Canine genitourinary carcinomas: where are we now and where are we going?

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The term canine genitourinary carcinomas (CGUC) encompasses all transitional cell carcinomas (TCCs), adenocarcinomas, and solid carcinomas involving the urinary bladder, urethra, and prostate (see Figure 1). This umbrella term is used to facilitate anatomical description of these tumours, but within this group significant differences in biological behaviour, and therefore treatment, exist.

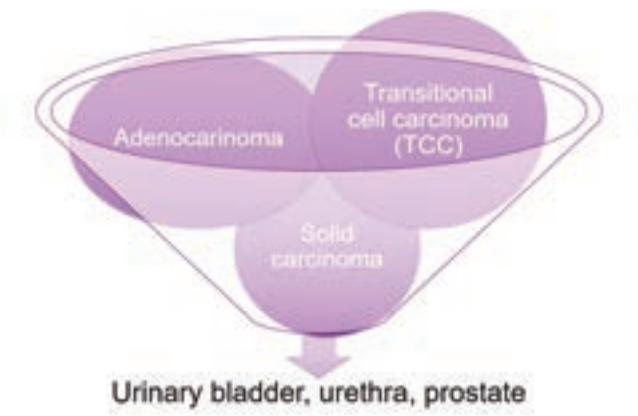

Figure 1: CGUCs encompass TCCs, adenocarcinomas, and solid carcinomas of the urinary bladder, urethra, and prostate.

GENERAL INFORMATION

CGUC involving the bladder and urethra comprises approximately 2% of reported cancers in dogs, while prostatic carcinoma comprises another 1%; however, the proportionate morbidity of CGUC reported at speciality hospitals is increasing. The typical signalment is middle-aged to older small-breed terrier dogs, including West Highland White Terriers, Scottish Terriers, Shetland Sheepdogs, Wirehaired Terriers and Beagles. Risk factors for development of CGUC include female sex, neuter status, breed, exposure to pesticides and older-generation flea and tick preventatives (not the newer topical products currently on the market) and exposure to lawn herbicides. Vegetable consumption (carrots, broccoli, etc.) at least three times per week has been associated with a reduced risk of TCC in high-risk breeds.

The most common presentation of urogenital tract neoplasia in the dog is a high-grade, invasive transitional cell carcinoma (TCC). The World Health Organization (WHO) criteria are used for staging canine bladder tumours: T stands for primary tumour, N for regional lymph node and M for distant metastases. Seventy-eight per cent of dogs present with T2 tumours (those that have already invaded the bladder wall), and 20% of dogs present with

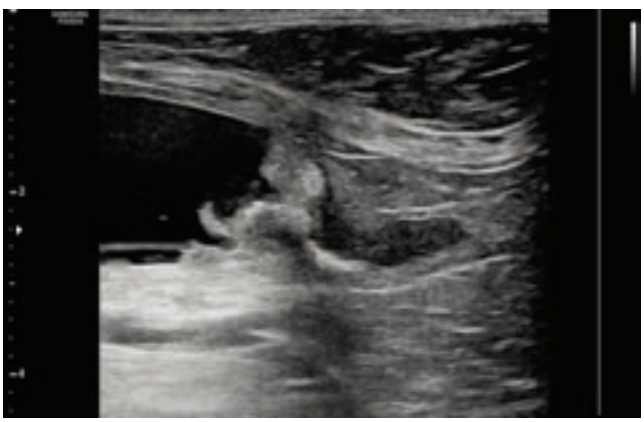

Figure 2: TCC in a 10-year-old small, mixed-breed female. On ultrasonographic examination, there is irregular mural thickening of the urinary bladder wall at the level of the trigone.

T3 tumours (those also invading neighbouring organs like prostate, uterus, vagina and pelvic canal). Most of the time, urinary-bladder TCC is located in the trigone, with urethral involvement (responsible for partial or complete obstruction) documented in more than 50% of dogs (see Figure 2); concurrent prostatic involvement is documented in about 30% of the cases in males.

