Philip J. Bergman
DVM, MS, PhD; Diplomate ACVIM, Oncology Director, Clinical Studies – VCA Antech Oncologist

Katonah-Bedford Veterinary Center

Philip.Bergman@vca.com

LOWER URINARY TRACT TUMORS

INTRODUCTION – Lower urinary tract tumors of the urinary bladder and urethra accounts for approximately 1-2% of reported malignancies in dogs. The most common tumor of the lower urinary tract is transitional cell carcinoma (TCC), but other differentials such as squamous cell carcinoma, undifferentiated carcinoma, adenocarcinoma, rhabdomyosarcoma, fibroma, other mesenchymal neoplasia and metastatic neoplasia exist. Unfortunately, most TCC's in veterinary medicine are aggressive and invasive intermediate to high-grade papillary tumors.
The etiology of bladder cancer, like most cancers across species is multifactorial. Risk factors identified to date include gender (female predisposition), breed (Scotties, Shelties, Beagles, Wirehaired Fox Terriers, Westies), cyclophosphamide administration, obesity and exposure to insecticides and/or herbicides. In a case control study of 166 Scottish Terriers, exposure to herbicides and/or insecticides through household lawn & garden chemicals was compared between Scotties with TCC vs. controls. There was no increased risk for TCC in lawns treated with insecticides alone, whereas the risk was statistically increased with herbicide use alone or with concomitant herbicide/insecticide use. Earlier case control studies have found an increased risk for topical application of flea and tick dips, but newer spot-on products were not associated with an increased risk of TCC.

The most common location for lower urinary tract TCC's is the trigone region. Due to this anatomical location, partial or complete urinary obstruction can be common sequelae. Prostatic involvement in the male dog is common, and it is more common for prostatic tumors to be prostatic urethral TCC than true prostatic adenocarcinoma. On presentation, approximately 15% of dogs with TCC will have local lymph node metastasis and/or distant metastasis, whereas upon death, approximately 50% of dogs with TCC will have distant metastasis. The WHO staging TNM-based system has tumor designations from Tis (carcinoma *in situ*) through T3 (invasion of neighboring organs) with approximately 75% of canine TCC's are T2 (invasion of bladder wall) and 20-25% are T3. These data further strongly suggest these are locally aggressive tumors with significant metastatic potential.

There are relatively scant data on urinary bladder TCC's in cats. Wilson et al reported on the clinical signs, treatments and outcomes of 20 cats with urinary bladder TCC. When compared to dogs, cats appear to have a reduced number of trigonal lesions, whereas most other aspects concerning this disease are similar between dogs and cats (i.e. clinical signs, metastatic propensity, response to various therapies, etc.).

DIAGNOSIS & STAGING – The most common clinical signs for dogs and/or cats with lower urinary tract tumors are hematuria, pollakiuria, dysuria and occasionally lameness due to hypertrophic osteopathy and/or bone metastasis. It is quite common for the urinary tract signs to temporarily resolve after antibiotic therapy. When a lower urinary tract tumor is suspected the minimum database should include a thorough physical exam, rectal exam (urethral thickening, mass effect and/or lymph node metastasis), CBC/Chem/UA (not cystocentesis-derived due to the chance for tumor tract seeding), urine culture, cystosonography or contrast cystography and 3 view chest radiographs. This author has found with an accomplished ultrasonographer, the utility of cystosonography is higher than with contrast cystography, especially when the bladder is not distended with urine and/or infused saline. Similarly, the ultrasound then allows for a complete examination of the abdomen looking for lymph node enlargement and/or other problems.

Histopathologic confirmation is the gold standard for diagnosis of lower urinary tract tumors, including TCC. This is because inflammation-reactive epithelial cells are commonly indistinguishable from neoplastic cells on cytologic examination. Similarly, false positive results can be common with urine antigen tests when the urine is hematuric. Furthermore, a urethral and/or bladder mass on workup can be caused by granulomatous disease, other malignant tumors or a benign tumor, so the presence of a mass does not equate to the diagnosis of TCC. Methodologies for obtaining tissue for histopathologic diagnosis include cystoscopy, cystotomy and less reliably through traumatic catheterization. For those patients with a specific lameness not explained through common neurologic and/or orthopedic diseases, X-rays of the problematic area and/or nuclear scintigraphy ("bone scan") should be seriously considered.

