

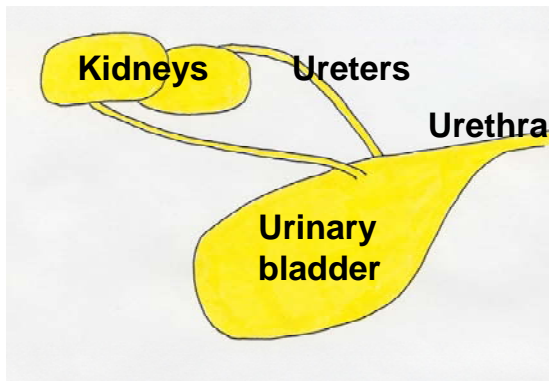
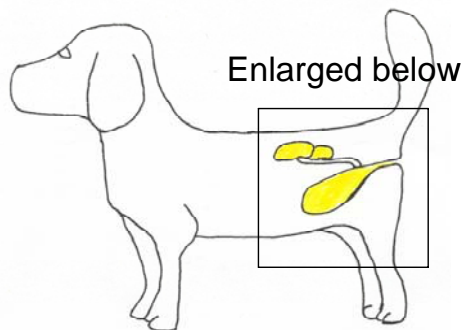
CANINE BLADDER CANCER



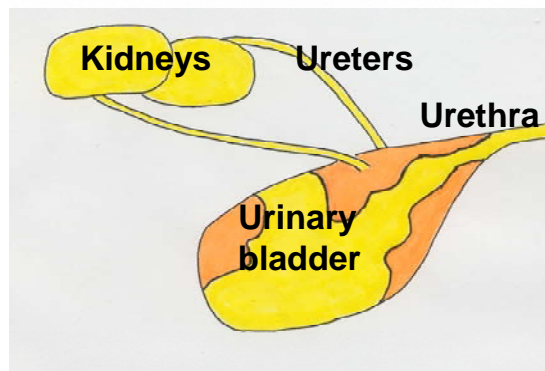
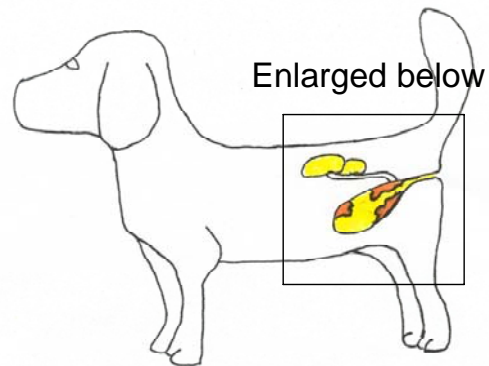
Cancer of the urinary tract in dogs can affect the kidneys, ureters, urinary bladder, prostate, or urethra (see Figure 1). Within the urinary system, the bladder is the location most frequently affected with cancer. Compared to cancer in other locations in the body, bladder cancer is unusual, comprising 1-2% of all cancers in the dog. With more than 70 million pet dogs in the United States, however, even unusual cancers like bladder cancer, are problems for thousands of dogs and their families.

What is bladder cancer? The most common cancer of the dog urinary bladder is invasive transitional cell carcinoma (TCC) of intermediate to high grade. TCC is also called urothelial carcinoma. TCC is a malignant tumor that develops from the transitional epithelial cells that line the bladder. In dogs, this tumor invades into the deeper layers of the bladder wall including the muscle layers. As the cancer enlarges in the bladder, it can cause obstruction to the flow of urine from the kidneys to the bladder or from the bladder to the outside of the body. Canine TCC also has the ability to spread to lymph nodes and to other organs in the body (lung, liver, others). TCC most frequently is found in the bladder, but can also develop in the kidneys, ureters, prostate, and urethra. In regards to human bladder cancer, most cases fall into two general categories: (1) lower grade, superficial tumors, and (2) higher grade, invasive tumors. It is fortunate that the majority of people with bladder cancer have the lower grade, superficial form of the disease. Dogs, on the other hand most often develop the higher grade, invasive form of bladder cancer.