Distant metastases are found in 20% of cases at the time of diagnosis, and a recent study performed at Purdue University revealed that 67% of TCC cases had metastases noted at the time of necropsy. These were cases of TCC treated at this institution that had achieved prolonged survival times with treatment, suggesting that development of distant metastases typically occurs late in the course of disease. The vast majority of patients succumb to direct complications of local disease rather than distant metastases, and as such our treatment strategies must focus heavily on ameliorating signs of disease at the primary tumour site.

Prostatic neoplasia most commonly affects dogs over 10 years of age, and most often, manifests as prostatic adenocarcinoma. The role of sex hormones in pathology has not been established, though there is a clear trend towards increased risk of prostatic neoplasia in early castrated males. Despite similar anatomic predilection, prostatic carcinomas manifest different biologic behaviour compared to urethra and bladder TCC. Prostate carcinomas are usually extremely locally aggressive (see Figure 3); the rate of metastases at necropsy reaches 80%, and almost half of the dogs will develop bone metastases

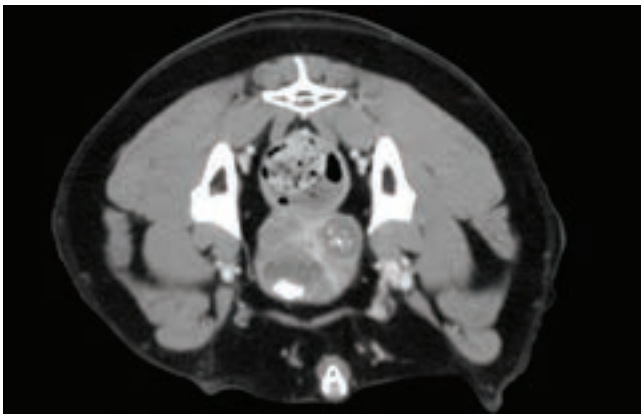

Figure 3: Prostatic carcinoma in an eight-year-old neutered German Shepherd. On transverse, post-contrast CT images (soft-tissue window), the prostate is markedly enlarged and asymmetric. It contains multiple coalescing foci of mineral attenuation and is heterogeneously contrast enhancing.

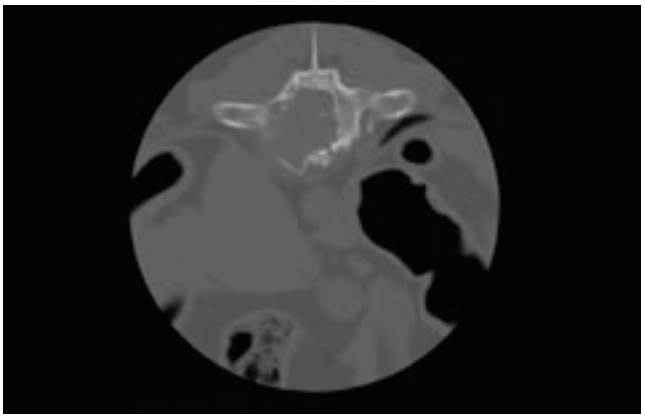

Figure 4: This is the same patient from Figure 3. On CT scan (bone window) there is a large-lytic lesion affecting the majority of the body of T12, the right pedicle and the head of the right-12th rib. Ventrally, there is irregular new bone formation.

(most commonly to lumbar vertebrae or pelvis, [see Figure 4]). These tumours also seem less responsive to medical treatment compared to TCC.

DIAGNOSIS

Dogs with CGUC present with a variety of non-specific clinical signs, including haematuria, stranguria and pollakiuria. Tenesmus (neurological or physical) or lameness (due to bone metastases) are less common primary-presenting complaints, but do occur. Clinical signs can be present for a few weeks to months' duration and are usually progressive.

