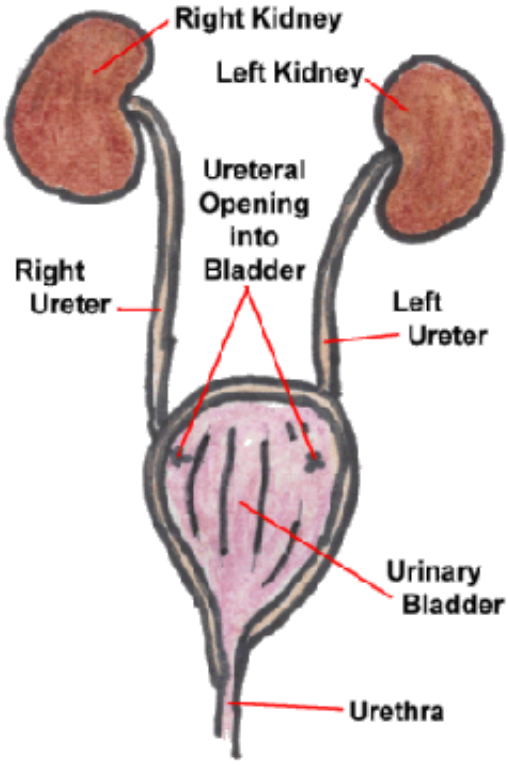
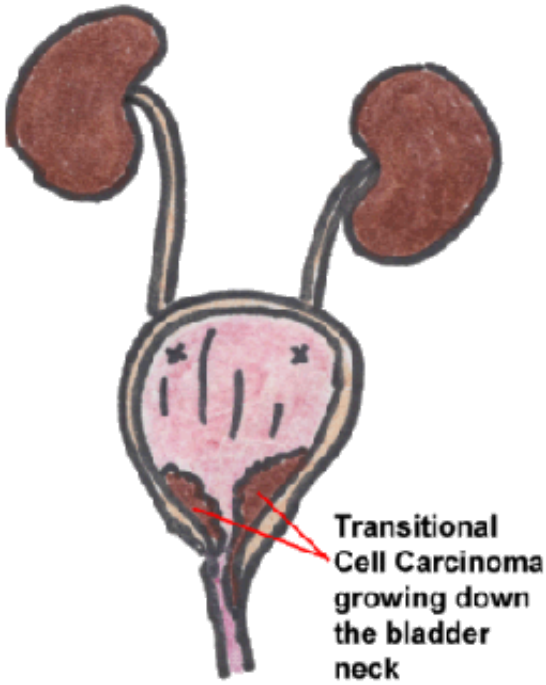
Transitional Cell Carcinoma

The Pet Health Care Library

The transitional cell carcinoma (frequently abbreviated TCC) is a particularly unpleasant tumor of the urinary bladder. In dogs, it usually arises in the lower neck of the bladder, where it is virtually impossible to surgically remove, and causes a partial or complete obstruction to urination. The urethra (which carries urine outside the body) is affected in over half the patients diagnosed with transitional cell carcinoma; the prostate gland of male animals may also be involved. In cats, the site of the tumor within the bladder is more variable. Bloody urine and straining to urinate are typically the signs noted by the owner.



Normal urinary tract showing kidneys, ureters, bladder, and urethra. This is called a half shell view as if the tract were opened vertically for viewing. Illustration by Wendy Brooks



Urinary tract with a transitional cell carcinoma growing in the bladder neck and down the urethra. Illustration by Wendy Brooks

Why is this Tumor Called a Transitional Cell Carcinoma? Is Something in Transition?

Epithelial cells are cells that line areas of the body that interface with the outside environment. There are many different types of epithelial cells depending on the immediate environment they contact. The skin, for example, is a barrier against irritants and wounds. The tough cells that make up the skin are called squamous epithelial cells because of their flat, overlapping, scale-like design that helps them form a barrier similar to the shingles of a roof-top. The epithelial cells of the respiratory tract secrete lubricant but also are designed to trap inhaled particles in secreted mucus and use tiny hair-like cilia to push them out of the lower tract and back upward where they can be coughed up. These are called ciliated columnar epithelial cells.

The urinary bladder is lined by transitional cells. They must protect the body from the caustic urine inside the bladder but also must maintain this barrier when the bladder stretches and distends with larger volumes of urine. A transitional cell carcinoma is a tumor of the transitional cell lining of the urinary bladder.

Arrows indicate the transitional cell lining of the normal dog's bladder.

While bladder tumors are somewhat rare as types of cancers go in pets, more than half (and possibly up to 70%) of the bladder tumors developed by pets are transitional cell carcinomas.