Normal Female Dog



Female Dog with TCC (see masses in bladder)



What causes TCC in dogs? The exact cause of TCC in an individual dog is usually not known. In general, canine TCC results from a combination of several factors including genetic predisposition and environmental factors. A genetic predisposition is suspected because TCC is more common in specific breeds of dogs. Scottish Terriers have an 18-20 fold higher risk of TCC than other dogs. Shetland Sheepdogs, Beagles, West Highland White Terriers, and Wire Hair Fox Terriers are 3 to 5 times more likely to develop TCC than other dogs. Environmental factors identified as risk factors in early studies have included pesticides and insecticides such as "old generation" flea dips. The greatest cause of TCC in humans is smoking. Further study is needed to determine the extent to which second hand smoke may contribute to TCC in dogs.

An association has been found between exposure to lawn herbicides and pesticides and the risk of TCC in Scottish Terriers. Investigators at the Purdue University School of Veterinary Medicine have completed a case control study in Scottish Terriers to determine risk factors for the development of TCC. As discussed above, Scottish Terriers have 18X higher risk for developing TCC than dogs of other breeds. The study was performed to determine if exposure to certain types of environmental chemicals would further increase the risk of TCC in this breed of dog. Environmental exposure histories were compared between 83 Scottish Terrier dogs with TCC (cases) and 83 Scottish Terrier dogs of approximately the same age with other health-related conditions (controls). A significantly increased risk of TCC was found for dogs exposed to lawns or gardens treated with herbicides and insecticides or herbicides alone, but not with insecticides alone, compared with dogs exposed to untreated lawns or gardens. These findings suggest that Scottish Terrier dogs, as well as other dogs of high-risk breeds for TCC, be restricted from lawns treated with herbicides until additional risk studies are conducted. Results of this case control study have been published in the Journal of the American Veterinary Medical Association (April 15, 2004; volume 224; pages 1290-1297). With the publication of these findings, the large number of requests for information related to this study has exceeded our capacity to respond on an individual basis. Further information can be obtained from: www.vet.purdue.edu/epi/herbicide_tcc_scotties.doc.

What clinical signs or symptoms do dogs with TCC have? Blood in the urine and straining to urinate are the most frequent signs of TCC in dogs. Pet owners must realize, however, that a urinary tract infection will cause these same symptoms, so the symptoms alone do not necessarily mean their dog has TCC. Less commonly, dogs with TCC can have lameness due to spread of the tumor into the bones or spread into the lungs and a paraneoplastic syndrome called hypertrophic osteopathy.

How is TCC diagnosed? A diagnosis of TCC requires a tissue biopsy. Several other types of growths in the bladder, bladder infection, bladder stones, or bladder inflammation can cause similar symptoms as those in dogs with TCC. Some of these other conditions can also cause "masses" to be seen on radiographs or ultrasound. Some of these other conditions can cause abnormal cells in the urine, which can be mistaken for TCC. Therefore, diagnosis of TCC requires a tissue biopsy. This is important because the treatment and prognosis depend entirely on exactly what is wrong with the bladder. A tissue biopsy can be obtained by surgery, cystoscopy (insertion of a fiberoptic scope into the bladder and biopsy through the scope), or in some cases with a urinary catheter.

What evaluation is needed for a dog with TCC? Once a diagnosis of TCC is made, it is important to determine the extent of the tumor, i.e. to perform "tumor staging". Tumor staging is performed to determine the best way to treat the cancer, to provide some information regarding prognosis, and to establish a baseline tumor measurement in order to determine if treatment is successful. Tumor staging for TCC includes radiographs ("x-rays") of the thorax to look for lung metastasis, radiographs and ultrasound (or CT scan) of the abdomen to look for metastasis in the abdomen and to assess any changes in the kidneys that result from obstructed urine flow, and imaging of the bladder to determine the exact location and size of the tumor within the bladder (see Figure 1). This information is needed to best plan how to treat the cancer. Also, these tests are repeated during treatment to know if the treatment is being effective.

How is TCC treated? For dogs with TCC that has not spread beyond the bladder, surgical excision could be considered. In order to surgically excise the tumor, however, it needs to be located away from the neck of the bladder and the urethra. Several vital structures in the neck of the bladder (junction with

ureters and urethra, urethral sphincter) usually prevent surgical excision of tumors in this location. This is especially true because malignant tumors, like TCC, need to be removed with a "margin" of normal tissue around the tumor. This "margin" often contains microscopic tumor cells that, left behind, would result in cancer regrowth. In addition, most canine TCCs invade down into the bladder wall and therefore, surgical excision requires removal of a complete full thickness section of bladder wall. [Note: in humans with superficial, low grade cancer, this is not typically the case.] Because most canine TCCs are invasive into the bladder wall and located in the neck of the bladder, surgical removal is usually not possible. It has not yet been completely determined what benefit would occur from removing part of the tumor (in dogs in which the entire tumor cannot be removed).

