Canine Bladder Cancer (VET-259)

Western Veterinary Conference 2004
Carolyn J. Henry, DVM, MS
University of Missouri-Columbia
Columbia, MO, USA

Objectives

- The objective of this presentation is to discuss the pros and cons of current diagnostic methods and treatment options for canine bladder cancer.

Key Points

- Early detection of canine bladder cancer may be facilitated by knowledge of relevant clinical signs and breed predispositions, as well as appropriate use of screening and confirmatory tests.

- Because canine bladder cancer often exhibits metastatic behavior, treatment plans should address both local disease and metastasis.

Overview

Of the malignancies reported to occur in the canine urinary bladder, transitional cell carcinoma (TCC) is the most common and will be the focus of this discussion. Because initial signs of bladder cancer may be subtle, TCC is often quite invasive by the time it is clinically detectable and diagnosed. The estimated metastatic rate at the time of diagnosis is <20%, but may exceed 50% later in the disease course. Therefore, early diagnosis is essential and should be followed by therapy that is aimed at addressing both local disease and the potential for development of metastatic lesions.

Clinical features and history

Most reports suggest that canine TCC is more commonly diagnosed in older female dogs, with Scotties, Shelties, West Highland white terriers, Airedale terriers, collies, and beagles considered to be at high risk. Typical presenting complaints include pollakiuria, stranguria, hematuria, or tenesmus. Occasionally, lameness due to bone metastasis may be the reason for initial clinical presentation. Oftentimes, the history of a dog with TCC will include an apparent improvement in clinical signs after administration of antibiotics prescribed for presumed cystitis.

Diagnostic approach

Diagnostic testing for bladder cancer generally begins with a urinalysis. Unfortunately, findings may be confusingly similar to those noted with cystitis, including pyuria, hematuria, and bacteruria. Urine sediment exam can reveal tumor cells in ≥30% of cases. However, reactive transitional cells may look very similar to TCC cells, thus cytology

should be interpreted carefully. Care should also be taken when obtaining urine for analysis because tumor cell transplantation may occur with manipulation of TCC. For this reason, the author cautions against cystocentesis in dogs for which TCC is suspected.

A urine dipstick test that detects a veterinary bladder tumor antigen (VBTA) is now available to screen for canine urinary tract TCC. In evaluating this test clinically, we have found that it functions best when run on spun urine samples and should be performed within 48 hours of urine sample collection. An initial published report showed that the test had 90% specificity and 78% sensitivity for the diagnosis of TCC. Subsequent reports, including one study by the author and others have yielded similar results. False positive test results may occur when samples contain blood, protein, or glucose. However, false negative test results are uncommon. Thus the VBTA test is a reasonable screening, but not confirmatory, test. The results of the VBTA test should be interpreted in light of other clinical findings, with further diagnostic testing pursued when positive results are obtained.

Tumor imaging and staging

Bladder imaging or direct tumor visualization, along with cytological or histopathological demonstration of neoplastic cells is needed to confirm the diagnosis of TCC. Contrast cystography is a reliable method to identify bladder masses in greater than 95% of all cases. Tumor staging procedures should include sublumbar lymph node imaging and 3-view chest radiographs (right lateral, left lateral, and ventrodorsal views) to assess for metastatic disease. Ultrasonography is a valuable tool for bladder imaging and for detection of metastatic lesions in abdominal organs and lymph nodes. It is also an ideal means to aid in procurement of biopsy samples via urinary catheterization. Alternatively, biopsies may be obtained via cystoscopy or laparotomy.

Surgery

The choice of surgery as a treatment option for dogs with TCC should be based upon tumor location and invasiveness, as well as client goals. Numerous surgical options exist, including partial cystectomy, total cystectomy with ureterocolonic or ureterourethral anastomosis, or permanent cystostomy tube placement. Often, the least invasive techniques are chosen based on issues of quality of life and convenience. In one report of partial cystectomy in 11 dogs, the procedure provided survival times ranging from 2 to > 48 months and a 54.5% one-year survival rate. Importantly, visual assessment at the time of surgery was noted to be an inaccurate method for determining tumor-free margins. Accordingly, if intraoperative evaluation of surgical margins (via cytology or frozen section) is not possible, margins should be taken as generously as is reasonable. Partial cystectomy is a viable option for treatment of localized TCC. One must bear in mind, however, that it does not address metastasis and is a poor treatment option for advanced TCC. As the entire bladder mucosa is likely to have been exposed to the inciting carcinogen that led to tumor development, multifocal lesions or diffuse disease may limit the ability to achieve complete surgical excision. In one published report, only two of 67

dogs undergoing surgery for TCC had complete surgical excision of their disease and both later had tumor recurrence/progression.