What Causes this Tumor?

As with most cancers, we do not know many specific causes. Presumably, repeated exposure to carcinogens in the urine is an important cause. We know that chemotherapy with cyclophosphamide is one cause. We know that female dogs tend to get more transitional cell carcinomas than male dogs, possibly because females do less urine marking and are thus possibly storing urinary toxins longer. In cats, however, males have an increased risk over females. Urban dwelling and obesity have been found to increase the risk for the development of this tumor. We know that Shetland sheepdogs, West Highland White terriers, Beagles, and Scottish terriers seem to be predisposed breeds. Beyond this, specifics remain unknown.

A recent study showed that exposure to phenoxy herbicide treated lawns increased the risk of developing TCC in the Scottish terrier. Another study investigating TCC in Scottish terriers found that the risk for development of this tumor could be reduced by feeding yellow/orange or green-leafy vegetables at least three times per week.

The average age at diagnosis in dogs is 11 years.
The median age at diagnosis in cats is 15 years.

What Kind of Testing Is Needed to Identify this Tumor?

Bloody urine with straining can be caused by many other conditions besides cancer. A severe bladder infection, a bladder stone, or feline lower urinary tract diseasewould be far more common and must be explored first. In other words, reaching a diagnosis is a step-by-step procedure whereby the most common conditions are individually ruled out until a diagnosis is confirmed.

First step: Urinalysis and culture.
Many people are confused by the difference between these two tests. A urinalysis is an analysis of urine including a brief chemical analysis and a microscopic examination of the cells contained in the sample. A culture involves plating a sample of urine sediment on growth medium, incubating for bacterial growth, identifying any bacteria grown, and determining what antibiotics are going to be effective.

Urinalysis and culture will rule in a bladder infection. (A documented infection absolutely does not rule out a tumor as tumors may easily become infected.)

About 30% of TCCs will shed tumor cells into the urine that may be identified as such on the urinalysis.

If an infection is identified in the bladder, it may be worthwhile to simply treat it with the appropriate antibiotic and see if the clinical signs resolve. There are some circumstances under which further testing may be recommended.

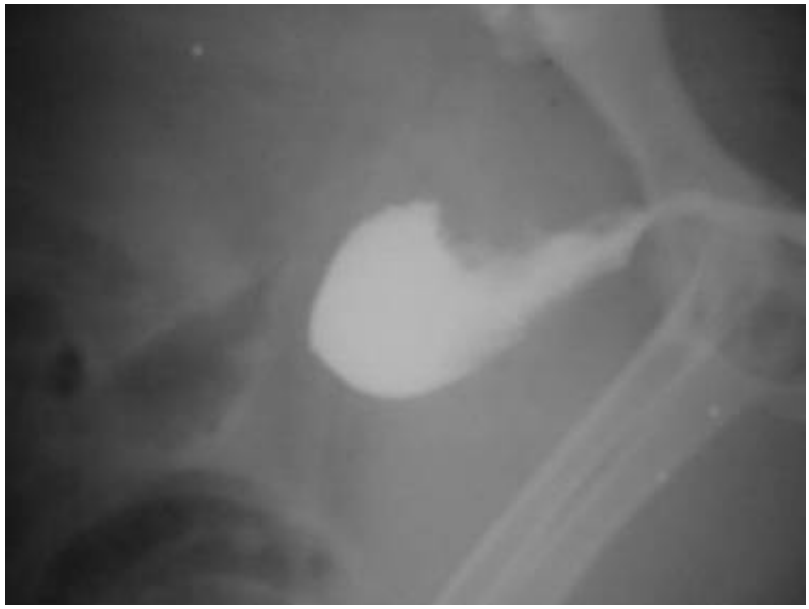
Second Step:
If no infection is found, if the urinalysis is normal despite obvious symptoms, or if a growth is palpable, radiographs would be the next step. The goal at this point would be to rule out a bladder stone. Bladder tumors are not visible on plain radiographs though sometimes some bony

proliferations grow on the pelvic bones in reaction to bladder tumors.

Third Step:
If no stone is visible on the radiographs, it may be a good idea at this point to do a bladder tumor antigen test (called a V-BTA test). This is an immunological test that detects antibodies generated in response to bladder tumor antigens. If the test is negative, there is a 90% chance that a bladder tumor is not present. If the test is positive, there is a reasonable possibility of a false positive so further testing is needed. In either case, further imaging is necessary so it is reasonable to skip to the next step without doing this test. It has been suggested that large amounts of blood in the urine will interfere with the accuracy of this test. Since the usual symptoms suggesting the possibility of transitional cell carcinoma include bloody urine, it may be difficult to get a sample that is adequately non-bloody. If interpretation of the test is likely to be confusing, it is often skipped.

