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TRANSITIONAL CELL CARCINOMA

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INTRODUCTION

Canine transitional cell carcinoma (TCC) of the bladder is generally not detected until it is invasive into the bladder wall; thus limiting efficacy of the available treatment options. As such, canine TCC is virtually incurable at this time. Keys to changing this will be earlier tumour detection and more effective prevention of metastatic disease. A summary of diagnostic methods and treatment options available today for canine TCC is provided below and updates of ongoing research will be discussed, time permitting.

CLINICAL FEATURES

Canine TCC is typically a disease of older female dogs, although males can be affected. Scotties, Shetland sheepdogs, West Highland white terriers, Airedale terriers, collies, and beagles are considered to be at high risk. Presenting complaints may include pollakiuria, stranguria, haematuria, or tenesmus. Oftentimes dogs with TCC of the urinary bladder exhibit apparent improvement in urinary tract signs after administration of antibiotics prescribed for presumed cystitis. Because of this, practitioners should have a raised index of suspicion for bladder cancer in older dogs with urinary tract signs and should not presume that improvement after antibiotic therapy confers a diagnosis of bacterial cystitis as the underlying pathology.

DIAGNOSTIC APPROACH

Urinalysis (UA) is often the first step in diagnosing TCC; however, findings may be similar to those noted with cystitis, including pyuria, haematuria, and bacteruria. Urine sediment exam may reveal tumour cells in 30% or more of all TCC cases, but reactive transitional cells may look very similar to TCC cells. Therefore, urine cytology must be interpreted with caution. A sample from the affected bladder tissue is often needed to confirm the diagnosis. Tumour seeding is a risk associated with cystocentesis and fine needle aspiration (FNA) of an identified bladder mass. The significance of this risk is often interpreted in light of one's own experience, which may also dictate the diagnostic approach taken for a dog with suspected bladder cancer. There are three reported cases in the veterinary literature of TCC transplantation subsequent to needle aspiration. The true incidence of this complication is unknown and would be difficult to assess prospectively. However, in the author's opinion, even one case of preventable tumour transplantation is one too many, provided there are safer alternatives for sample procurement. Collection of urine and diagnostic samples via catheterization may still dislodge tumour cells that could transplant on urethral surfaces, but is considered the method of choice by the author, especially if ultrasound guidance is available.

A less invasive method to screen for canine urinary bladder TCC is to test a free-catch urine sample with the veterinary bladder tumour antigen (V-BTA) test, a dipstick test that detects a glycoprotein complex in the urine of dogs with TCC. The test functions best on centrifuged urine samples and when it is performed within 48 hours of sample collection. The initial published report evaluating a veterinary tumour antigen test for

canine bladder cancer indicated 90% sensitivity (likelihood of detecting TCC in affected dogs) and 78% specificity (likelihood of a negative test result in a dog that is free of TCC). Subsequent studies, including a multi-institutional study evaluating over 250 samples, have reported similar results. False positive test results may occur when samples contain blood, protein, or glucose, but false negative test results are unlikely. Many practitioners have questioned the value of the VBTA because dogs with TCC often have haematuria and proteinuria. However, one must remember that the VBTA test is a *screening* test, not a confirmatory test, just as the prostate specific antigen (PSA) test is a screening test for human prostate cancer, but does not diagnose the disease. VBTA test results should be interpreted in light of other clinical findings, with further diagnostic testing pursued when the test is positive. If test results are negative, a diagnosis of TCC is very unlikely; thus, a less aggressive diagnostic approach is appropriate. The V-BTA test is commercially available and moderately priced such that it is a reasonable screening test for at-risk dogs. We at the University of Missouri, as well as others, are actively investigating other biomarkers with the potential to facilitate earlier detection of TCC.

TUMOUR IMAGING AND STAGING

Diagnostic confirmation of TCC requires bladder imaging or direct tumour visualization, as well as demonstration of neoplastic cells on cytology or tissue preparations. Contrast cystography reliably identifies bladder masses in the vast majority of TCC cases. Subsequent tumour staging should include imaging of the sublumbar lymph nodes and 3-view chest radiographs to assess for metastatic disease. Ultrasound is a valuable tool for imaging the bladder and for the detection of metastatic lesions within abdominal organs and lymph nodes. Ultrasonography is also helpful in guiding biopsy sampling via urinary catheterization. Alternatively, tumour biopsy samples may be obtained with cystoscopy or laparotomy.

SURGICAL TREATMENT OPTIONS

The choice of whether or not to pursue surgery for dogs with TCC is predicated upon information regarding tumour location and depth of invasion, as well as a full understanding of the client's goals. There are several surgical options, including partial cystectomy, total cystectomy with urinary diversion (ureterocolonic or ureterourethral anastomosis) or permanent cystostomy tube placement. Clients often opt for the least invasive of these techniques, due to issues of patient quality of life and client convenience. In a report of partial cystectomy in 11 dogs, survival times ranged from 2 to >48 months and the one-year survival rate exceeded 54%. An important finding of the study was that visual assessment at the time of surgery was inaccurate for determining tumour-free margins. Accordingly, if surgical excision is attempted, margins should be taken as generously as possible. Partial cystectomy may be reasonable for localized TCC, but it does not address the problem of metastasis and is a poor treatment option for advanced TCC. Due to the phenomenon referred to as "field carcinogenesis" it is thought that the entire bladder mucosa has likely been exposed to the inciting carcinogen in most cases of bladder TCC. As such, multifocal lesions or diffuse disease often make complete surgical excision impossible. Indeed, in one published report that included 67 dogs undergoing surgery for TCC, only two had

complete surgical excision of their disease and both later had tumour recurrence or progression. A recent report describing the use of carbon dioxide (CO₂) laser ablation to treat TCC of the trigone and proximal urethra in eight dogs suggested that this procedure is well tolerated and results in rapid resolution of clinical signs. The dogs were also treated with adjuvant mitoxantrone and piroxicam, as described below.