Unfortunately, empiric antibiotic treatment is often incorrectly prescribed without performing urinalysis (UA) or bacterial culture, and this might reduce the initial clinical signs initially as dogs with TCC commonly develop secondary urinary tract infections (UTIs), but this often delays the diagnosis and limits early interventions that could alter long-term clinical outcome. While it is always recommended to perform UA and culture in patients suspected of having a UTI, if clinical signs recur despite symptomatic treatment, a full workup including UA, culture and abdominal ultrasound should be conducted. The latter typically reveals a mass in the trigone area or enlarged and heterogeneous prostate.

Differential diagnoses include other less common bladder neoplasms (squamous cell carcinoma, rhabdomyosarcoma, lymphoma, hemangiosarcoma, fibroma, etc.), inflammatory bladder polyps, fibroepithelial polyps, inflammatory pseudotumour, granulomatous cystitis, cystourethroliths, sterile inflammatory cystitis and recurrent or relapsing UTI.

Diagnosis of CGUC is possible from samples obtained via spontaneous urination, traumatic catheterisation, fine-needle aspiration (FNA), cystoscopy and in the case of prostatic involvement, prostatic wash and ultrasound-guided FNA histopathology is required for definitive diagnosis, but a diagnosis can often be obtained from cytology samples of free catch urine, with up to 30% of TCC patients having neoplastic cells; diagnosis may be impaired by high numbers of inflammatory cells in the urine however, as inflammatory reactions can create atypical-looking cell populations that make pathologists more reluctant to give a diagnosis. Urine samples collected for this purpose should have fresh smears made from spun-down urine sediment immediately after collection: refrigerating the urine for even a few hours can create artefacts that can be misleading for pathologists interpreting the slides.

In the vast majority of the cases that can't be diagnosed with a urine cytology test, the diagnosis of bladder/urethra TCC can be obtained via traumatic catheterisation, ideally using ultrasound guidance to visualise the catheter coming into contact with the mass. Otherwise, cystoscopy will be the next diagnostic step, though the patient must be large enough to accommodate an 8Fr catheter in the urethra to permit insertion of a standard rigid cystoscope with a sampling channel to collect biopsies. In male dogs, visualisation obtained with flexible urethroscopes is often limited and challenging, which can hinder diagnostic accuracy of the procedure.

In rare occasions, when less invasive ways of obtaining diagnosis fail and clinical presentation is atypical (eg. the mass has a non-trigonal location), cystotomy may be performed. While it provides good visualisation of the bladder, it has been associated with risk of tumour seeding into the abdomen.

This same concern is raised in discussion of percutaneous sampling of CGUC. TCCs have been reported to seed the abdominal wall as a complication of FNA of bladder masses, therefore, percutaneous sampling should be avoided if alternative methods of obtaining a diagnosis are possible; however, the risk of tumour seeding is highest with surgical biopsy/cystotomy so FNA of the bladder would be attempted before resorting to this option in most cases. In a report of 544 dogs with TCC seen at Purdue University, 24 had documented spread to the abdominal wall but the majority of these cases were in dogs undergoing cystotomy (18 versus six cases that did not undergo cystotomy).

TCC in the abdominal wall typically behaves aggressively and does not respond to conventional medical therapy very

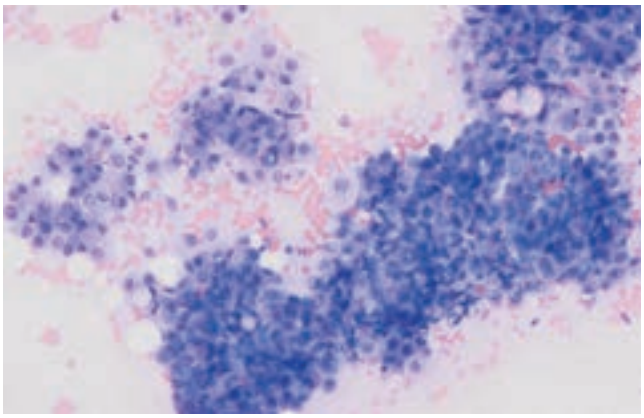

Figure 5: FNA from a prostatic mass. There are abundant variably-sized and variably-pleomorphic, loose to dense clusters of neoplastic epithelial cells. Features of malignancy include moderate anisocytosis and anisokaryosis, macrokaryosis (up to 30um), frequent bi- and occasional multinucleation, nuclear molding, angular or large nucleoli, high N:C ratios, and cytoplasmic ballooning. Diagnosis: prostatic carcinoma. Photo: Dr Balazs Szladovits MRCVS Dip ACVP).

well (median survival time is 57 days).