Fourth Step:
At this point, specific imaging methods are needed to see inside the urinary bladder. This can be done with contrast radiography, ultrasound, or cystoscopy.

Contrast Radiography
With this technique, a combination of radiographic dye and air are injected into the bladder via a urinary catheter. This allows definition of structures within the bladder such as bladder stones, which are radiolucent (i.e., do not show up on plain radiographs; polyps, which are benign growths in the bladder caused by chronic inflammation; or tumors. The procedure is simple and probably the least expensive of all three methods as most animal hospitals have the equipment to perform contrast radiography. The problem is that female animals are rather difficult to catheterize. If the patient is a female, ultrasound may be a better choice.



Radiograph of a bladder injected with radiographic dye. The top right of the bladder oval is obscured, because of a filling defect: A transitional cell carcinoma is taking up that space in the bladder, preventing the dye from filling up the entire space.

Ultrasound
Ultrasound uses sound waves to create an image of structures within the urinary bladder. This offers a non-invasive way to detect radiolucent stones, polyps, or tumors within the bladder. If a growth is found, a needle can be used to withdraw cells from it using ultrasound guidance to possibly make a positive diagnosis. Ultrasound is also necessary to determine the extent of tumor spread after diagnosis has been confirmed (see below). Ultrasound is not available in all hospitals but your veterinarian can give you a referral.

Cystoscopy
With cystoscopy a tiny camera on a flexible thin rod is inserted into the urethra and the bladder can be visualized. Small biopsy instruments can travel up the channel to collect tissue samples. This equipment is highly specialized and is not available in many areas even at referral facilities.

Finding a mass in the neck of the bladder, even with inconclusive tissue samples, is often all that is needed to make a TCC diagnosis.

Transitional Cell Carcinoma has been Diagnosed. Now What?

When your pet is diagnosed with cancer most people want to know how long their pet has to live and what treatments are available. Prognosis depends on the stage of the disease (i.e., whether the tumor is invading other local organs, whether there is evidence of lymph node spread, if there is evidence of distant tumor spread.)

In one study, median survival time was 118 days for dogs with evidence of tumor invasion of other local organs compared with 218 days for dogs with no evidence of invasion beyond the urinary bladder.

Dogs with no involvement of local lymph nodes had a 234-day survival time compared to 70 days for dogs with local lymph node involvement.

Dogs with evidence of distant tumor spread had a median survival time of 105 days while those without distant spread had a survival time of 203 days.

In one study of 20 cats with TCC, the median survival time was 261 days.

Ultrasound of the belly is needed to assess the involvement of local lymph nodes and whether or not other organs have been invaded. Radiographs of the chest are the usual way to screen for distant tumor spread; most tumors will spread to the lung, leaving visible round opacities there.

What are the Treatment Options?

Any way you look at it, a transitional cell carcinoma is bad news. It is aggressively malignant and generally grows in an area not very amenable to surgical removal. If the tumor becomes so large and deeply invasive that the patient cannot urinate, an unpleasant death ensues in a matter of days.

Surgical Options

Partial Removal of the Bladder
If the tumor is fairly small at the time it is detected, it may be worth attempting to remove it and this means removing part of the bladder. If you are lucky, complete removal or long-term survival is possible. (In one study over half the patients were alive a year after surgery!) There are problems with this therapy. It is not possible to determine with the naked eye what the margins of the tumor actually are, so it is easy for surgeons to believe they have removed enough tissue when in fact they haven't. Also, the reduced storage capacity of the remaining bladder leads to a need to urinate more frequently. If recurrence happens, it generally does so within one year of surgery and is thought to occur from either inadequate tumor removal during surgery or development of a new tumor via the same mechanism that led to the development of the original one.

Permanent Urinary Catheter
A permanently placed urinary catheter can be implanted in the patient's urinary tract to create more comfortable urination. The placement of a foreign body in this way will predispose the patient to bladder infection and frequent screening cultures will be needed; still, in one study six out of seven owners reported satisfaction with results. Obviously, this procedure does nothing to hinder the tumor's growth. Owners will need to empty the bladder with a drainage tube at least three times a day to avoid stagnation of urine. The entrance to the catheter must be kept clean and must be cleaned daily. Tube dislodgement is a serious complication. Newer tubes are short and a longer drainage tube is attached during bladder emptying. More traditional permanent catheters are longer and will require some sort of wrap or garment for protection. If a tube dislodges, it must be replaced by within 48 hours as scar tissue rapidly forms to close the opening into the bladder. Sedation is required for tube replacement; it is not something an owner can do at home.