Medical therapy/chemotherapy

A multitude of medical therapies and combination chemotherapy protocols have been evaluated for the treatment of canine TCC. The systemic therapies that have been reported in the literature or evaluated by the author are reviewed below:

Piroxicam

The nonsteroidal anti-inflammatory drug (NSAID), piroxicam, has shown efficacy, both as a single agent and in combination therapy, against canine TCC. Although the complete mechanism of action of piroxicam is unclear, it may relate to inhibition of cyclooxygenase 2 (COX-2) expressed on TCC cells and to inhibitory effects on tumor angiogenesis. In the first prospective evaluation of piroxicam for treatment of canine bladder TCC, responses were noted in 6/34 dogs for a median of 7 months. Side effects may include gastrointestinal (GI) irritation and nephrotoxicity. Regular evaluation of PCV, BUN, creatinine, and urine specific gravity are advised in order to monitor for renal toxicity and GI bleeding.

Doxorubicin and Cyclophosphamide

Although not evaluated prospectively, the combination of doxorubicin and cyclophosphamide provided a median survival time of 259 days for dogs with TCC, compared to 57 days with intravesicular thiotepa and 86 days with surgery alone in one retrospective study. Because these results compare favorably to those obtained using other protocols and the drugs are relatively inexpensive, it may be worthwhile to prospectively evaluate this combination therapy for canine TCC.

Cisplatin

Cisplatin is used to treat human invasive bladder cancer, but has been disappointing as a single agent for the treatment for canine TCC. Response rates have been < 25%, with median survival times of 6 months or less. When single-agent cisplatin was compared to the combination of cisplatin and piroxicam, none of the dogs receiving cisplatin alone experienced remission, while ten of 14 dogs receiving the combination protocol responded. Unfortunately, renal toxicity was frequent (12/14 dogs; 87%) and dose limiting in the combination protocol group. Until dosage modifications or substitution of other NSAIDs are found to result in a safe and effective combination protocol, the author does not recommend routine use of cisplatin and NSAIDs together in clinical practice for treatment of TCC.

Carboplatin

In a prospective clinical trial, the combination of carboplatin and piroxicam provided five partial remissions in 13 dogs and did not cause nephrotoxicity.While this 38% remission rate compared favorably to that of dogs treated with carboplatin alone, the median survival time of dogs treated with the combination (93 days) was not better than what has been achieved with either single-agent carboplatin (132 days) or piroxicam (180 days).

Mitoxantrone

The synthetic anthracycline, mitoxantrone, in combination with piroxicam is currently the protocol the author utilizes for first-line therapy of canine TCC. Mitoxantrone (5 mg/m^2 IV) is administered every 3 weeks for four treatments and piroxicam (0.3 mg/kg PO) is given daily. In a prospective multi-institutional study, our initial response rate was 35%, with subjective improvement in ¾ of all patients and a median survival time of 350 days. When considering this protocol, one must ensure that patients have normal renal function prior to treatment. Monitoring for GI and renal side effects is necessary, although our rate of toxicity was less than 15%.

Additional Detail

Radiation therapy is a reasonable treatment option in the palliative or adjuvant setting for select TCC cases. While intraoperative radiation therapy has provided promising results, it is a technically challenging alternative that requires facilities and personnel adept at coordinating the surgical and radiation treatments during one anesthetic event. Initial results of experience with external beam radiation therapy and chemotherapy for canine TCC suggest that relief of symptoms may be superior to that achieved with chemotherapy alone, although overall survival times have been similar.

Summary

Canine bladder cancer presents veterinarians with treatment challenges due to its invasive nature and likelihood of metastasis. An understanding and appropriate utilization of available diagnostic tools is necessary for early detection of canine TCC. In the setting of early detection, many options are available to provide relief of symptoms and prolongation of good quality of life for dogs with bladder cancer.