There are not many papers published regarding seeding from prostatic carcinoma: to the authors' knowledge there is only one existing case report of percutaneous seeding of prostatic TCC following FNA. As such, in cases where prostatic wash is nondiagnostic, prostatic FNA can be considered (see Figure 5). Urethral masses should not be sampled percutaneously and traumatic catheterisation or cystourethroscopy are recommended.

Tests to aid early diagnosis of TCC have been explored. The bladder tumour antigen test is highly sensitive, but has a high false positive rate in the presence of haematuria and lower urinary tract inflammation so has not proven helpful in differentiating TCC from other differentials. Recently, the canine BRAF-V595E mutation was detected in ~80% of CGUC. A droplet digital polymerase chain reaction (PCR) assay for detection of the mutation was developed and the preliminary data showed that it identified the mutation in free-catch urine samples from 83% of affected patients. The test is available only in the US at the moment, but should soon be available in Europe and the UK, and may prove useful for earlier diagnosis and monitoring of treatment efficacy in these patients.

TREATMENT

In general, the treatment of choice for solid carcinomas in veterinary oncology is usually surgical resection with optional adjuvant chemotherapy and radiation therapy if complete resection is not achieved. However, in case of CGUC disease where it is usually too advanced at time of diagnosis for surgical resection to be possible due to extensive trigone involvement precluding ability to get clean surgical margins without damaging the ureters and urethra, infiltrative growth often present into other adjacent organs at time of diagnosis, and the risk of tumour seeding within the abdomen.

Complete removal of the diseased bladder via total cystectomy and urinary diversion has been described, but it is not recommended due to high complication rates and limited survival. Reported complications include dehiscence of ureterostomy sites, pyelonephritis, oliguria, azotaemia and ureteral obstruction. In cases where the bladder mass is located in the bladder apex away from the trigone, surgical removal via partial cystectomy has been successfully attempted. At least 1cm margins are desired and dogs should be followed up with medical treatment to maximise survival time. In a study evaluating clinical outcome of partial cystectomy for TCC in 37 dogs it was found that dogs with non-trigonal bladder TCC undergoing full-thickness partial cystectomy and daily piroxicam (+/- chemotherapy) may have improved outcome compared with dogs treated to medical therapy (median survival times of 772 days).

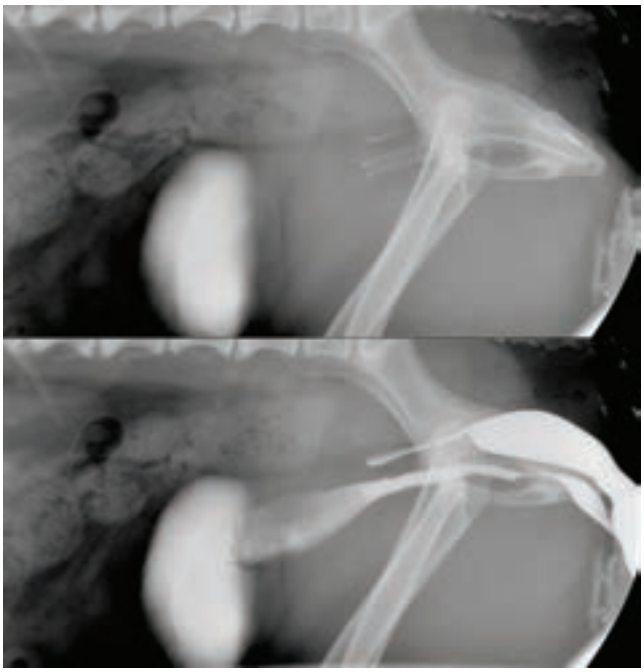

Figure 6: Positive contrast retrograde vaginourethrography study of a seven-year-old female spayed Labrador with urethral stent in place.

