Overview of Canine Bladder Cancer: Although urinary bladder cancer comprises only 2% of all canine cancer, with the estimated six million new canine cancer cases each year in the US, there are tens of thousands of dogs with bladder cancer.\textsuperscript{1-3} The vast majority of bladder cancer in dogs consists of intermediate to high grade, invasive transitional cell carcinoma (TCC), also referred to as invasive urothelial carcinoma, which is the focus of this presentation.\textsuperscript{2,3}

Presentation, Diagnosis, and Staging: Hematuria and stranguria are the most common clinical signs associated with TCC in dogs.\textsuperscript{3} Since these signs are much more commonly due to urinary tract infection (UTI), it is important to first investigate that possibility. Should infection not be present, or if clinical signs do not resolve upon treatment of a UTI, then the veterinarian should look for other causes including stones and TCC. It is common for dogs to have TCC and UTIs concurrently, but the persistence or recurrence of clinical signs after appropriately treating the infection indicates the need to look further. Dysplastic epithelial cells in urine increase suspicion for TCC, although these cells can be present in dogs with UTIs as well.\textsuperscript{2,3} A mass observed with ultrasound or physical exam, or a urethral mass detected by rectal exam also increases suspicion for TCC. Differential diagnoses for bladder/urethral masses include: TCC, other neoplasia, chronic cystitis, granulomatous cystitis/urethritis, polypoid cystitis, calculi, and inflammatory pseudotumor.\textsuperscript{2-5} It is important to distinguish non-TCC conditions from TCC because the treatment and prognosis differ considerably and are dependent on the condition that is present. A tissue biopsy is used to make the definitive diagnosis of TCC. A tissue biopsy can be obtained by cystotomy, cystoscopy, or in some cases by catheter sampling.\textsuperscript{2,3,5-9} Cystoscopy allows the visual inspection of the urethra and bladder, and tissue biopsy collection in a non-invasive manner. With the small size of cystoscopic biopsies, the operator must be diligent to collect sufficient tissue for diagnosis. A wire stone collection basket can be used to obtain biopsies from pedunculated masses, and placing tissues in a histology cassette prior to processing helps prevent loss of small samples. Currently, diagnostic biopsies can be obtained in more than 95% of female dogs and in more than 85% of male dogs via cystoscopy performed by an experienced operator. Percutaneous aspiration and biopsy methods can lead to tumor seeding and are best avoided.\textsuperscript{10-12} In poorly differentiated carcinomas, immunohistochemistry for uroplakin III (UPIII) can aid in distinguishing TCC from other carcinomas. UPIII is expressed in >90% of canine TCC, and has been considered specific for TCC, although there are reports of UPIII expression in prostatic carcinoma, possibly from TCC of the prostatic ducts.\textsuperscript{13,14}

TCC is most often located in the trigone region of the bladder. It also involves the urethra in more than half of dogs, and the prostate in approximately one third of male dogs.\textsuperscript{2,3} It is important to perform a rectal exam if TCC is suspected. This could reveal urethral thickening or masses not detected by imaging. A thorough physical exam can be useful in detecting thickening of the urethra and trigone region of the bladder, enlargement of iliac and inguinal lymph nodes, and sometimes a mass in the bladder or a distended bladder. However, a normal physical exam does not rule out TCC.

In dogs with confirmed or suspected TCC, overall health should be assessed through CBC, serum biochemistry profile, urinalysis, +/- urine culture, and the cancer staged via thoracic radiography, abdominal ultrasonography, and urinary tract imaging (or by computed tomography, “CT”).\textsuperscript{2,3,5} Approximately 15-20% of dogs with TCC have metastasis at diagnosis, and more than half have distant metastasis at death.\textsuperscript{2,3,5} Common sites of metastases include lymph nodes, liver, and lung. Less common metastatic sites include bone and other organs. Urinary tract imaging is used to assess the TCC location for potential surgical intervention and to map and measure TCC masses in order to subsequently determine response to medical therapy. Mapping TCC in the bladder, proximal urethra, and prostate can be accomplished by cystosonography, cystography, or CT.\textsuperscript{3,5,15,16} Cystosonography has advantages over the other techniques in that it is less expensive and can be performed in most dogs without sedation/anesthesia. But, to use cystosonography to measure bladder and urethral masses over time, it is imperative to standardize the procedure from exam to exam in the same dog. The cystosonography protocol in use at our institution includes the same operator, machine, patient position, probe angle, same two imaging planes, and similar level of bladder distension. When carefully employing this technique, the inter-exam variability detected over multiple exams on the same
day is <10%. If a standardized imaging protocol is not followed, regardless of whether cystosonography or other imaging technique is used, measurements cannot be accurately compared from visit to visit.