If surgery is not possible, what other treatment options are available? Radiation therapy has been used to successfully control TCC growth in the bladder in dogs. Unfortunately, radiation of the bladder can lead to harmful complications including a scarred, shrunken bladder, and irritation to surrounding organs. To use radiation therapy successfully in canine TCC, different treatment schemes need to be developed.

The vast majority of TCC cases are treated with medical therapy, i.e. with drugs. Two broad categories of drugs have been used to treat TCC. Traditional chemotherapy (including cisplatin, carboplatin, adriamycin, and others) has been used in canine TCC. The response has been rather disappointing with <20% of dogs having remission with chemotherapy alone. The other type of drug that has been used against TCC is a nonsteroidal antiinflammatory drug (NSAID), piroxicam. NSAIDs block the cyclooxygenase (cox) enzyme, and are also referred to as "cox inhibitors". Cox inhibitors include piroxicam, aspirin, ibuprofen, naproxen, and others. Oncologists at Purdue University became interested in piroxicam when it was being used for pain relief in dogs with cancer, and unexpected remissions were noted. Two of the first dogs treated (one with metastatic carcinoma, one with undifferentiated sarcoma) had advanced cancer, and these dogs had remission of their cancer when only receiving piroxicam. This has led to numerous studies of piroxicam in animals with cancer at Purdue. In 62 dogs with TCC treated with piroxicam, the tumor went into complete remission in 2 dogs, decreased in size by $\geq 50\%$ in 9 dogs, remained "stable" in size (<50% change) in 35 dogs, and increased in size by $\geq 50\%$ in 16 dogs. The median survival (195 days) compared favorably to survival with chemotherapy in other studies.

Piroxicam has been combined with a chemotherapy drug called mitoxantrone. In a study performed by the veterinary Cooperative Oncology Group, this combination treatment resulted in a remission rate of approximately 35%. In addition to dogs that had remission, some dogs also had "stable disease" where the cancer did not grow for a period of time. "Average" survival times with mitoxantrone/piroxicam have been in the 250-300 day range. Some dogs live much longer than this, while others do not live this long. In an attempt to improve upon the results, veterinarians at Purdue University have tested different combinations of drugs. In one study, dogs were randomized to receive either the chemotherapy drug cisplatin alone or cisplatin combined with piroxicam. The dogs receiving cisplatin and piroxicam had a much higher chance of remission, but toxicity to the kidneys limits the use of this approach. Recently, oncologists at Purdue University and at the University of Missouri have conducted a trial comparing the effects of cisplatin alone to cisplatin combined with a cox-2 inhibitor. It was thought that some of the renal toxicity that occurred when piroxicam was combined with cisplatin in the earlier study was due to blocking the enzyme cox-1. [Piroxicam blocks both cox-1 and cox-2.] Therefore, it was expected that the cox-2 inhibitors (that do not block cox-1) would have less negative effects on the kidneys when combined with cisplatin. Patient enrollment in this trial has been completed, and follow-up and analyses are pending.

Many pet owners have observed humans undergoing chemotherapy and are concerned that the side effects of chemotherapy in humans will also be observed in pet dogs. Fortunately, most dogs treated with chemotherapy, experience much less toxicity than humans receiving chemotherapy. The side effects of chemotherapy are considered acceptable in most dogs. Treatment protocols are selected with the goal of maintaining or improving quality of life, at the same time the cancer is attacked. The pet owner should discuss the possible benefits and risk of specific medications that their dog may receive with the attending veterinarian. Cox inhibitors like piroxicam have few side effects. In some dogs (<20%), however, piroxicam will irritate the stomach or intestine. Therefore, if a dog on piroxicam has loss of appetite, vomiting, or dark tarry-looking stools, it is safest to stop the piroxicam and consult the veterinarian before starting the medication again. The new cox inhibitors, selective cox-2 inhibitors, are not expected to cause stomach irritation as frequently as piroxicam does.