The most common life-threating complication of TCC is complete urinary obstruction. In this situation, there are interventional procedures that can be used in a palliative manner. Cystostomy tubes have been used in cases of urethral obstruction in the past; now urethral stents are placed more commonly instead for several reasons (see Figure 6).

Firstly, stents don't have external components that dog can chew and pet owners do not need to drain the bladder. Secondly, stents can be placed non-surgically with fluoroscopic guidance. Cystotomy tubes also often get infected which contributes to patients' morbidity and additionally can delay chemotherapy treatment. In the two largest studies evaluating urethral stent placement, 58/61 dogs had successful relief of their urethral obstruction was successful. Incontinence rate varied between 26-39%. This might be of particular concern in patients receiving chemotherapy, since additional measures must be taken

to prevent the leakage of chemotherapy-containing urine around the home. Other reported complications include stent migration, tumour growth within the stent and increased risk of urinary tract infections. Owners should be aware that stranguria will not typically resolve with the urethral stent, in fact, and may actually worsen following stent placement.

When the tumour invades the ureter, ureteral obstruction can occur and lead to hydronephrosis and impaired renal function. Nowadays, attempts are made to maintain the function of both kidneys for as long as possible, therefore, ureteral stenting or subcutaneous ureteral bypasses (SUB) have been performed in these patients. Placement of both ureteral stent and SUB is only technically feasible when renal pelvic dilation exceeds 5-6mm dilation of renal pelvis of at least 5-6mm, so patients with trigonal masses where owners would consider ureteral stent placement should be closely monitored with serial ultrasound to determine the optimal time for intervention.

Before considering any of these procedures, urine culture should be performed and appropriate antibiotics started at least 24-48 hours before stent placement if secondary infection is detected.

The current mainstay of treatment for CGUC is medical therapy, optionally combined with radiotherapy. Medical therapy consists of non-steroidal anti-inflammatory drugs (NSAIDs), utilized for cyclooxygenase inhibition (proven effective as single agents), ideally combined with cytotoxic drugs (see Table 1).

Drug	Number of dogs	% of complete and partial remission	% stable disease	Median survival (days)
Deracoxib	24	17	71	323
Firocoxib	15	20	33	152
Piroxicam	76	21	59	244
Mitoxantrone/piroxicam	48	35	46	291
Vinblastine	28	36	50	147
Carboplatin/piroxicam	29	38	45	161
Chlorambucil (metronomic)	30	3	67	221

Table 1: Summary of most commonly used medical therapies of TCC in dogs.

While this rarely provides a cure, it can significantly slow progression and improve quality of life with minimal toxicities. There are several chemotherapeutics with documented activity against urinary TCC; if resistance to one of them occurs, others may still be effective. With combinations of drugs, attaining multisystemic therapy (MST) of one year or more, is a realistic goal for many of these patients. Drugs with reported efficacy include mitoxantrone, vinblastine, gemcitabine and carboplatin. Partial or complete remissions are documented in approximately 35% of dogs and 45-50% of dogs achieve stable disease.

While cytotoxic drugs are commonly used for CGUC worldwide, knowing these drugs' mechanisms of action and the biology of the tumour, we must analyse if they truly provide significant benefit individually and what the reason for treatment failure after a few doses could be.

Firstly, TCCs tend to be slow-growing tumours, which is an issue as cytotoxic drugs administered at a maximally tolerated dose will only work on actively dividing cancer cells.

Secondly, it is difficult to take for granted results of existing studies on cytotoxic drugs for TCC, as most studies are retrospective, lack a control group, the numbers of dogs included are small and most of them were concurrently treated with non-steroidal anti-inflammatory drugs (NSAIDs) for COX-2 inhibition, and we know this drug class has been proven to be effective as a single agent in TCC, with reported MST up to 261 days.