RADIATION THERAPY

Although reports of external beam radiation for treatment of canine TCC are sparse, it is considered a reasonable palliative or adjuvant treatment option for selected cases. Intra-operative radiation therapy was initially reported as an option for treatment of canine bladder cancer in the 1980s. However, it is technically challenging to perform and requires specialized facilities and personnel who are adept at coordinating surgery and radiation under one anaesthetic event. In the few published reports, external beam radiation and chemotherapy together have provided symptomatic improvement that is superior to that achieved with chemotherapy alone. However, this has not resulted in an improvement in overall survival times. When reviewing reports of case outcome with radiation therapy, it is important to realize that clinical results in the past may have been biased by case selection in which radiation was considered a “last resort”. Prospective evaluation of radiation for treatment of dogs with minimal disease is necessary in order to accurately assess the efficacy and to better understand the risk of complications such as bladder fibrosis and stricture of the intestinal tract or urethra. While these adverse events were once thought to be essentially inevitable after bladder irradiation, more recent work suggests otherwise.

MEDICAL THERAPY AND CHEMOTHERAPY

Nonsteroidal anti-inflammatory drugs

The nonsteroidal anti-inflammatory drug (NSAID), piroxicam, has been evaluated extensively for the treatment of canine TCC. Because piroxicam is a non-selective cyclo-oxygenase (COX) inhibitor, it has effects on both COX-1 and COX-2. Thus, side effects may include gastrointestinal (GI) irritation and nephrotoxicity. Monitoring of PCV, BUN, creatinine, and urine specific gravity are advised. Newer, more COX-2 selective drugs are being evaluated for treatment of canine TCC, in hopes that they will have a wider safety margin, yet provide similar or improved efficacy. The exact mechanism of action of piroxicam against canine TCC is not entirely understood, but may relate to both antiangiogenesis and effects on COX-2 (which is over-expressed in canine TCC). Recent work has shown that COX-1 overexpression may also occur in canine TCC. Of canine TCC samples evaluated by immunohistochemistry in one study, 39% demonstrated COX-1 overexpression. This may help explain some of the differences in clinical responses of canine TCC to various NSAIDs.

Chemotherapy

Various chemotherapy agents have been evaluated for their activity against canine TCC, either as single agents or in combination with other chemotherapy drugs or NSAIDs. Results of some of these studies are summarized on the next page. In addition, at least two funded clinical trials are ongoing to investigate novel protocols for canine TCC. One at the University of Illinois was designed to evaluate the combination

of mitoxantrone and carprofen. Another at Purdue University and the University of Missouri is evaluating a new anti-inflammatory drug with enhanced COX-2 selectivity, both alone and in combination with cisplatin. Updates will be provided if available.

Chemotherapy protocols evaluated for treatment of canine TCC						
Protocol	# of dogs	Trial type	RR	MST (days)	Comments	ref
Cisplatin 50 mg/m ² q4wks	15	R	20%	132		Moore 1990
60 mg/m ² q3wks	18	P	16%	130		Chun 1996
Carboplatin alone	14	P	0	132		Chun 1997
Piroxicam alone	34	P	18%	181		Knapp 1994
Carboplatin and piroxicam	29	P	38%	161	Of 31 enrolled, 29 evaluated; No renal toxicity reported; Frequent GI and marrow toxicity	Boria 2005
Doxorubicin and cyclophosphamide	11	R		259		Helfand 1994
Mitoxantrone and piroxicam	49	P	35%	350	49 of 55 enrolled evaluated for response	Henry 2003
Laser ablation, then Mitoxantrone and piroxicam	8	P	100%	299	RR related to the fact that all dogs underwent surgery	Upton 2006
Cisplatin and piroxicam	14	P	71%	246	Renal toxicity in 12/14	Knapp 2000
Cisplatin, then piroxicam	8	P	0% , then 25%	309	No responses to cisplatin only; 2/8 responded once started on piroxicam	Knapp 2000

R = retrospective; P = prospective; RR = response rate; MST = median survival time

PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) is being investigated as a treatment alternative for dogs with TCC. In PDT, a photosensitizing agent is administered either systemically or locally and then activated at the tumour site with laser light of an appropriate wavelength. One compound being evaluated for this purpose at Purdue University is 5-aminolevulinic acid (ALA), which has a photoactive metabolite, protoporphyrin IX. The progression-free intervals following this therapy in five dogs ranged from four to 34 weeks, with a median of 6 weeks. Further investigation is necessary to determine the ideal patient selection criteria for this treatment option.

REFERENCES AVAILABLE UPON REQUEST