

Canine Bladder Cancer Part 2

By Deborah W. Knapp, DVM, Dipl. ACVIM

What is the prognosis for dogs with Transitional Cell Carcinoma (TCC)?

Early studies reported survival in dogs with TCC as “0 days”. At that time, it was thought there was “no hope” and many 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 (“average”) survival in 55 dogs treated with surgery alone (before drugs that could help were identified) was 109 days. The median survival in dogs treated with early chemotherapy alone (cisplatin or carboplatin) at Purdue University was 130 days. Median survival with piroxicam treatment in 62 dogs with TCC was 195 days. As mentioned above, approximately 35% of dogs receiving mitoxantrone and piroxicam have remission, and the average survival is around 250-300 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, dogs who live the longest are those that receive more than one treatment protocol (one after the other switching therapies when the cancer begins to grow) during the course of the cancer. 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 50-60% have metastasis at death.

Although progress has been made, and TCC is considered a very “treatable” disease, there is still much to be learned. We are not satisfied with the “efficacy” of current therapy, especially long term. Therefore, we are continuing to study TCC to determine better ways to prevent, manage, and treat this cancer.

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. A frustrating aspect of urinary tract infections

that is being encountered more often in recent years is the development of bacterial infections that are resistant to commonly used antibiotics. These infections often require treatment with injectable antibiotic therapy.

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. Urethral stents are typically placed with fluoroscopic guidance



in a non-surgical procedure. Ureteral stents can be placed surgically, and in some cases non-surgically. 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.

Can TCC be prevented?

Steps that can be taken to reduce the risk of TCC in dogs, especially in dogs in high-risk breeds (Scottish Terriers, West Highland White Terriers, Wire Hair Fox Terriers, Shetland Sheepdogs, Beagles) include: (1) avoiding older generation flea control products, i.e., flea dips, (2) avoiding lawns treated with herbicides and pesticides, and (3) feeding vegetables at least three times per week. These will reduce the risk of TCC, although some dogs will still develop the cancer if these recommendations are followed. There are other causes for

(Continued on page 5)

TCC that have not yet been identified. The role of exposure to cigarette smoke in bladder cancer risk in dogs requires more study, but it would be best to limit exposure to smoke as it can cause other disease in dogs too.

TCC screening for early detection.



The Wellness Clinic in the Purdue University Veterinary Teaching Hospital is providing a TCC screening program for older dogs in high-risk breeds (Scottish Terriers, West Highland White Terriers, Wire Hair Fox Terriers, Shetland Sheepdogs, Beagles). The screening includes an ultrasound exam of the bladder and tests performed on the urine at six-month intervals. This program is considered optional in the care of dogs. Although the screening is expected to lead to earlier diagnosis and the chance to treat the cancer before it becomes advanced, it is not yet known if this screening program will improve the outlook for dogs or not. Pet owners who wish to schedule an appointment or check the availability and costs of the program can call the Purdue Small Animal Clinic at 765 494-1107. Stay tuned, as an expanded option for TCC screening has been under development since 2013.

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 clinical trials in humans with TCC at the Indiana University School of Medicine.

Canine Bladder Cancer Clinic at Purdue University.

Within the Oncology Section in the Purdue University Veterinary Teaching Hospital, a Canine Bladder Cancer Clinic

has been established to care for dogs that have TCC or dogs suspected of having TCC. The clinic is staffed by Dr. Deborah Knapp, other veterinarians specializing in oncology, veterinary technicians, and assistants. Diagnostic procedures including cystoscopy, cancer staging tests, and multiple types of therapy are offered. The Canine Bladder Cancer Clinic also has ongoing clinical trials to help dogs with TCC while learning new information that can help other dogs and potentially humans with this cancer. Veterinarians in the Bladder Cancer Clinic work closely with primary care veterinarians in the dog's home town to provide the most complete care. If you would like to schedule an appointment, please call the reception staff at 765 494-1107, or you may call our Clinical Trials Coordinator, Ms. Patty Bonney at 765 494-1130.

Recent Publications and Selected Earlier Publications Related to Bladder Cancer:

- Dhawan D, Ramos-Vara JA, Naughton JF, Cheng L, Low PS, Rothenbuhler R, Leamon CP, Parker N, Klein PJ, Vlahov IR, Reddy JA, Koch M, Murphy L, Fourez LM, Stewart JC, Knapp DW. Targeting folate receptors to treat invasive urinary bladder cancer. *Cancer Res* 2013;73:875-84.
- Knapp DW, Henry CJ, Widmer WR, Tan KM, Moore GE, Ramos-Vara JA, Lucroy MD, Greenberg CB, Greene SN, Abbo AH, Hanson PD, Alva R, Bonney PL. Randomized trial of cisplatin versus firocoxib versus cisplatin/firocoxib in dogs with transitional cell carcinoma of the urinary bladder. *J Vet Intern Med* 2013; 27:126-133.
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- Dhawan D, Ramos-Vara JA, Hahn NM, Waddell J, Olbricht GR, Zheng R, Stewart JC, Knapp DW. DNMT1: An emerging target in the treatment of invasive urinary bladder cancer. *Urol Oncol* 2012 May 18. [Epub ahead of print].
- Zhang J, Wei S, Liu L, Nagana Gowda GA, Bonney P, Stewart J, Knapp DW, Raftery D. NMR-based metabolomics study of canine bladder cancer. *Biochim Biophys Acta* 2012;1822:1807-14.
- Hahn NM, Bonney PL, Dhawan D, Jones DR, Balch C, Guo A, Hartman-Frey C, Fang F, Parker HG, Kwon EM, Ostrand EA, Nephew KP, Knapp DW. Subcutaneous 5-azacitidine treatment of naturally-occurring canine urothelial carcinoma: a novel epigenetic approach to human urothelial carcinoma drug development. *J Urol* 2012;187:302-9.
- McMillan SK, Knapp DW, Ramos-Vara JA, Bonney PL, Adams LG. Outcome of urethral stenting for management of obstruction secondary to transitional cell carcinoma in 19 dogs (2007-2010). *J Amer Vet Med Assoc* 2012;241:1627-32.
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- Childress MO, Adams LG, Ramos-Vara J, Freeman LJ, He S, Knapp DW. Comparison of cystoscopy vs surgery in obtaining diagnostic biopsy specimens from dogs with transitional cell carcinoma of the urinary bladder and urethra. *J Amer Vet Med Assoc* 2011;239:350-6.
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- Arnold EA, Childress MO, Fourez LM, Tan KM, Stewart JC, Bonney PL, Knapp DW. Phase II clinical trial of vinblastine in dogs with transitional cell carcinoma of the urinary bladder. *J Vet Intern Med* 2011; 25:1385-1390.

(Continued on page 6)

(Canine Bladder Cancer Part 2 continued from page 5)

Abbo AH, Jones DR, Masters AR, Stewart JC, Fourez L, Knapp DW. Phase I clinical trial and pharmacokinetics of intravesical Mitomycin C in dogs with localized transitional cell carcinoma of the urinary bladder. *J Vet Intern Med* 2010;24:1124-30.

Dhawan D, Craig BA, Cheng L, Snyder PW, Mohammed SI, Stewart JC, Zheng R, Loman RA, Foster RS, Knapp DW. Effects of short-term celecoxib treatment in patients with invasive transitional cell carcinoma of the urinary bladder. *Mol Cancer Ther* 2010;9:1371-1377.

Dhawan D, Ramos-Vara JA, Stewart JC, Zheng R, Knapp DW. Canine invasive transitional cell carcinoma cell lines: in vitro tools to complement animal model of invasive urinary bladder cancer. *Urolog Oncol* 2009; 27:284-292.

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Knapp DW, Adams LG, Degrand AM, Niles JD, Ramos-Vara JA, Weil AB, O'Donnell MA, Lucroy MD, Frangioni JV. Sentinel lymph node mapping of invasive urinary bladder cancer in animal models using invisible light. *Eur Urol* 2007; 52:1700-1708.

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; 5:329-336.

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;12:353-360.

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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;2:183-188.

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Knapp DW, Richardson RC, Chan TCK, Bottoms GD, Widmer WR, DeNicola DB, Teclaw R, and Bonney PL. Piroxicam therapy in 34 dogs with transitional cell carcinoma of the urinary bladder. *J Vet Intern Med* 1994;8:273-278.

Knapp DW, Richardson RC, Bottoms GD, Teclaw R, Chan TC. Phase I trial of piroxicam in 62 dogs bearing naturally occurring tumors. *Cancer Chemother Pharmacol* 1992;29:214-218.



Request for Samples

RESEARCH PROJECT	SAMPLES NEEDED	CONTACT INFORMATION
Genetic marker for Atopic Dermatitis	Saliva swabs or blood samples from dogs with skin disease or from normal dogs 5 years of age or older from family lines free of allergies	Kim Williams North Carolina State University 919-513-7235 kdwilli4@ncsu.edu
Genetic susceptibility of Transitional Cell Carcinoma (TCC) (Bladder Cancer)	Blood samples from dogs diagnosed with TCC and dogs over the age of nine who have no known cancers	Gretchen Carpintero Ostrander Lab National Human Genome Research Institute 301-451-9390 Dog_genome@mail.nih.gov
Study to validate the diagnosis of Transitional Cell Carcinoma	Free-catch urine sample, access to dog's clinical records relating to the cancer, and access to biopsy specimen	Breen Lab NCSU info@breenlab.org
Genetic marker for Addison's Disease	DNA from cheek cells and/or blood from affected dogs and unaffected dogs over the age of 7	Dr. A.M. Oberbauer UC Veterinary School (Davis) 530-752-4997 http://cgap.ucdavis.edu/
Genetics of Idiopathic Pulmonary Fibrosis (IPF)	Cheek swab samples from dogs diagnosed with IPF	To order DNA kits go to the following website: Canine.Tgen.org Click on IPF study
Clinical Features and Genetic Basis of Pulmonary Fibrosis	Blood samples from dogs diagnosed with PF and healthy dogs over age 8 without lung disease	Katie Minor University of Minnesota 612-624-5322 minorok@umn.edu
Dry Eye Syndrome (keratoconjunctivitis sicca)	Dogs diagnosed with dry eye and dogs over 7 years old with no ocular abnormalities *participants must be available for appointments at UC Davis Veterinary Center (CA)	Dr. Sara Thomasy UC Veterinary School (Davis) 530-752-1770 smthomasy@ucdavis.edu

For more information about any of the above projects visit www.westiefoundation.org