Treatment: The objective of TCC treatment should be to eradicate the cancer when possible, BUT, this is usually not possible. Therefore, the main objective usually becomes to control or shrink the cancer, and to provide as long a period of good quality life as possible. The “good news” is that TCC is highly treatable, even when not curable. More than 75% of dogs can enjoy months to a year or more of good quality of life. The use of surgery and stent placement, and drugs to treat TCC will be discussed.

Surgery and Stent Placement: Because of the trigonal location, frequent urethral involvement of the cancer, and in some cases metastases, complete surgical resection of TCC is usually not possible in dogs. In addition, many dogs develop multifocal TCC in the bladder, consistent with the “field effect” in which the entire bladder lining is thought to undergo malignant change in response to carcinogens in the urine. Thus, the indications for surgery in dogs with confirmed or suspected TCC include: (1) obtaining tissue for a diagnosis, (2) removing the TCC within the bladder if lesions are away from the trigone, and (3) restoring urine flow. If surgery is performed, it is essential to take measures to avoid seeding the cancer in the abdominal wall and other locations. TCC in the abdominal wall, once established, has responded very poorly to medical therapy.

Surgery and other “non-surgical” interventional procedures can be important in restoring or maintaining urine flow. Ureteral stents, when needed, have traditionally been placed surgically, although less invasive techniques have also been described. Prepubic cystostomy tubes that bypass urethral obstruction are another option, although, the placement of urethral stents has gained favor over cystotomy tubes in many cases because external tubes are avoided, and the pet owner does not have to drain the bladder. The survival following stent placement can vary considerably from dog to dog and can range from a few days to over a year. Urinary stents can be placed nonsurgically with fluoroscopic guidance. A technique using ultrasound-guided transurethral laser ablation to debulk TCC lesions has been reported, although the risks versus the potential benefit of this approach require further study. One of the challenges in transurethral resection is the difficulty in judging the deeper aspects of the tumor and the risk of cutting too deep and perforating the urinary tract. Similarly, an more complete understanding of the benefits and risk, and optimal protocols for radiation therapy of TCC are also awaiting further study.

Systemic and Local Medical Therapy: Systemic medical therapy is the mainstay of TCC treatment in dogs. This usually includes chemotherapy, cyclooxygenase (COX) inhibitors (nonselective and COX-2 inhibitors), and combinations of these. Although medical therapy is not usually curative, several different drugs can lead to remission or stable disease of TCC, and most therapies are well-tolerated. While remission is obviously preferred, stable disease with maintained good quality of life is considered a beneficial response to treatment. Resistance to one drug does not necessarily mean resistance to other drugs. The dogs with TCC that tend to do the best for the longest periods of time are those that sequentially receive multiple different treatment protocols over the course of their disease. The approach used to treat dogs with TCC in the Purdue Comparative Oncology Program is to obtain baseline measurements of the TCC masses, to initiate a starting treatment, to monitor the response to that treatment at 4-8 week intervals, and to continue that treatment as long as the TCC is controlled, side effects are acceptable, and quality of life is good. If the TCC progresses or unacceptable toxicity occurs (that persists following dose adjustments), then a different treatment is instituted. Subsequent treatment changes are based on tumor response and treatment tolerability. With this approach, TCC growth can be controlled in approximately 75% of dogs, the dogs’ quality of life is usually very good, and survival times can extend well beyond a year. Although it could be tempting to simultaneously combine multiple chemotherapy agents in dogs with TCC, the benefit of this has not been determined, and the potential development of resistance to multiple drugs at the same time could limit the options for subsequent therapy.

There is no one defined “best” treatment that all dogs with TCC should receive. In fact, there may be as many as a dozen different drugs that could help dogs with TCC. In deciding which treatment to pursue at our Veterinary Teaching Hospital, options that are discussed with the dog owner include oral medications, intravenous treatments, and treatments that have been used for years vs new treatments that are part of a clinical trial. If the cancer is causing urinary obstruction or an immediate risk for blocking urine flow into or out of the bladder, then intravenous drugs are preferred as they have a better chance of shrinking the tumor when compared to oral medications. If complete urethral obstruction is present, this is life threatening, and a stent or
some other urinary bypass would also be required.] Similarly, if the dog’s clinical signs are very bothersome, then intravenous medicines are usually recommended to provide the best chance of shrinking the cancer. If the cancer is not at risk for causing obstruction, and the clinical signs are mild, and the dog owner prefers a conservative approach, then oral medications may be selected. Clinical trials offer the opportunity for the dog to receive a new medicine that could work better than traditional drugs, that would be expected to be well tolerated, and that in most instances would cost less than traditional chemotherapy; although the efficacy and safety of the new drugs are not fully proven yet – that is the purpose of the trial. At the same time the dog is treated in a clinical trial, the veterinary team learns important information that can help other dogs and humans with invasive TCC. There is a subset of human TCC that closely resembles the cancer in dogs, and this is why new successes in dogs could lead to new successes in humans. This will be expanded on in the two presentations.

