

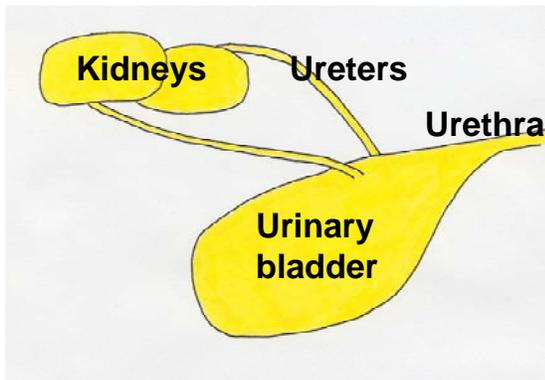
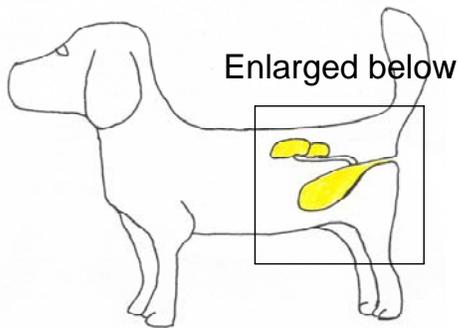
CANINE BLADDER CANCER



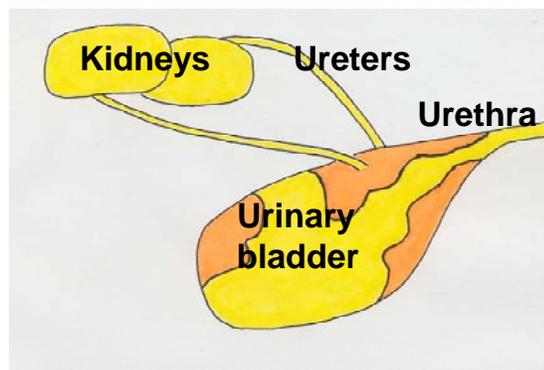
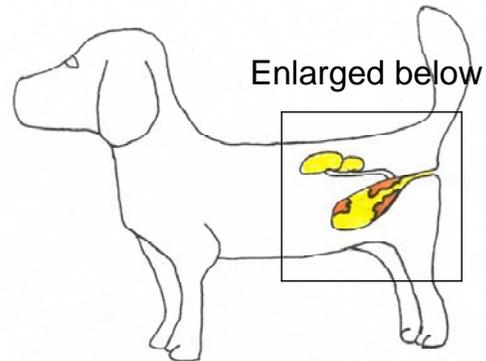
Cancer of the urinary tract in dogs can affect the kidneys, ureters, urinary bladder, prostate, or urethra (see Figure 1). Within the urinary system, the bladder is the location most frequently affected with cancer. Compared to cancer in other locations in the body, bladder cancer is unusual, comprising 1-2% of all cancers in the dog. With more than 65 million pet dogs in the United States, however, even unusual cancers like bladder cancer, are problems for numerous 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 a malignant tumor, i.e. cancer, 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, including Scottish Terriers (18 fold increased risk compared to other breeds), Shetland Sheepdogs (4 fold increased risk), Beagles (4 fold increased risk), West Highland White Terriers (3 fold increased risk), and Wire Hair Fox Terriers (3 fold increased risk). Environmental factors identified as risk factors in previous studies have included pesticides and insecticides including "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 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 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.

In an attempt to improve the response of TCC to therapy, oncologists at Purdue University conducted a study comparing chemotherapy (cisplatin) alone to chemotherapy plus piroxicam. In this study the combination of cisplatin and piroxicam was more effective against the cancer, but the combination treatment caused a rise in the urea level in a blood test. Although dogs did not have outward symptoms of kidney problems, this rise in urea level in the blood indicated that the combined therapy was being toxic to the kidneys. In fact, in most instances, the cisplatin therapy was withdrawn (so as to not cause kidney damage) while the tumors were still shrinking. Combining piroxicam with other chemotherapies has not been as successful. Currently, oncologists at Purdue University are conducting a study of cisplatin chemotherapy combined with a newer type of cox inhibitor (cox-2 inhibitor) with the expectation that tumor remission will occur with less toxicity from the treatment. Cox-2 inhibitors are expected to cause less side effects to the stomach and intestinal tract and to the kidneys. Recently, concerns have been published regarding a potentially small increase in risk for heart attack and stroke in people receiving cox-2 inhibitors. Cox-2 inhibitors are not thought to pose this risk for dogs because dogs do not develop disease in their blood vessels (atherosclerosis or "hardening of the arteries") like humans do. For more information on our study of cox-2 inhibitors and chemotherapy in dogs, please see link to "Clinical Trials in Pet Dogs with Urinary Bladder Cancer".

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 (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 have died after only a few days, while others have lived more than two years. 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. Longer survival times have been reached when chemotherapy is combined with piroxicam, but the optimal combination treatment is still being determined.

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 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. If the flow of urine out of the bladder is blocked, a cystostomy tube (small diameter tube that goes from the bladder through the wall of the abdomen to the outside) can be placed to allow emptying of the bladder. Complete obstruction can rapidly lead to a build up of urea and life-threatening complications. The tube can be used to "void" urine when the urethra is blocked. It is important for pet owners to observe their dog with TCC to be sure he/she is able to pass the urine.



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 being performed at the Dept. of Urology at the Indiana University School of Medicine. In the first trial, people with early stage bladder cancer (carcinoma in situ) are being treated with piroxicam after failing "standard" treatment. Of 5 patients treated to date, 2 have had complete remission of their cancer! A second trial for people with more locally advanced TCC is also underway with encouraging findings.

Studies in Dogs with Urinary Bladder Cancer

Purdue Comparative Oncology Program
Purdue University Veterinary Teaching Hospital

***Clinical trial of intravesical therapy.** This study is now complete. Followup of entered cases is ongoing. Check back in the fall, 2008, for more detailed results.

* **Clinical trial of “metronomic” therapy.** Ongoing trial testing a new therapy approach involving oral medication with minimal to no toxicity. Drugs very well tolerated to date.

***Epigenetic targeted drug trial.** This trial will test a drug (given intravesically or SQ) that will alter specific genes in cancer cells to stop cancer growth. Partial industrial support will offset pet owner expenses.

***Urethral and ureteral stent placement.** Through efforts of urologists at Purdue, we now offer urethral and ureteral stent placement to relieve urinary obstruction (major cause of death in dogs with bladder cancer) in dogs with cancer and in dogs with other urologic conditions.

***Bladder cancer genetics.** Blood samples from dogs with bladder cancer are being collected for genome scanning at the National Cancer Institute. Please help is obtain samples to allow us to determine the genetic factors that cause bladder cancer.

DNA methylation as a therapeutic target in cancer. A new drug will be administered aimed at reactivating tumor suppressor genes in the cancer cell. There must be (1) biopsy proof of TCC, (2) a measurable tumor mass, (3) normal kidney function, and (4) expected survival of 6 weeks or longer. (See more detailed explanation below)

For more information, please contact:

Ms. Patty Bonney at 765 494-1130, or one of the oncology clinicians at 765 494-1107. Thank you!

Clinical Trial of a Demethylating Drug in Dogs with Urinary Bladder Cancer (Transitional Cell Carcinoma, TCC)

What are demethylating drugs, and how do they work against cancer?

We have recently initiated a clinical trial of a new type of cancer therapy for dogs with bladder cancer. Briefly, in normal cells there is a balance between genes (pieces of DNA) in the cell that tell the cell to divide forming new cells, and genes that tell the cell when it should not divide. The genes that tell the cell not to divide are called tumor suppressor genes. In cancer cells, the tumor suppressor genes often do not work properly, and thus the cancer cells keep dividing, and the cancer keeps growing. If the tumor suppressor genes could be made to work properly, then the cancer should not grow and should regress. One of the things that keeps tumor suppressor genes from working like they should is a process called methylation. In methylation, extra material called methyl groups is attached to the DNA, and the methyl groups keep the genes from working correctly. We are testing a “demethylating” drug that is expected to remove this abnormal material (the methyl groups) from the tumor suppressor genes. This is expected to make the tumor suppressor genes work correctly again, and therefore to make the cancer regress.

What is involved in the study?

To participate in the study, dogs must have histopathologically diagnosed TCC, i.e. there must be a tissue biopsy to confirm the diagnosis of TCC. The dogs also must have normal kidney function, be in good general health, and have an expected survival of at least 6 weeks. Pet owners must read information about the study, talk to one of the veterinary oncologists in our group, and provide their consent in writing in order for the dog to participate. Before receiving the treatment, the dogs undergo complete evaluation including physical exam, blood count, blood chemistries, urinalysis, ultrasound, radiographs (x-rays), and cystoscopy. The treatment involves receiving an injection of the new drug under the skin once a day for 5 days in a row. Initially the 5-day treatment will be done once per month. It is possible the treatment may be increased to twice a month later in the study. To tell how well the new drug is working, the blood work, urinalysis, ultrasound, x-rays and cystoscopy will be repeated periodically following treatment. The evaluation and treatments must be done at the Purdue University Veterinary Teaching Hospital. Although it is not required, receiving permission from the pet owner to perform a necropsy (“autopsy”) when the dog dies (even if months to years after being in the study) would provide very helpful information.

The study is partially funded by a pharmaceutical company. Therefore, a large percentage of the expenses involved with treatment and evaluation are paid by the pharmaceutical company

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