What is the prognosis for dogs with TCC? Studies published several years ago reported survival in dogs with TCC as "0 days". At that time, it was thought there was "no hope" and most dogs were euthanized at the time of diagnosis. It is not known how long dogs with TCC that are not treated will live. Survival is affected by the growth rate of the tumor, the exact location of the tumor within the bladder, and whether the tumor has spread to other organs or not. The median survival in dogs treated with chemotherapy alone (cisplatin or carboplatin) at Purdue University was 130 days. Median survival with piroxicam treatment in 62 dogs with TCC was 195 days. The survival times in all of these studies, however, varied tremendously from dog to dog. Some dogs died after only a few days, while others lived more than two years. As mentioned above, approximately 35% of dogs receiving mitoxantrone and piroxicam have remission, and average survival is around 250-300 days. Factors that have been identified in our studies that negatively affect survival time include more extensive tumor within the bladder, spread of tumor beyond the bladder, and involvement of the tumor in the prostate gland. Regarding metastasis of TCC in dogs, approximately 20% of dogs with TCC have detectable metastasis at diagnosis, and 50% have metastasis at death.

Although progress has been made, and TCC is considered a "treatable" disease, there is still much to be learned. We are not satisfied with the "efficacy" of current therapy. Therefore, we are continuing to study TCC to determine better ways to prevent, manage, and treat this cancer. Please see link to Studies in Dogs with Urinary Bladder Cancer - <http://www.vet.purdue.edu/pcop/studiesindogs.pdf>

What symptomatic care can be given to dogs with TCC?

Dogs with TCC are very prone to developing bacterial infection (cystitis) in the bladder. Therefore, frequent urinalysis, culture, and treatment with antibiotics may be necessary. A secondary bacterial infection can result in a sudden worsening in symptoms (blood in urine, straining to urinate) in dogs with TCC, and these dogs will improve with treatment with antibiotics.

TCC can block the flow of urine into and out of the bladder. Complete obstruction can rapidly lead to a buildup of urea and life-threatening complications. If urine flow is obstructed, stents (small tubes) can be placed in the ureters or urethra, as needed, to open up the "channels" and restore urine flow. Our group is working closely with Dr. Larry Adams, a veterinary urologist at Purdue, to provide this opportunity for dogs that need it. Another approach to bypass urethral obstruction is to place a cystostomy tube (small diameter tube that goes from the bladder through the wall of the abdomen to the outside) to allow emptying of the bladder.



What can be learned from dogs with TCC that will help human cancer patients?

In the Purdue Comparative Oncology Program at Purdue University, we study specific forms of naturally-occurring cancer in pet dogs in order to learn new information to help animals and to help human cancer patients. This is possible because certain naturally occurring canine cancers greatly resemble that same form of cancer in humans. This is true with bladder cancer. Canine TCC is almost identical to human invasive TCC in histopathologic characteristics, molecular features studied to date, biologic behavior (sites and frequency of metastasis), and response to medical therapy. Our laboratory is studying the risk factors (environmental and genetic) for TCC, methods to detect TCC earlier, and methods to more effectively treat TCC. These studies are expected to benefit both animals and humans with cancer. In fact, our work has already led to two clinical trials in humans with TCC at the Indiana University School of Medicine.

Some publications describing work in these areas are provided here:

1. Knapp DW, Glickman NW, DeNicola DB, Glickman LT. Naturally-occurring canine transitional cell carcinoma of the urinary bladder, relevant model of human invasive bladder cancer. *Urolog Oncol.* 2000;5:47-59.
2. Knapp DW, Glickman NW, Widmer WR, DeNicola DB, Adams LG, Kuczek T, Bonney PL, deGortari AE, Han C, Glickman LT. Cisplatin versus cisplatin combined with piroxicam in a canine model of human invasive urinary bladder cancer. *Cancer Chemother Pharmacol.* 2000;46(3):221-226.
3. Mohammed SI, Bennett PF, Craig BA, Glickman NW, Mutsaers AJ, Snyder PW, Widmer WR, DeGortari AE, Bonney PL, Knapp DW. Effects of the cyclooxygenase inhibitor, piroxicam, on tumor response, apoptosis, and angiogenesis in a canine model of human invasive urinary bladder cancer. *Cancer Res.* 2002;62(2):356-358.
4. Mohammed SI, Craig BA, Mutsaers AJ, Glickman NW, Snyder PW, deGortari AE, Schlittler DL, Coffman KT, Bonney PL, Knapp DW. Effects of the cyclooxygenase inhibitor, piroxicam, in combination with chemotherapy on tumor response, apoptosis, and angiogenesis in a canine model of human invasive urinary bladder cancer. *Mol Cancer Ther.* 2003;2(2):183-188.
5. Noblitt LW, Bangari DS, Shukla S, Knapp DW, Mohammed S, Kinch MS, Mittal SK. Decreased tumorigenic potential of EphA2-overexpressing breast cancer cells following treatment with adenoviral vectors that express EphrinA1. *Cancer Gene Ther.* 2004;11(11):757-766.
6. Mohammed SI, Khan KN, Sellers RS, Hayek MG, DeNicola DB, Wu L, Bonney PL, Knapp DW. Expression of cox-1 and 2 in naturally-occurring canine cancer. *Prostaglandins Leukot Essent Fatty Acids.* 2004;70(5):479-483.
7. Raghavan M, Knapp DW, Dawson MH, Bonney PL, Glickman LT. Topical flea and tick pesticides and risk of transitional cell carcinoma of the urinary bladder in Scottish Terriers. *J Amer Vet Med Assoc.* 2004; 225(3):389-394.
8. Boria PA, Murry DJ, Bennett P, Glickman NW, Snyder PW, Merkel BL, Schlittler D, Mutsaers AJ, Knapp DW. Evaluation of cisplatin combined with piroxicam for the treatment of oral malignant melanoma and oral squamous cell carcinoma in dogs. *J Amer Vet Med Assoc.* 2004;224(3):388-394.
9. Glickman LT, Raghavan M, Knapp DW, Bonney PL, Dawson MH. Herbicide exposure and the risk of transitional cell carcinoma of the urinary bladder in Scottish Terriers. *J Amer Vet Med Assoc.* 2004;224(8):1290-1297.
10. Mutsaers AJ, Mohammed SI, DeNicola DB, Snyder PW, Glickman NW, Bennett PF, deGortari AE, Bonney PL, Knapp DW. Pretreatment tumor prostaglandin E2 concentration and cyclooxygenase-2 expression are not associated with the response of canine naturally occurring invasive urinary bladder cancer to cyclooxygenase inhibitor therapy. *Prostaglandins Leukot Essent Fatty Acids.* 2005;72(3):181-186.
11. Boria PA, Glickman NW, Schmidt BR, Widmer WR, Mutsaers AJ, Adams LG, Snyder PW, DiBernardi L, deGortari AE, Bonney PL, Knapp DW. Carboplatin and piroxicam therapy in 31 dogs with transitional cell carcinoma of the urinary bladder. *Vet Comp Oncol.* 2005;3(2):73-80.
12. Raghavan M, Knapp DW, Bonney PL, Dawson MH, Glickman LT. Evaluation of the effect of dietary vegetable consumption on reducing risk of transitional cell carcinoma of the urinary bladder in Scottish Terriers. *J Am Vet Med Assoc.* 2005;227(1):94-100.
13. Zabell KM, Laurence JS, Kinch MS, Knapp DW, Stauffacher CV. Expression and purification of the intact cytoplasmic domain of the human ephrin receptor A2 tyrosine kinase in Escherichia coli. *Protein Expr Purif.* 2006;47(1):210-216.
14. Abraham S, Knapp DW, Cheng L, Snyder PW, Mittal SK, Bangari DS, Kinch M, Wu L, Dhariwal J, Mohammed. Expression of EphA2 and Ephrin A-1 in carcinoma of the urinary bladder. *Clin Cancer Res.* 2006;12(2):353-360.
15. Mohammed SI, Deepika D, Abraham S, Snyder PW, Waters DJ, Lu M, Wu L, Zheng R, Stewart J, Knapp DW. Cyclooxygenase inhibitors in urinary bladder cancer: in vitro and in vivo effects. *Mol Cancer Ther.* 2006;5(2):329-336.
16. Knapp DW, Adams LG, DeGrand AM, et al. Sentinel lymph node mapping of invasive urinary bladder cancer in animals using invisible light. *Eur Urol.* 2007;52(6):1700-1709.
17. Dhawan D, Jeffreys AB, Zheng R, Stewart JC, Knapp DW. Cyclooxygenase-2 dependent and independent antitumor effects induced by celecoxib in urinary bladder cancer cells. *Mol Cancer Ther.* 2008;7(4):897-904.