Treatment

Surgery

Surgical excision with complete margins is typically not feasible with urinary bladder TCC due to its common trigonal location. Historically, urinary diversion through numerous means has been tried, but has been met typically with significant biochemical and/or logistical side effects and survival times less than 5 months. Recent reports/abstracts have delineated techniques for bladder neck and proximal urethral extirpation with preservation of dorsal vascular and neuro pedicles in small numbers of patients. In patients with tumor located away from the trigone, the goal with surgery should be complete extirpation through partial cystectomy. Unfortunately, recurrence rates are high due to either local recurrence or through de novo tumor recurrence. If small pinpoint lesions are noted on cystotomy away from the primary lesion, these should be biopsied and they commonly will be carcinoma *in situ* (now more appropriately termed "intra-epithelial") or early TCC lesions on histopathologic examination. This is thought to be due to a so called "field effect" whereby the entire bladder lining undergoes changes related to malignant transformation from carcinogens in the urine.

Numerous palliative surgical options exist for patients with lower urinary tract tumors. This can be accomplished through surgical debulking, prepubic cystotomy catheters, or more recently through interventional radiological techniques. Weisse et al have reported outcomes associated with the transurethral placement of self-expanding or balloon-expandable metallic stents for management of malignant urethral obstructions in dogs. This is an exciting revolutionary mechanism for dealing with malignant urethral obstructions that appears safe and effective.

Medical Therapy

Medical therapies for lower urinary tract tumors, and specifically urinary bladder TCC has consisted of cyclooxygenase inhibitors and/or various forms of chemotherapy. When looking at over 10 studies utilizing various medical therapies, a few themes become apparent: 1) combinations are more efficacious than single agents (this is not surprising on multiple levels, the most important of which is that complete response rates are typically low for most types of non-liquid gross carcinomas or sarcomas treated with chemotherapy); 2) Carboplatin as a single agent has minimal to no activity; 3) Mitoxantrone and piroxicam appears to be the best combination based on response rates and toxicity (cisplatin and piroxicam is not recommended due to unacceptable renal toxicity); 4) the addition of doxorubicin to a protocol appears to improve survival and 5) the only NSAID to date to show activity in the context of EBM principles is piroxicam/Feldene.

Recent reports/abstracts suggest that the response rates and lengths of responses are longer when urinary bladder TCC's are debulked prior to being given combinatorial medical therapy. This is not surprising as it is well known that chemotherapy response rates against gross carcinoma/sarcoma typically improve when utilized in a minimal disease setting. Therefore, the author's favorite protocol for a trigonal TCC is debulking for histopathologic confirmation and therapeutic benefit followed by an adjuvant medical therapy protocol consisting of piroxicam and alternating mitoxantrone and doxorubicin.

Radiation

Radiation therapy has been utilized in a number of ways for lower urinary tract tumors in dogs and cats. Unfortunately, the complications of radiation therapy to the urinary bladder translate into significant pollakiuria and/or stranguria leading to a poor quality of life for the patient and owner without a significant prolongation in quantity of life. This is likely due to fibrosis and scarring of the urinary bladder leading to poor distension and significantly reduced bladder capacity. More precise mechanisms for delivery of radiation through IMRT or Gamma Knife applications may reduce the chances for significant side effects and therefore possibly become viable radiation treatment options in the future.

Laser Ablation

Recent reports and abstracts on laser ablation have elucidated an additional mechanism for cytoreducing tumors in the lower urinary tract of dogs. This treatment modality holds particular promise in the context of its ease and repeatability of use in comparison to cystotomy-based cytoreduction. Upton et al reported on the use of a

CO2 laser ablation followed by adjuvant mitoxantrone/piroxicam in 8 dogs with trigonal and proximal urethral TCC. Two dogs experienced mild side effects and the overall median survival was similar to that previously published for mitoxantrone/piroxicam. This author has experience with multiple patients receiving repeated laser ablation (by Dr. Dean Cerf in New Jersey) with adjuvant medical therapy and outcomes which appear significantly longer than with standardized therapies.

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