<td>Races (eg, African Americans)53</td>
</tr>
<tr>
<td>Environment</td>
<td>Increased risk in urban areaa</td>
<td>Increased risk in urban areaa</td>
</tr>
<tr>
<td>Benzene</td>
<td>Increased risk with exposure to insecticides containing benzene and other &quot;inert&quot; ingredients6</td>
<td>Increased risk with exposure to benzene and Polycyclic aromatic hydrocarbons48</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>TCC reported in small number of dogs receiving cyclophosphamide for other malignancies7,8</td>
<td>Increased risk with exposure12</td>
</tr>
<tr>
<td>Histopathology</td>
<td>Invasive TCC of intermediate to high grade (&gt;90% grade 2 and 3)</td>
<td>Invasive TCC of intermediate to high grade (70% grade 2 and 3)</td>
</tr>
<tr>
<td>Other cellular features</td>
<td>DNA ploidy 79% aneuploid15</td>
<td>Aneuploidy correlates with advanced stage and grade25</td>
</tr>
<tr>
<td>Tumor associated glycoprotein</td>
<td>Immunoreactivity to TAG-72 antibodies43</td>
<td>Immunoreactivity to TAG-72 antibodies47</td>
</tr>
<tr>
<td>Urine bFGF concentration</td>
<td>Increased in TCC41</td>
<td>Increased in TCC41</td>
</tr>
<tr>
<td>p53 (mutated) expression</td>
<td>Detected in a small number of canine TCC tissue samples and in TCC cell line</td>
<td>Correlates with advanced stage and grade129 and poor survival76,77</td>
</tr>
<tr>
<td>Cyclooxygenase (Cox) expression</td>
<td>Cox-2 overexpressed, increased PGE2 concentrations in tumor tissue and in plasma23,28,31</td>
<td>Cox-2 overexpressed in tumor tissue29</td>
</tr>
<tr>
<td>Clinical signs</td>
<td>Hematuria, dysuria, urinary tract infection most common; bone pain infrequent</td>
<td>Hematuria, urinary tract infection most common; bone pain less common48</td>
</tr>
<tr>
<td>Metastasis at diagnosis</td>
<td>20% of dogsb</td>
<td>5–20% of patients48</td>
</tr>
<tr>
<td>Sites of metastasis</td>
<td>Regional nodes and lung most common</td>
<td>Regional nodes and lung most common44</td>
</tr>
<tr>
<td>Response to single-agent chemotherapyc</td>
<td>Cisplatin 12–20%6,65</td>
<td>17–34%66</td>
</tr>
<tr>
<td></td>
<td>Carboplatin &lt;10%6</td>
<td>15%64</td>
</tr>
<tr>
<td>Prognostic factors</td>
<td>TNM stage Advanced TNM stage associated with decreased survival</td>
<td>Advanced TNM stage associated with decreased survival64,78</td>
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<tr>
<td></td>
<td>Prostate involvement Associated with distant metastasis at diagnosis and with decreased survival</td>
<td>Associated with decreased survival, especially when stroma of gland is involved89</td>
</tr>
<tr>
<td><strong>II. Differences</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male : female ratio</td>
<td>0.5 : 1</td>
<td>2.8 : 1</td>
</tr>
<tr>
<td>Tumor location within the bladder</td>
<td>Majority trigonal</td>
<td>Lateral wall (37%), posterior wall (18%), trigone and neck (23%), other sites (22%)90</td>
</tr>
</tbody>
</table>

bFGF, basic fibroblast growth factor; PGE, prostaglandin E; TCC, transitional cell carcinoma; TNM, tumor/node/metastasis classification scheme.

*a p53, when mutated, has a prolonged half-life, allowing detection by immunohistochemistry (IHC) or Western blotting. It is estimated that IHC is 90% accurate in detecting p53 mutations in human TCC.72
*b Of the 102 dogs with TCC evaluated at the Purdue University Veterinary Teaching Hospital, 20% had metastasis at diagnosis. An earlier study reports 37% of dogs had metastasis at diagnosis.1
*c Comparison to multiagent protocols is not possible. These have not been used in the dogs because of toxicity.

20and validated to work toward this goal. However, even with our current knowledge, we can identify groups of dogs at risk (eg, Scottish Terriers and dogs exposed to insecticides) that could be evaluated more frequently by veterinarians.

30It is most important to improve treatment of existing disease. Effective therapy must involve moving beyond non-

and the development of proteomic technology.63,64 Studies of both areas, genetic factors and environmental factors in TCC, are currently ongoing.

Until TCC can be prevented, work is needed to improve treatment of existing disease. Better treatment will most certainly require earlier detection. Tests must be developed and validated to work toward this goal. However, even with our current knowledge, we can identify groups of dogs at risk (eg, Scottish Terriers and dogs exposed to insecticides) that could be evaluated more frequently by veterinarians.
specific cytotoxic agents. As is the case for the vast majority of solid tumors in dogs and in humans, chemotherapy is simply not adequately effective and is too toxic. In fact, sublethal doses of chemotherapy could actually make cancer worse.⁶⁵ New targets for therapy must be identified that are present in TCC tissue (or the TCC environment) but are not present in normal tissues. Treatments must then be developed that are directed to those new targets. Cyclooxygenase, for instance, might be one such target, but inhibiting cox as a single treatment is not good enough (as is often seen with other forms of monotherapy directed at one target). It is likely that successful treatment, even when directed at new and specific targets, will require a combination therapy.

It is of note that some factors (eg, TNM stage) are important prognostic factors for canine TCC. Advanced TNM stage should not be seen as a reason not to treat dogs. It simply means that better therapy is needed for these cases. In addition, development of better therapy for metastatic disease is important in comparative oncology research. Most human TCC deaths, and an increased number of canine TCC deaths when the primary tumor can be controlled, are due to metastatic disease.

As part of the efforts to develop a more effective therapy, we must continue to define and develop the best methods to stage bladder cancer. Imaging of early and advanced TCC remains a challenge, especially when lesions are small or when attempting to accurately stage the disease at multiple time points during treatment. Although the protocol that involves urinary catheterization, bladder distention, ultrasonography, and cystography is useful in tumor measurement, it is laborious and time consuming and has some risk (anesthesia risk, bladder or urethral perforation risk). Objective methods for the detection of tumor response are needed in the evaluation of the success or failure of new treatment strategies, because protocol comparisons cannot be made from studies reporting clinical improvement and survival data only.

There is still much to be learned about canine TCC and the most effective strategies to treat, and ideally prevent this disease. Canine TCC is a good model for human invasive urinary bladder cancer, and work in this field will benefit both dogs and humans.

Footnotes

¹ Cytotoxan, Bristol-Meyers Squibb Co, Princeton, NJ
² Bion Diagnostic Sciences Inc, Redmond, WA
³ Abbott Laboratories Animal Health, Abbott Park, IL
⁴ Adriamycin, Pharmacia-Upjohn Co, Kalamazoo, MI
⁵ Novantrone, Immunex Corp, Seattle, WA
⁶ Platinol, Bristol-Meyers Squibb Co, Princeton, NJ
⁷ Paraplatin, Bristol-Meyers Squibb Co, Princeton NJ
⁸ Thioplex, Immunex Corp, Seattle, WA
⁹ Taxol, Bristol-Meyers Squibb Co, Princeton NJ
¹⁰ Gemzar, Eli Lilly, Indianapolis, IN
¹¹ Sigma Chemical Co, St Louis, MO
¹² Feldene, Pfizer, New York, NY

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21. Allen DK, Waters DJ, Knapp DW, Kuczek T. High urine con-
63. Ostrander EA, Ginger E. Insights from model systems. Semper