Urethral Stenting
In this procedure, a metal stent is placed in the urethra to allow urine passage through the tumor. This is a similar concept as the permanent catheter but more high tech. The stent is placed either surgically or with a video radiography called fluoroscopy. The procedure is relatively simple and not invasive but does require specific equipment. Urinary incontinence is unfortunately a common problem after this procedure, and special garments or diapers may be needed indoors.

Ureterocolonic Anastomosis
With this procedure the entire urinary bladder is removed. The kidneys (where urine is produced) normally deliver urine to the bladder for storage via tiny tubes called ureters. After the bladder is removed, the ureters are attached to the colon so that the patient effectively passes urine rectally along with stool. This is a radical surgery and potential complications can include scarring of the ureters and loss of kidney function, infection, and blood biochemical abnormalities. Special diets are required after surgery as well as long-term antibiotics, frequent blood test monitoring, and free

access to an area for urination (pets will need to urinate approximately every 4 hours).

Laser Ablation with Chemotherapy
A study was published in the February 15, 2006, issue of the Journal of the AVMA where seven dogs with transitional cell carcinomas were treated with a combination of laser ablation, piroxicam (see below) and mitoxantrone (see below). Laser ablation has been used for many years in humans with urinary tract cancer. In short, a surgical laser is used to vaporize the tumor from the surface of the bladder and urethra. In the study above, the eight dogs received this treatment followed by chemotherapy and their symptoms and survival were tracked. Median disease-free interval (i.e. the time without significant symptoms) was 200 days and median survival time was 299 days. These survival times were felt to be similar to those achieved with chemotherapy alone and no surgery at all; however, a more lasting resolution of symptoms was felt to have been achieved with this combination treatment. Please note only seven dogs were studied (an eighth received treatment but died after the first chemotherapy treatment from an automobile accident); information from a larger population would be helpful in solidifying these interpretations.

Medication (Chemotherapy)

Doxorubicin (Adriamycin)
This intravenous medication in combination with cyclophosphamide(yes, the same cyclophosphamide that is known to cause bladder tumor development), provided a median survival time of 259 days in one study. Another study using doxorubicin in combination with cisplatin achieved a median survival time of 358 days. More studies are needed for more definitive response information.

Piroxicam
This medication is a non-steroidal anti-inflammatory drug (NSAID), previously used to treat canine arthritis but largely abandoned for that after development of safer products. It is not clear if this medication works because of its anti-inflammatory effect or if it actually has anti-tumor effects, both therapeutically and preventively. This medication is inexpensive, given once a day (or less in cats), available through most human pharmacies, and administered orally. Because of these qualities, it is popular as a conservative therapy. Side effects include potential for stomach ulcers and effects on the kidney, though these can be addressed with additional medications should they become problematic.

Mitoxantrone
A combination of piroxicam and mitoxantrone has been studied and yielded a measureable response in 35% of patients. Approximately 18% had intestinal side effects and 10% had kidney-related side effects. The median survival time was 350 days. For many oncologists, this protocol is the first choice in therapy. Daily oral piroxicam is used and intravenous mitoxantrone is given every 3 weeks for four treatments.

Radiation Therapy

Specialized facilities are required to deliver radiation therapy so if you choose this treatment some travel is likely to be needed. Here, the patient is anesthetized, the bladder is surgically exposed and a radiation beam targets the tumor. In other techniques, the bladder is not surgically exposed and the radiation beam targets the tumor externally. It is not clear if one method produces better results. In most cases, surgery or chemotherapy is performed in conjunction with radiotherapy. Results have been variable with some long survival times and some patients with short survival times. The urinary bladder tends to scar with exposure to radiation, which leads to incontinence. More work is needed to develop a more clearly beneficial radiation therapy protocol for the treatment of bladder tumors.

Links

Transitional cell carcinoma is a disease that not all veterinarians are comfortable treating. Discuss with your veterinarian whether referral to a specialist would be best for you and your pet.

Cancer treatment for a pet can be an expensive and emotionally exhausting. Sometimes participation in a study where treatment is free is helpful. Animal Clinical Investigation LLC is a Maryland-based Limited Liability Company founded by Chand Khanna, DVM, PhD, Diplomate - American College Veterinary Medicine (Oncology). The mission of Animal Clinical Investigation LLC is to help in the development of new treatment opportunities for pet animals with cancer through the design and implementation of prospective clinical trials. To review on-going studies and learn how you might be

able to qualify for free treatment, visit www.animalci.com