Oral medicines for TCC typically include COX inhibitors and low dose oral chemotherapy. As a single agent, the nonselective COX inhibitor, piroxicam (0.3 mg/kg po daily), can provide excellent quality of life, and in a series of 76 dogs induced complete remission (CR, regression of all clinically-detected cancer) in 2.6%, partial remission (PR >50% reduction in tumor volume) in 18.4%, stable disease (SD, <50% change in tumor volume) in 59.2%, and progressive disease (PD, >50% increase in tumor volume, and/or new TCC lesions) in 19.7% of dogs. The median progression free interval (PFI) was 120 days (range 17-1256 days), and median survival was 244 days (range 6-1256 days) although some dogs received other therapies after failing piroxicam. For dogs that only received piroxicam, the median survival was 176 days. For comparison, the median survival of 55 dogs in the Purdue Comparative Oncology Program Tumor Registry that did not receive medical therapy, but received cytoreductive surgery alone was 109 days. Although most dogs tolerate piroxicam well, it is important to instruct the pet owner to monitor for gastrointestinal (GI) toxicity. If vomiting, melena, and anorexia occur, the drug must be withdrawn and supportive care provided as needed until the toxicity resolves. Otherwise, GI ulceration could occur. In these cases, it is usually considered safest to then switch to a COX-2 inhibitor if further COX inhibitor treatment is indicated.

The COX-2 inhibitors, deracoxib (Deramaxx, Novartis) and firocoxib (Previcox, Merial) have also been evaluated in dogs with TCC. The tumor response to deracoxib, given as a single agent at a dosage of 3 mg/kg PO daily to 26 dogs with TCC, included 4 (17%) PR, 17 (71%) SD, and 3 (12%) PD. The median survival following deracoxib and subsequent therapies was 323 days. The dose of deracoxib in the study (3 mg/kg per day) was higher than the dose of deracoxib typically given for inflammation and pain. Mild GI toxicity occurred in 20% of the dogs with TCC in the study, and 4% of dogs had renal or hepatic side effects. Firocoxib has also had antitumor activity in dogs with TCC with 20% having remission in a small series of dogs (n=12). It is not yet known if nonselective COX inhibitors and COX-2 inhibitors are equally effective in treating TCC. COX-2 inhibitors do offer the advantage of less GI toxicity. Another important feature of COX inhibitors is that they enhance the activity of chemotherapy.

Another oral drug used in dogs with TCC is leukeran (chlorambucil), an alkylating agent given in low dose daily “metronomic” chemotherapy. In a clinical trial of leukeran (4 mg/m² daily) in dogs with TCC, 1 dog (3%) had PR, 20 dogs (67%) had SD, and 9 dogs (30%) had PD (1 dog was lost to follow-up). The median PFI was 119 days (range, 7 to 728 days), and median survival time from the initiation of chlorambucil until death was 221 days (range, 7 to 747 days). After many months of treatment, chronic bone marrow suppression can occur from daily leukeran treatment, thus it is essential to monitor CBCs, and withdraw the drug is needed.