In recent years, metronomic chemotherapy has gained a lot of attention in both human and veterinary medicine. It entails administration of low doses of chemotherapeutic drugs and NSAIDS given daily, with the goal of delaying or preventing further tumour progression. There are multiple mechanisms for how it targets the tumour: initially it was thought to have only anti-angiogenic effects, but it is clear now that there are many other mechanisms including an immunostimulatory and apoptotic effect; intensive research continues to discover more on this topic.

At author's institution the chemotherapy treatment of choice for urinary TCC is oral-metronomic chemotherapy or injectable vinblastine.

Despite vinblastine being a traditional cytotoxic drug, the low doses typically given to our canine patients more closely resemble human-metronomic regimes. Vinblastine is a commonly used drug in human metronomic chemotherapy protocols, and it is possible to attain survival times similar to those of cytotoxic drugs with much lower toxicity, which is always a key goal in veterinary oncology. The chemotherapy drugs used in metronomic regime include alkylating agents (chlorambucil 4mg/m^2 daily, or cyclophosphamide 12.5-15mg/m^2 daily) and vinblastine (2mg/m^2 intravenously every other week). One of the potential side effects of cyclophosphamide is sterile haemorrhagic cystitis, which might be mistaken for progressive disease in patients with CGUC. Should an acute worsening in haematuria, stranguria or pollakiuria occur, the cyclophosphamide should be discontinued and UA, culture and repeat abdominal ultrasound should be performed to rule out an infection or progression of the primary tumour. Patients receiving metronomic chemotherapy should have haematology performed regularly (initially every four weeks, then every eight weeks long-term) along with creatinine and urea levels to monitor efficacy of therapy.

Little is currently known about optimal-medical management for prostatic carcinoma in dogs. While clear survival benefit was demonstrated with use of NSAIDs, the role of chemotherapy has been less clear.

A recent multi-institutional study on prostatic carcinoma showed benefit to use of chemotherapy compared to a control group, but specific agents have not yet been clearly defined. In addition, a recent paper provided

preliminary evidence that the -1 antagonist prazosin could be beneficial in managing dysuria in dogs with prostatic carcinomas, and likely has similar effect in TCC involving the urethra and prostate. It works by reducing urethral pressures via smooth muscle relaxation (dosing at 0.1–0.4mg/kg/day, and monitoring for possible hypotension and weakness).

Patients with CGUC are at increased risk of secondary UTIs. Bacterial cultures should be performed routinely in these patients and every time clinical signs progress.

As discussed above cystocentesis should be avoided, so a midstream free catch sample is recommended for culture. Measures such as oral cranberry, D-mannose, probiotics and estriol (in female dogs) can be considered to try and reduce reinfection risk in patients with recurrent UTI, and trimming of hair around the vulva and prepuce can be performed to try and minimise wicking of bacteria up the urethra.

Treatment with radiotherapy (RT) for CGUC is challenging for numerous reasons. The location of the urinary bladder changes constantly due to volume shifts and rectal compression. Since RT normally should include the primary tumour, its microscopic extension and also the field including varying location due to bladder-size changes, this results in an expanded radiation field.

Organs at risk in this area include colon and rectum and if they unnecessarily receive high doses of radiation therapy, the patient could suffer from acute gastrointestinal toxicity and consequential late RT side effects (rectal stricture, urethral stricture, bladder fibrosis, etc). Initial reports on use of RT for bladder tumours documented common complications including cystitis, urinary incontinence, colitis and colonic stricture.

A pilot study of 10 dogs receiving chemotherapy and weekly-coarse fraction external-beam RT, showed that the treatment was well tolerated but showed no significant survival benefit over medical treatment alone. To try and improve radiotherapy treatment of CGUC it is necessary to maximise the dose of radiation therapy delivered to the tumour (thus, improving local tumour control) while minimising exposure of organs at risk (in order to reduce side effects).

The most important recent advances in RT include intensity modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT) and stereotactic radiation therapy (SRT). IMRT controls the intensity of each beam through motorised collimator leaves that move during treatment, allowing the dose to be shaped around important normal anatomy. IGRT utilises an imaging system built into the RT machine to frequently confirm the location of the target.

Before each session, CT scan is performed and compared with the initial CT used for treatment planning. This allows the oncologists to confirm the location of the treatment target. Intensity modulated image guided radiation therapy (IG/IMRT) combines the dose precision of IMRT with daily CT to minimise exposure of organs at risk to dose of radiation.

A recent study assessed IG/IMRT in 21 CGUC patients demonstrated improved clinical signs was documented in 60% of treated dogs with MST 654 days and tolerable side early and late side effects. Stereotactic radiation therapy (SRT) involves giving very high doses per fraction but treating only the tumour via stereotactically-verified positioning and treatment delivery techniques, thus sparing the adjacent organs due to a dramatic drop of radiation between the target and organs at risk. This technique is unlikely to be safely applied to the bladder due to the frequent variation in size/location, but there is potential for treatment of prostatic and urethral tumours that have more static location.

FUTURE DIRECTIONS

Early detection of cancer is a primary goal in human and veterinary oncology. Detection of the BRAF mutation in urine may serve as the forefront of a new revolution in the development of molecular tests to aid in early diagnosis of CGUC. While medical treatment remains the cornerstone treatment modality, multi-agent drug protocols and metronomic chemotherapy need to be investigated with prospective studies. As radiation therapy becomes more available, hopefully it will also become a part of standard treatment for CGUC.

ACKNOWLEDGMENTS

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READING LIST AVAILABLE ON REQUEST

READER QUESTIONS AND ANSWERS

1: WHICH OF THE FOLLOWING IS TRUE REGARDING METASTATIC RATE OF CANINE GENITOURINARY CARCINOMAS (CGUC)?

A Urinary bladder and urethra TCC have high rate of distant metastases at the time of diagnosis.
B Urinary bladder and urethra TCC have low rate of distant metastases at the time of diagnosis.
C Urinary bladder and urethral carcinoma has usually higher rate of metastases than prostatic carcinoma.
D Distant metastases in bladder TCC are often cause of death.

2: WHICH OF THE FOLLOWING DIAGNOSTIC TOOLS SHOULD BE USED TO INVESTIGATE URINARY BLADDER MASS WHEN URINE SEDIMENT FROM A FREE-CATCH SAMPLE DOES NOT PROVIDE SUFFICIENT INFORMATION?

A Surgical biopsy.
B Percutaneous fine needle aspiration.
C Cystoscopy.
D Traumatic catheterisation.

3: WHAT IS THE CURRENT TREATMENT OF CHOICE FOR CGUC?

A Medical treatment optionally combined with radiation therapy.
B Surgical resection.
C Urethral and ureteral stents.
D Radiation therapy alone.

4: WHICH OF THE PALLIATIVE MEASURES ARE RECOMMENDED IN CASE OF URETERAL OBSTRUCTION?

A Total cystectomy with ureteral transposition.
B Cystotomy tube.
C Ureteral stent/subcutaneous ureteral bypass (SUB).
D Ureteronephrectomy.

5: WHAT ARE THE MAIN DISADVANTAGES OF CYSTOSTOMY TUBES?

A They often get infected, dogs can chew the external parts.
B They often get blocked.
C They require very expensive equipment.
D They often need to be replaced.

6: ONE OF THE SIDE EFFECTS OF CYCLOPHOSPHAMIDE THAT IS IMPORTANT ESPECIALLY IN PATIENTS WITH CGUC IS:

A Severe neutropenia that occurs during metronomic chemotherapy.
B Severe gastrointestinal side effects that occur during metronomic chemotherapy.
C Sterile-haemorrhagic cystitis as this can be mistaken for progressive cancer disease.
D Anaphylactic reactions associated with prolonged use.

ANSWERS: 1: B; 2: D; 3: A; 4: C; 5: A; 6: C.