References

1. BorjessonDL, Christopher MM, Ling GV. Detection of canine transitional cell carcinoma using a bladder tumor antigen urine dipstick test. Vet Clin Path 1999;28(1):33-38.

2. Chun R, Knapp DW, Widmer WR, et al. Phase II clinical trial of carboplatin in canine transitional cell carcinoma of the urinary bladder. J Vet Intern Med 1997;11(5):279-283.

3. Chun R, Knapp DW, Widmer WR, et al. Cisplatin treatment of transitional cell carcinoma of the urinary bladder in dogs: 18 cases (1983-1993). J Am Vet Med Assoc 1996;209(9):1588-1591.

4. Helfand SC, Hamilton TA, Hungerford LL, et al. Comparison of three treatments for transitional cell carcinoma of the bladder in the dog. J Am Anim Hosp Assoc 1994;30:270-275.

5. Henry CJ. Management of transitional cell carcinoma. Vet Clinics of North America Small Anim Prac 2003;33:597-613.

6. Henry CJ, Tyler JW, McEntee MC, et al. Evaluation of a bladder tumor antigen test as a screening test for transitional cell carcinoma of the lower urinary tract in dogs. Am J Vet Research 2003;64(8):1017-20.

7. Henry CJ, McCaw DL, Turnquist SE, et al. Clinical evaluation of mitoxantrone and piroxicam in a canine model of human invasive urinary bladder carcinoma. Clinical Cancer Research 2003;9:906-911.

8. Knapp DW: Tumors of the urinary system. In Withrow SJ, MacEwen EG (eds): Small Animal Clinical Oncology, ed 3. Philadelphia, WB Saunders, 2001:490-499.

9. Knapp DW, Glickman NW, DeNicola DB, et al. Naturally-occurring canine transitional cell carcinoma of the urinary bladder. A relevant model of human invasive bladder cancer. Urol Oncol 2000;5:47-59.

10. Knapp DW, Glickman NW, Widmer WR, et al. Cisplatin versus cisplatin combined with piroxicam in a canine model of human invasive urinary bladder cancer. Cancer Chemother Pharmacol 2000;46(3):221-226.

11. Knapp DW, Richardson RC, Chan TCK, et al. Piroxicam therapy in 34 dogs with transitional cell carcinoma of the urinary bladder. J Vet Intern Med 1994;8(4):273-278.

12. Moore AS, Cardona A, Shapiro W, et al. Cisplatin (cisdiaminedichloroplatinum) for treatment of transitional cell carcinoma of the urinary bladder or urethra. A retrospective study of 15 dogs. J Vet Intern Med 1990;4(3):148-152.

13. Norris AM, Laing EJ, Valli VEO, et al. Canine bladder and urethral tumors: a retrospective study of 115 cases (1980-1985) J Vet Intern Med 1992;6(3):145-153.

14. Nyland TG, Wallack ST, Wisner ER. Needle-tract implantation following US-guided fine-needle aspiration biopsy of transitional cell carcinoma of the bladder, urethra, and prostate. Vet Radiol & Ultrasound 2002;43(1):50-53.

15. Smith JD, Stone EA, Gilson SD. Placement of a permanent cystostomy catheter to relieve urine outflow obstruction in dogs with transitional cell carcinoma. J Am Vet Med Assoc 1995;206(4):495-499.

16. Stone EA, George TF, Gilson SE, et al. Partial cystectomy for urinary bladder neoplasia: surgical technique and outcome in 11 dogs. J Sm Anim Pract 1996;37(10):480-485.

17. Stone EA, Withrow SJ, Page RL, et al. Ureterocolonic anastamosis in ten dogs with transitional cell carcinoma. Vet Surgery 1988;17(3):147-153.

18. Walker M, Breider M: Intraoperative radiotherapy of canine bladder cancer. Vet Radiol 1987;28:200-204.

19. Withrow SJ, Gillette EL, Hoopes PJ, et al. Intraoperative irradiation of 16 spontaneously occurring canine neoplasms. Vet Surgery 1989;18(1):7-11.

Speaker Information
(click the speaker's name to view other papers and abstracts submitted by this speaker)

Carolyn J. Henry, DVM, MS, DACVIM
Assistant Professor, Oncology
University of Missouri, CVM
Columbia, MO