Multiple intravenous chemotherapy drugs have been evaluated in dogs with TCC. The two that are used most frequently at our institution are vinblastine and mitoxantrone. Mitoxantrone has been in use longer than vinblastine in dogs with TCC. In a study of 55 dogs with TCC treated with mitoxantrone (5 mg/m² X 5 doses) and piroxicam, 35% of dogs had remission with minimal toxicity, and the median survival was 291 days. In a phase II study of 28 dogs with TCC treated with vinblastine, 36% of dogs had PR, 50% of dogs had SD, and the majority of dogs had failed other therapies. In a follow-up study, 51 dogs with TCC were randomized to receive vinblastine (2 to 2.5 mg/m² depending on body weight) and piroxicam given concurrently or vinblastine alone followed sequentially by piroxicam alone if the dogs failed vinblastine alone. For dogs receiving vinblastine and piroxicam concurrently, tumor responses included 58% PR, 33% SD, and 8% PD. The response to vinblastine alone included 22% PR, 70% SD, 4% PD, and 4% NA. Thus, currently, at our
institution, the intravenous treatment of choice for dogs that would most benefit from rapid tumor reduction consist of intravenous vinblastine plus oral piroxicam given simultaneously. It was interesting to note in the study, however, that the median overall survival time for dogs receiving vinblastine alone followed by piroxicam alone (n=20, 531 days) was significantly longer (P=0.03) compared to dogs receiving vinblastine and piroxicam simultaneously (299 days). This is in line with an earlier study in which the remission rate of dogs receiving cisplatin and piroxicam concurrently was higher than cisplatin alone, but the survival of dogs receiving cisplatin alone followed by piroxicam alone appeared longer than those receiving the two drugs simultaneously. This raises intriguing possibilities including the potential “priming” effects of chemotherapy for subsequent response to COX inhibitor treatment, and the potential value in giving drugs sequentially in order to prevent the development of resistance to both drugs simultaneously which would affect second line treatment success. A sequential drug approach could be considered in dogs with TCC with minimal clinical signs, and in which the cancer is not likely to impinge on urine flow in the near future.

Other intravenous treatments have shown activity in dogs with TCC. Cisplatin, is likely to be the most effective agent, but is rarely given to dogs due to consistent toxicity including renal damage. Carboplatin combined with piroxicam induced remission in 38% of dogs with TCC in a phase II trial, although toxicity was relatively common compared to other protocols. The use of gemcitabine and piroxicam, as well as other drugs, have also been reported in dogs with biopsy confirmed or cytologic evidence of TCC.

Intravesical therapy is commonly used in humans with superficial TCC, i.e. tumors that are not invading the bladder wall, and pet owners will sometimes ask about using this approach in their dog with TCC in which the tumor is typically invading the bladder wall. Intravesical therapy with mitomycin C was investigated in dogs with bladder-confined TCC, but unpredictable severe bone marrow and GI toxicity (from presumed systemic absorption of the drug) limit this approach. Intravesical BCG treatment, which is often used in humans, has not been studied in formal trials in dogs with TCC; concerns for its use include risk of systemic absorption and granuloma formation, lack of evidence for its effectiveness in dogs, and limited drug availability.

Secondary UTIs are common in dogs with TCC. If clinical signs worsen in the face of stable tumor size, a UTI should be ruled in/out via urinalysis, and if indicated urine culture and sensitivity. To avoid the risk of seeding TCC through cystocentesis, urine may be collected by free catch or catheterization. If a catheter is to be passed, care must be taken to avoid penetrating the diseased bladder or urethral wall.

Prevention of TCC: There is considerable information which the veterinarian can use to reduce the risk of TCC in dogs and to know which dogs are at higher risk in order to act on urinary tract signs quickly. TCC risk factors include exposure to older generation flea control products and lawn chemicals, obesity, possibly cyclophosphamide exposure, female gender (female: male ratio of 1.7-1.9), and very strong breed-associated risk. Neutered dogs of both genders are more likely to develop TCC than intact dogs, although the mechanisms for this increased risk have not been determined. Regarding breed-associated risk, Scottish Terriers have an 18-20X increased risk; and Shetland Sheepdogs, Eskimo Dogs, West Highland White Terriers, Keeshonds, Samoyeds, and Beagles have a 3-6X increased risk. In these breeds, it would appear prudent to avoid exposures that could further increase risk (old generation flea control products, lawn chemicals), to maintain a healthy body weight, and to make note and follow-up on urinary tract signs. In Scottish Terriers, the consumption of vegetables at least three times per week was associated with a 70% decreased risk for TCC (OR, 0.30; 95% CI 0.01-0.97; P < 0.001), feeding vegetables to Scotties and to other dogs in high risk breeds could be suggested. The owners of dogs in high-risk breeds should be informed of the TCC risk and encouraged to contact their veterinarian about any potential urinary tract signs. Prospective studies to determine the value of TCC screening and early detection are in progress.

In summary, the outlook for dogs with TCC has improved substantially over the last several years, and is actually quite good in the majority of cases. TCC has truly become a “treatable” disease with at least 75% of dogs having a beneficial response to therapy. As will be discussed in the follow-up talk: “Research in Canine Bladder Cancer Improving the Outlook for Dogs and Humans”, the outlook for the future is even more exciting.
References:


