DROP A HINT: DIAGNOSING & TREATING CANINE UROTHELIAL TUMORS

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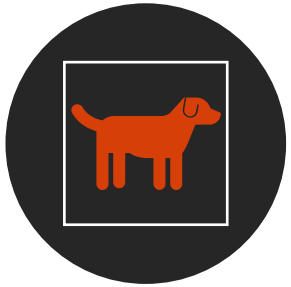
Oregon State University

Sponsor

Objectives



Identify at-risk breeds and other risk factors for urothelial carcinoma in dogs

Identify common treatment options, both palliative and curative-intent

Review different diagnostic tests used to diagnose canine urothelial carcinomas

Describe clinical outcomes related to canine urothelial carcinoma

Overview

Urinary cancer accounts for ~2% of all canine malignancies

- Etiology is multifactorial

Invasive urothelial carcinoma (iUC) is most common

- AKA: Transitional cell carcinoma (TCC) or Urogenital carcinoma
- Common to be intermediate- to high-grade, papillary, infiltrative tumors

Other tumor types

- Squamous cell carcinoma, adenocarcinoma, rhabdomyosarcoma, lymphoma, hemangiosarcoma, fibroma

Female to Male Ratio

- 1.71:1 - 1.95:1

Risk Factors

Breed	# Dogs in that Breed in Database	# TCC cases in that Breed	Odds Ratio compared with mixed breed	95% confidence interval
Mixed breed	42,777	269	1.0	NA
Scottish Terrier	670	79	21.12	16.23-27.49
Eskimo Dog	225	9	6.58	3.34-12.96
Shetland Sheepdog	2521	93	6.05	4.76-7.69
West Highland White Terrier	1234	44	5.84	4.23-8.08
Keeshond	381	10	4.26	2.25-8.07
Samoyed	471	10	3.43	1.81-6.49
Beagle	3236	62	3.09	2.34-4.08
Dalmatian	1253	19	2.43	1.52-3.89

AKC

- Breeds at risk
- Monitor at risk breeds for development of iUC?
  - Urinary tract ultrasonography, urinalysis + sediment q 6 months
  - Cystoscopy and biopsy of suspicious lesions
  - May increase response to treatment if detected earlier in disease course

Risk Factors

- Female gender
- Neutered pets
- Obesity
- Exposure to older generation flea control and lawn chemicals
- Cyclophosphamide exposure
- Decreased risk in Scottish Terriers that eat vegetables at least 3x/week

Clinical Presentation

Common signs mimic urinary tract infections

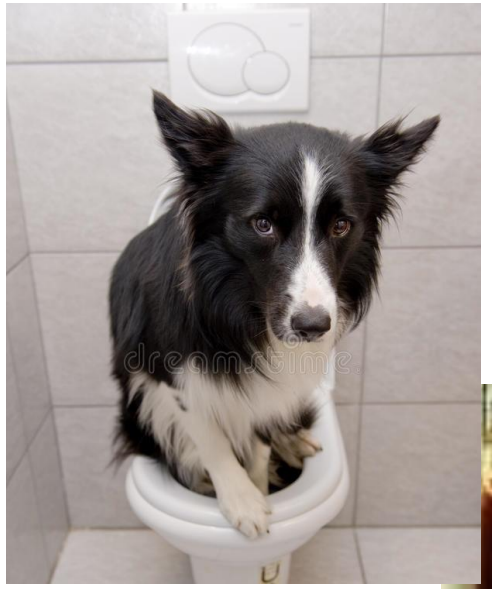
- Dysuria- 80%
- Hematuria- 50%
- Pollakiuria- 37%
- Stranguria
- Pyuria- 55%

Can have concurrent UTI

- Concern for iUC when signs do not resolve following antibiotic trial

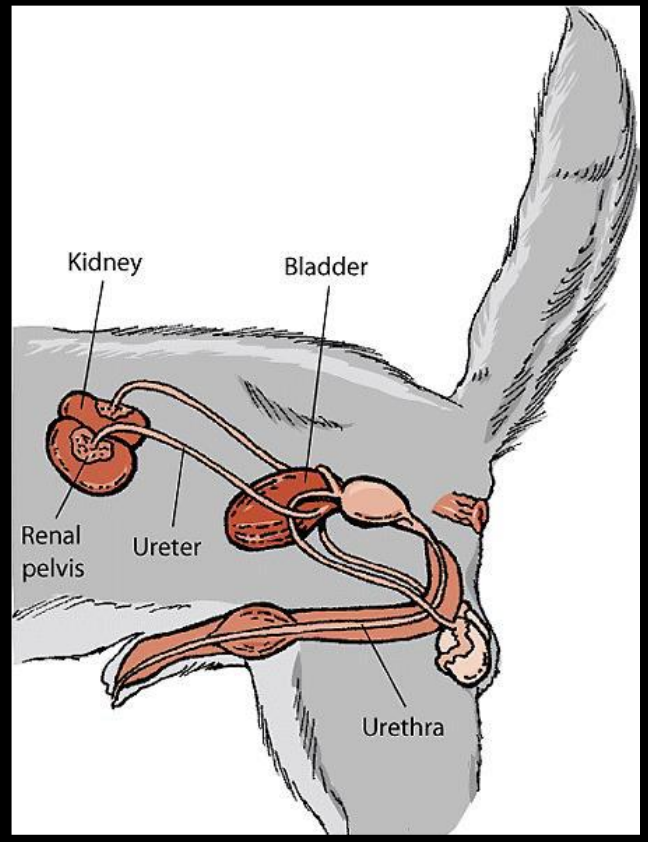
Rarely present with lameness

- Bone metastasis or hypertrophic osteopathy



The University of Chicago

Physical Exam Findings



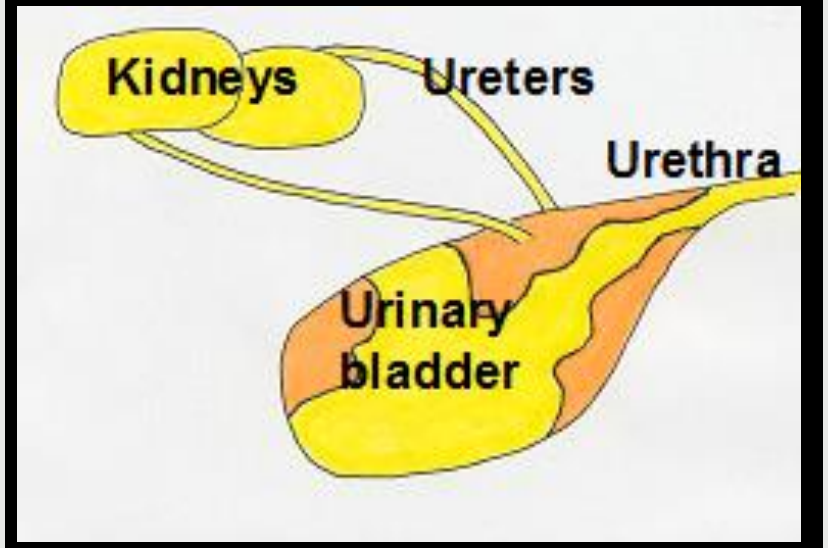
MSD Veterinary Manual

- Rectal Examination Findings
  - Thickened urethra or trigone region of bladder
  - Enlargement of lymph nodes
  - Prostatomegaly in male dogs
  - Mass in bladder
  - Distended bladder

Differential Diagnoses

- Chronic cystitis
- Polypoid cystitis
- Fibrepithelial polyps
- Granulomatous cystitis/urethritis
- Gossypiboma
- Calculi
- Inflammatory pseudotumor
- Other neoplasia

Clinical Presentation



Purdue Veterinary Medicine

- iUC is often located in trigone of bladder
  - Can make local interventions difficult
    - Urethral opening
    - Ureter connections
- Can also involve
  - Urethra (56%)
  - Prostate (29%)

Diagnostic Work-Up

Complete blood count

Serum chemistry

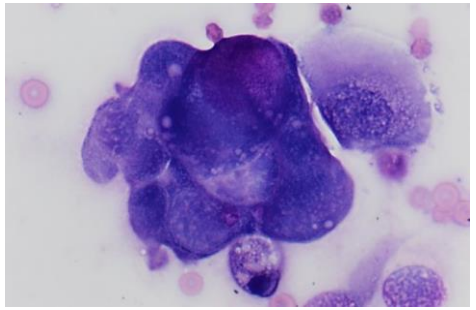
Urinalysis

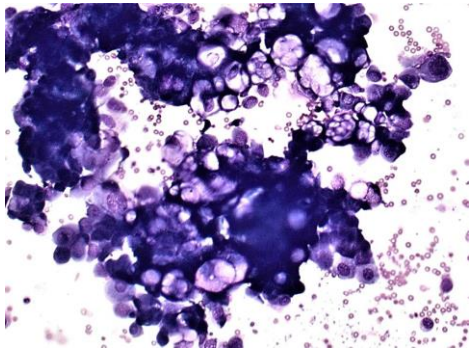
- Free catch or catheterization
- FNA could cause TUMOR SEEDING
- Evaluate for abnormal cells

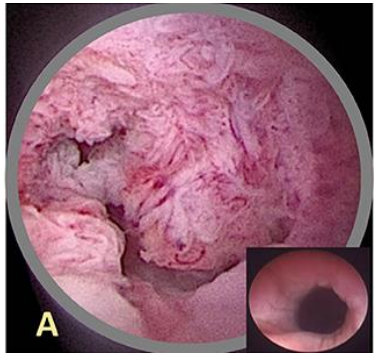
Urine culture

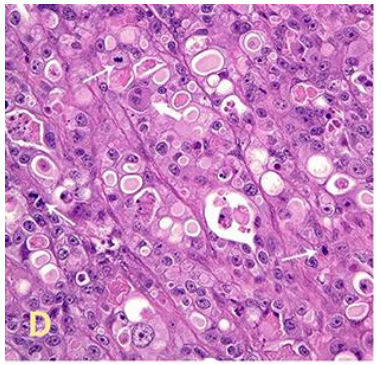
Definitive diagnoses may require histopathology

- Cystoscopy, traumatic catheterization, cystotomy
- IHC: uroplakin III and GATA-3





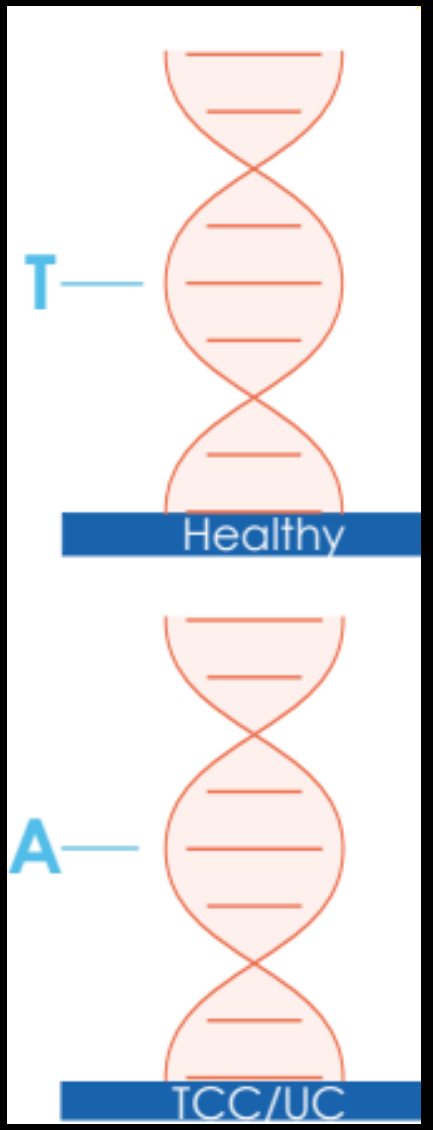




Knapp et al. Front Oncol 2020

Diagnostic Work-Up

- BRAF
  - Mutation present in urine samples from >80% of all iUC cases
    - 0/37 dogs with either normal bladders or cystitis
  - Can detect as few as 10 mutation bearing cells up to 4 months before clinical signs
- CADET BRAF Test
  - Evaluates free-catch urine for presence of mutation in cells
  - Turn around time is ~2 weeks
  - CADET BRAF Plus:
    - Detects DNA copy number changes to identify >2/3 of iUC cases not identified by CADET



Clinical Uses for CADET BRAF

- Non-invasive way to rule in/out iUC
- Confirm iUC in patient with suspected urine sediment
- Early detection or screening in at risk breeds
- Monitoring treatment response*

Case Example

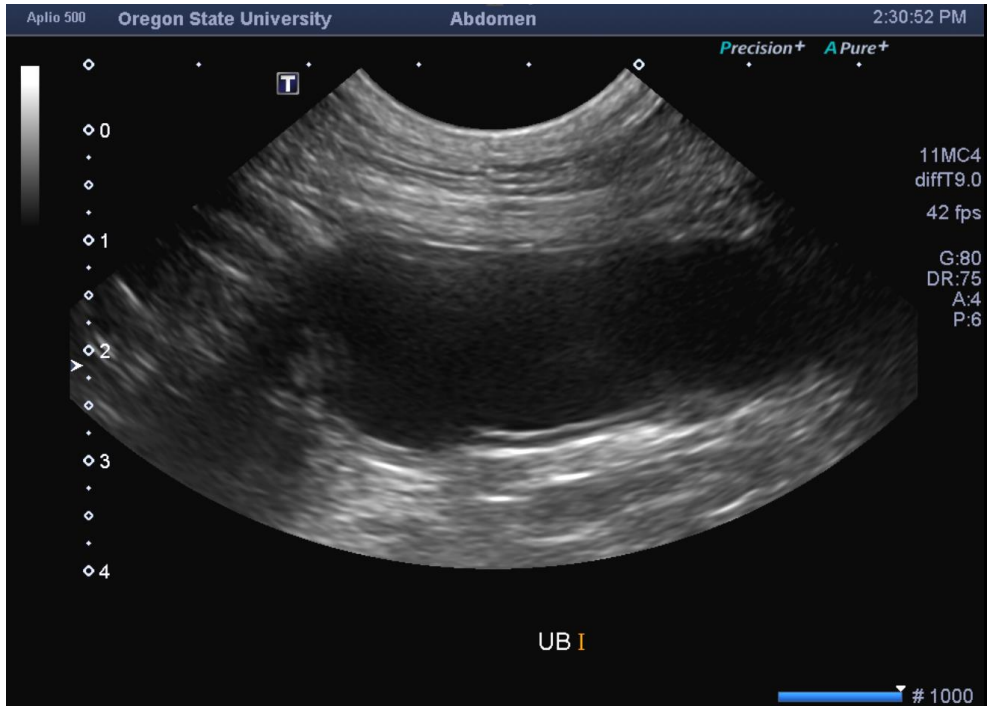
- Westly
  - 9-year-old, NM West Highland White Terrier
  - 7.6kg
- Presentation
  - September 2019
  - Owner elected to have BRAF mutation screening test performed
  - Asymptomatic, no changes in urination

Species	Breed	Sex	Pet Age	Reported
Canine	WHT	CM	9Y	09/02/2019 09:05 AM

Test Requested	Results	Reference Range	Units
CADET BRAF			
BRAF Mutation Status	DETECTED		
Comment: Result is diagnostic for transitional cell carcinoma/urothelial carcinoma.			
Volume of urine received	43		ml
Fract. abundance of BRAF mutation		12	%
% of cells with BRAF mutation	up to 24		%
Fractional abundance (FA) is the proportion of BRAF alleles in the specimen that are mutant.			
BRAF mutation is generally detected in one of the two copies (alleles) of the gene in each cell. The proportion of cells detected with the mutation is thus up to double the percentage of mutant alleles (fractional abundance) detected.			

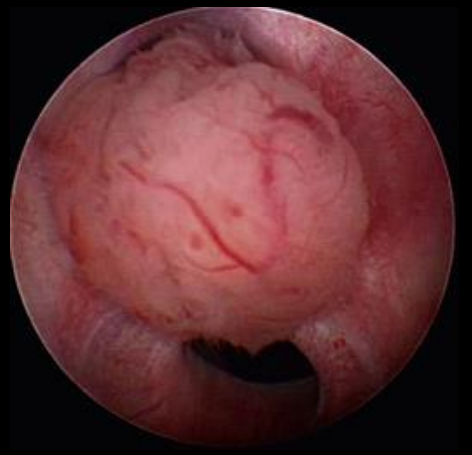
Case Example

- Initial Diagnostic Work-Up
  - CBC and Serum Chemistry- WNL
  - Urinalysis and Urine culture- WNL, no growth
- Imaging
  - Thoracic radiographs- No signs of metastasis
  - Abdominal ultrasound-



Impressions: 1. Single intraprostatic cyst, likely incidental. The mildly heterogeneous echogenicity of the right lobe of the prostate in the area of the cyst is likely secondary to the cyst, or inflammation. A neoplastic process is considered less likely,
2. No sonographic abnormality of the remainder of the urogenital tract are noted.

Case Example



Prostatic wash

Interpretation:
Cytologically within normal parameters

BLADDER TISSUE/MASS (1 slide):
The sample is moderately cellular. Several aggregates of epithelial cells are identified among few scattered erythrocytes with rare neutrophils. Cells in some aggregates are ruptured with nuclear streaming seen among bare nuclei. Other aggregates reveal a population of pleomorphic oval to polygonal transitional cells. These are occasionally in disorganized, dense aggregates which obscures cellular details. Intact cells have round nuclei with coarsely-stippled chromatin and distinct nucleoli. They are surrounded by small to moderate amounts of cytoplasm. Cells with higher N:C ratios have more basophilic cytoplasm and many cells have small discrete vacuoles. Moderate anisocytosis and anisokaryosis are observed. Mitotic activity is not seen.

Interpretation:
Epithelial proliferation - suspect transitional cell carcinoma

Comment:
Features of the cells exhibit moderate atypia. These findings coupled with prior positive BRAF results supports neoplastic transformation.

Cystoscopy

URINARY BLADDER	**Normal**	Mass		
Visualize ureters	**Yes**	No	L	R

Lesion	*Code*	*Comments (include location)*
Can't inflate lumen	0	
Hyperemia/vascularity	1	
Edema	1	
Discoloration	0	
Friability	0	
Hemorrhage	0	
Erosion/ulcer	0	
Contents	2	Mass in proximal urethra

CODE: ***Normal = 0*** ***Slight = 1*** ***Moderate = 2*** ***Severe = 3***

Comments and recommendations
Patient was placed in right lateral recumbency. The prepuce was clipped and sterilely prepped. The flexible scope allowed visualization of the urethra. In the distal urethra, no abnormalities were seen. After the pelvic flexure, mild erythema was seen in the urethra. 22 cm into the urethra, a pink, lobulated non-obstructive mass was seen in the lumen. The scope was advanced into the bladder where urine and white swirl of debris was seen. No masses were visualized in the bladder. Retroflexion was not perfromed due to obscured visualization. The urethral mass was biopsied - the sample was impressed on slides for cytoloy prior to adding into the formalin jar. The bladder and urethra were visualized again - there were iatrogenic superficial hemorrhage of the urinary bladder. Urine was removed at the site of urethral mass for collection.

Case Example

Treatment

- Radiation therapy- 2.5 Gy x 20 fractions
- Chemotherapy- 5 doses of Mitoxantrone

Follow-Up

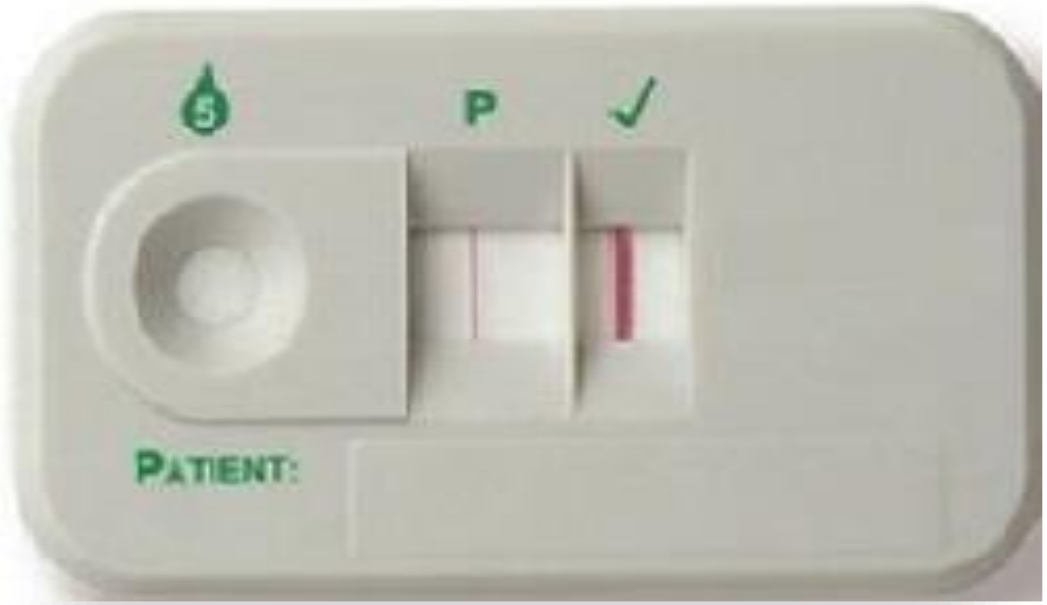
- Active monitoring program
- Repeat diagnostics every 3-4 months to look for signs of disease progression

Case Example

- Last seen at OSU in September 2021
  - CT scan + cystoscopy
  - Penile and pelvic urethra unremarkable
  - Mural urinary bladder thickening
    - Progressive disease?
  - Repeat BRAF- mutation still present
    - Lower value than at time of diagnosis

Diagnostic Work-Up

- Bladder Tumor Antigen (BTA) Test
  - Used as screening test
  - Sensitivity: 90%
  - Specificity: 40-80%
    - May improve Sp by centrifugation of urine
  - Fallen out of favor with BRAF test



Staging for iUC

Metastasis

- Hematogenous or lymphatic route

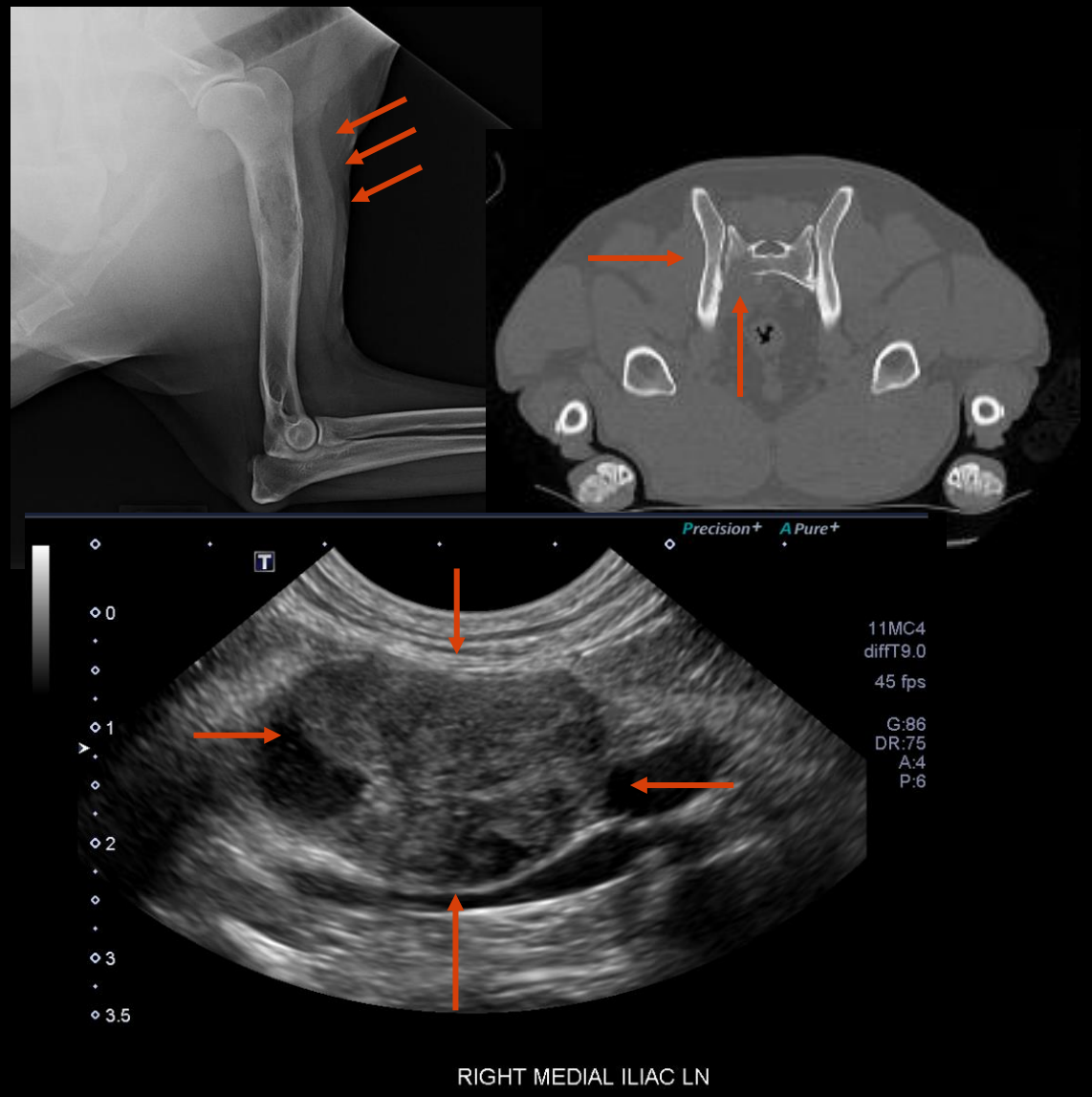
Metastatic Rate

- On presentation: 14-16%
- At euthanasia/necropsy: 42-58%

Sites

- Regional lymph nodes
- Lungs
- Other- liver, bone, kidney, adrenal gland, skin, heart, brain, and GI tract

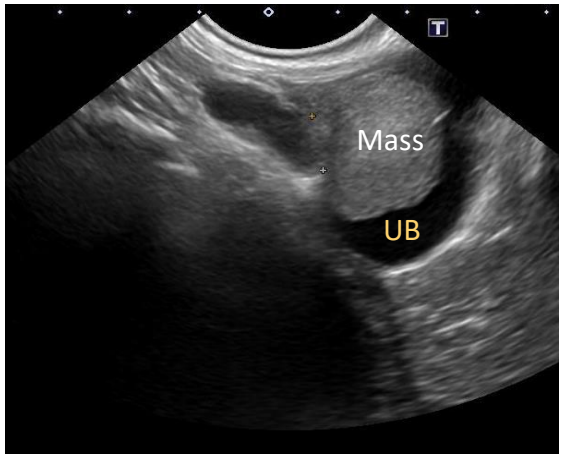
13% Noted to have second primary tumors

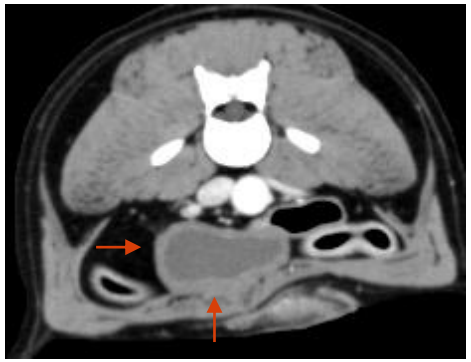


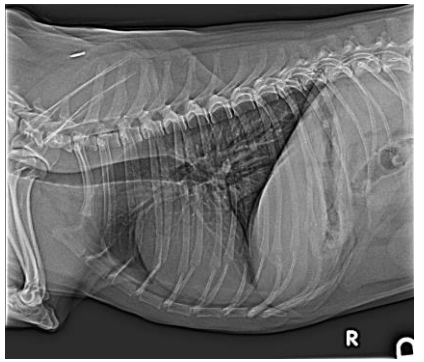
RIGHT MEDIAL ILIAC LN

Staging for iUC

Imaging of the thoracic cavity	• Three-view thoracic radiographs • Computed tomography
Imaging of the abdominal cavity	• Abdominal ultrasound • Computed tomography
Other	• Spinal radiographs • Limb radiographs if patient presents with lameness
Mindful to be consistent with imaging approach to monitor response	• Modality, bladder size, patient positioning, etc.







TNM Stage

Box 29-1 TNM Clinical Staging System for Canine Bladder Cancer

T—Primary Tumor

Tis	Carcinoma in situ
T0	No evidence of a primary tumor
T1	Superficial papillary tumor
T2	Tumor invading the bladder wall, with induration
T3	Tumor invading neighboring organs (prostate, uterus, vagina, and pelvic canal)

N—Regional Lymph Node (Internal and External Iliac Lymph Node)

N0	No regional lymph node involvement
N1	Regional lymph node involved
N2	Regional lymph node and juxtaregional lymph node involved

M—Distant Metastases

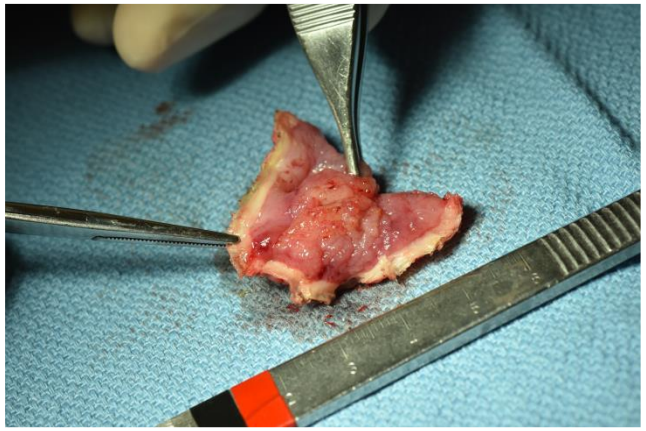
M0	No evidence of metastasis
M1	Distant metastasis present

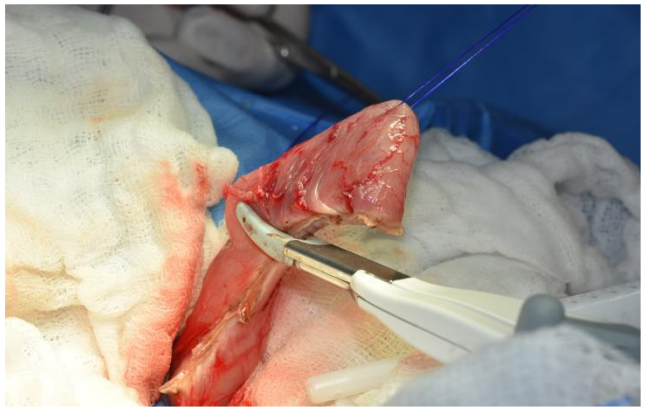
Modified from Owen LN: *TNM classification of tumours in domestic animals*, Geneva, 1980, World Health Organization.

- Dogs
  - 78% have T2
  - 20% have T3
- Humans
  - 66% have T1

Treatment

- Surgical interventions
- Radiation therapy
- Chemotherapy
- NSAID
- Palliative and supportive care





Treatment- Surgery

- Indicated only to:
  - Obtain tissue for definitive diagnosis
  - Eradicate lesions amendable to wide excision (distant from trigone)
  - Relieve urinary tract obstruction
- Rarely curative!
  - Not possible in most cases due to location
  - “Field effect”- malignant transformation of entire urothelium
- Risks
  - Procedural risk, recurrence, seeding

Treatment- Surgical Procedures

Full-Thickness removal of discrete iUC lesions away from trigone

- Sx + NSAID +/- chemo
  - PFI 235 days
  - MST range from 348 days to 722 days
- Even with “clean” margins can recur

Total cystectomy + urinary diversion strategies

- Serious complications limit success

Prepubic cystostomy catheter

- Palliative
- Complications 49%: urine leakage, tumor seeding, infection, displacement, damage

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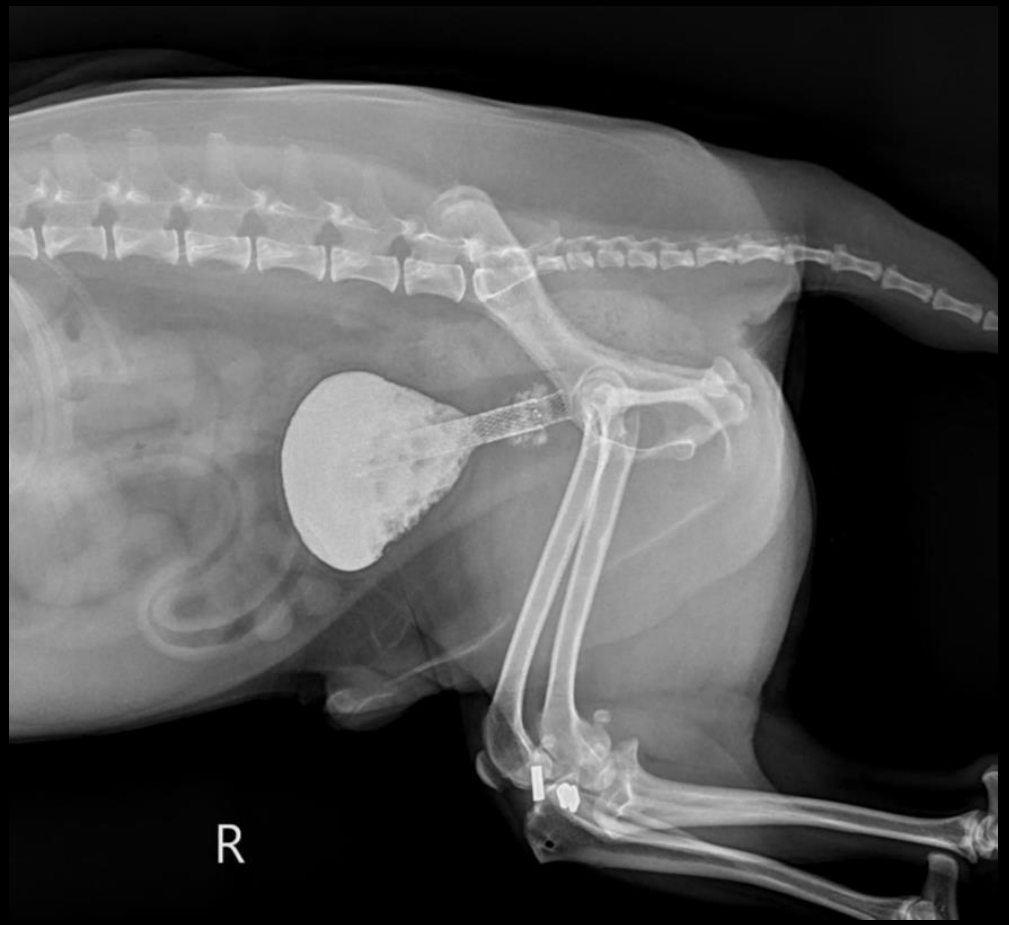
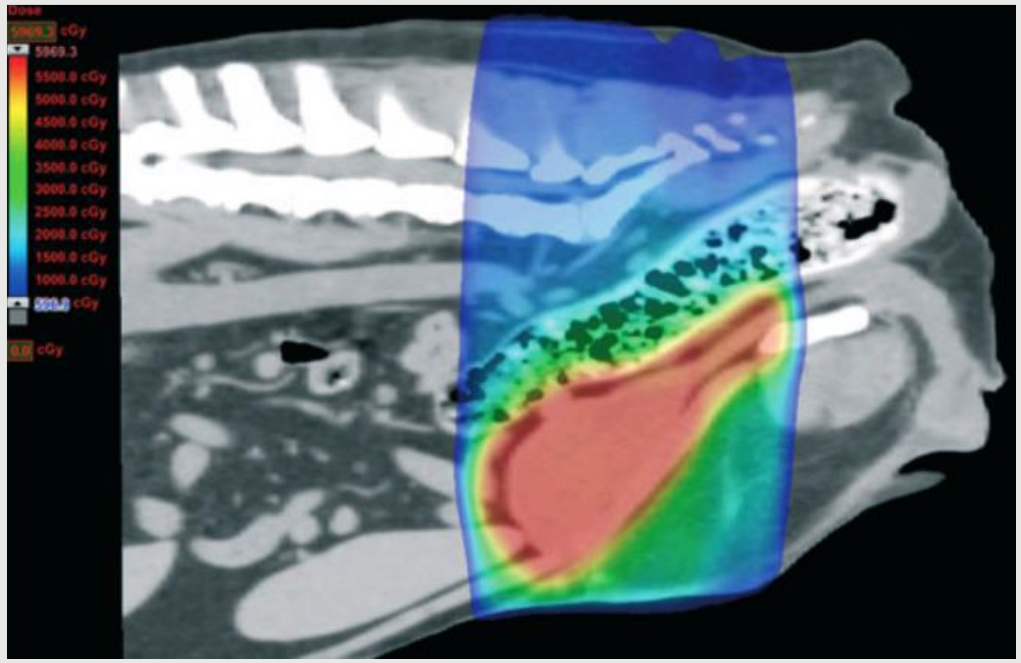
Treatment- Other Localized Therapy



- Stents
  - Urethra and ureters can be stented in case of obstruction
  - Minimally invasive in most, but palliative
    - MST ranged from 20-78 days
  - Risks: incontinence (25-39%), stent fracture, migration, tumor progression
- Laser ablation
  - Carbon dioxide (CO_2) or near-infrared diode laser
  - Complications: perforation, transient postprocedural worsening of stranguria/hematuria, urethral stenosis and infection



Nolan et al. JVIM 2012

Treatment-Radiation Therapy

- iUC considered moderately radioresistant
  - Use higher doses and less fractionation
- Intensity-Modulated and Image-Guided RT (IMRT/IGRT)
  - Acute side effects mild and self limiting
  - Late side effects <10%
  - Median event-free survival of 317 days
  - MST of 654 days
- Low Dose Palliative RT
  - 10 daily fractions
  - Acute side effects mild, no late side effects
  - Complete remission or partial remission in 61%, stable disease in 38%

Treatment-Chemotherapy

Systemic therapy is mainstay of treatment

- Cox inhibitors, chemotherapy or combination

Usually not curative but can lead to remission or stable disease

Clinical signs do not consistently follow changes in tumor size

- Remeasure iUC masses is essential
- Every 8-12 weeks intervals

If cancer progression or unacceptable toxicity occurs- switch treatment

iUC growth can be controlled in ~75-80% of dogs, QOL is usually very good, and MSTs have extended well beyond a year

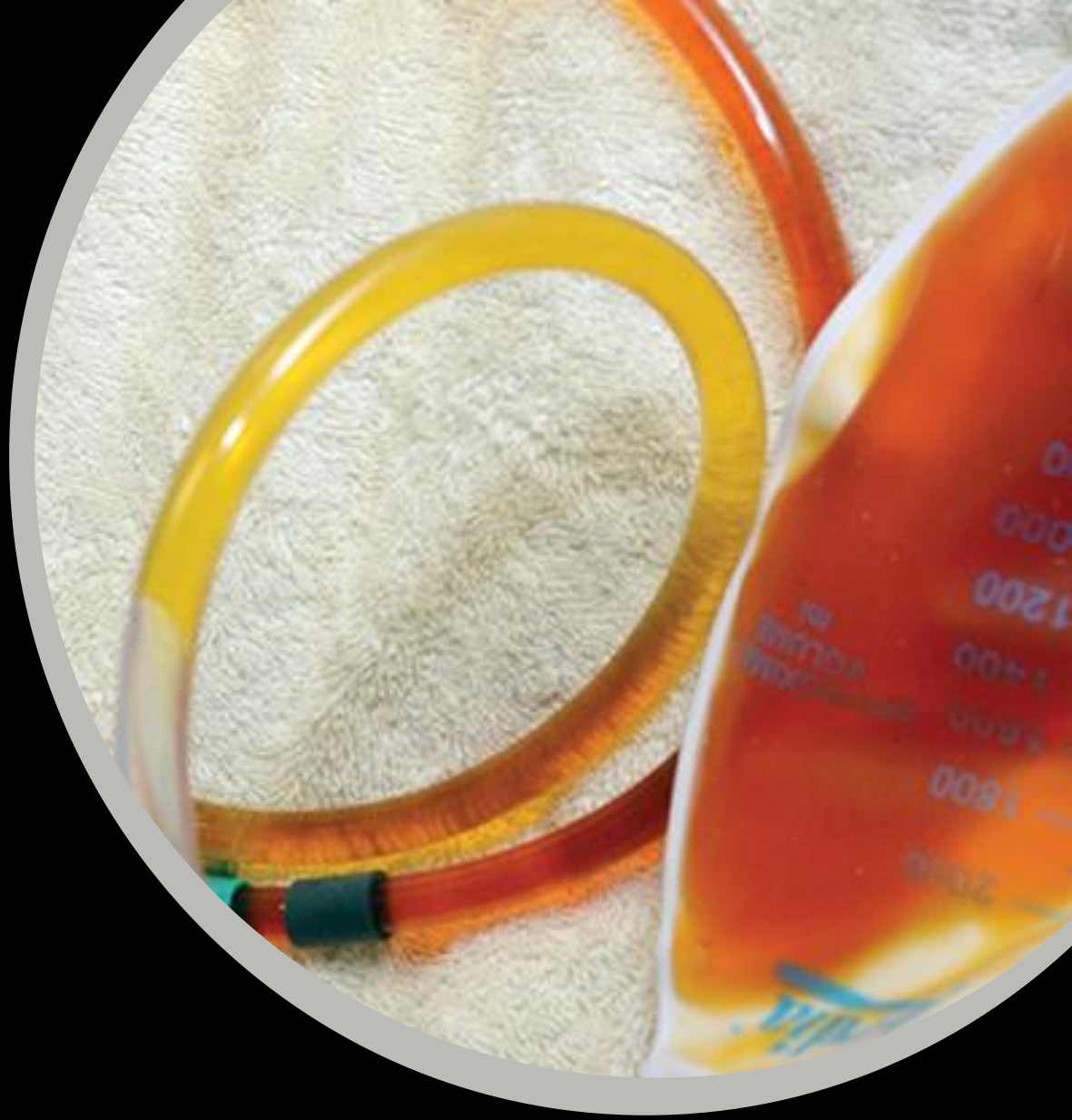
Treatment- Chemotherapy

Protocol	Response	Progression Free Interval (PFI)	Median Survival Time (MST)
Piroxicam	3% CR, 18% PR, 59% SD, 20% PD	120 days	244 days
Deracoxib	0% CR, 17% PR, 71% SD and 12% PD	133 days	323 days
Vinblastine + Piroxicam	0% CR, 58% PR, 33% SD and 8% PD	199 days	299 days
Mitoxantrone + Piroxicam	0% CR, 8% PR, 69% SD, 23% PD	106 days	247 days
Carboplatin + Piroxicam	0% CR, 13% PR, 54% SD, 33% PD	73 days	263 days
Cisplatin + Piroxicam	14% CR, 57% PR, 28% SD, 0% PD	124 days	246 days
Metronomic chlorambucil	0% CR, 3% PR, 67% SD, 30% PD	119 days	221 days

- Some MST account for multiple agents being used subsequently
- Most chemotherapy protocols have response of stable disease

Treatment- Palliative & Supportive

- NSAID/Pain management
- Catheterization
  - Temporary or surgical placement previously discussed
  - To help relieve blockage and reduce risk of hydronephrosis
- Other supportive medications
  - Anti-nausea medication
  - Appetite stimulants



Treatment- Palliative & Supportive

Table 1. Frequency of bacterial isolates from all positive cultures and frequency of dogs with positive culture having cultured specific bacterial organisms.

Bacterial Type	% of Isolates	% of Dogs With At Least One Positive Culture
Staphylococcus spp.	23.9	23.4
Escherichia coli	19.8	32.0
Streptococcus spp.	18.2	27.6
Enterococcus spp.	7.4	19.1
Pseudomonas spp.	7.4	14.9
Pasteurella spp.	5.8	12.8
Mycoplasma spp.	3.3	8.5
Proteus spp.	2.5	6.3
Bacillus spp.	1.7	4.3
Enteric spp.	1.7	4.3
Actinomyces spp.	1.7	4.3
Aerococcus spp.	1.7	4.3
Other	5.0	12.8

Budreckis et al. JVIM 2015

- Risk of concurrent UTIs is high in dogs with iUC
  - Urine retention, abnormal epithelium/barrier, compromised immune function
- Worsen clinical signs and give false impression of cancer progression
- Need to appropriately treat UTI but refrain from prescribing when not indicated
  - Common uropathogens Table 1 to the left
  - Antimicrobial choice should be based on urine culture
    - Initial choice: Clavamox or TMS

Prognostic Factors

Location and tumor extent:

- Prostatic involvement has an increased risk of distant metastasis

Stage of disease:

- Higher T stage has an increased risk of nodal and distant metastasis

Age:

- The younger the age, the higher the risk of nodal metastasis

Treatment plan selected:

- Palliative vs. curative intent or multimodal therapy

Summary- 5 Key Points

1. Several breeds at high risk for iUC: Scottish terriers and West Highland White Terriers
   - Discuss with clients about annual screening diagnostics to diagnose this tumor in earlier stages
2. Diagnosing canine iUC can be challenging
   - Newer, non-invasive diagnostics such as the BRAF mutation test, are improving diagnostics
3. Radiation therapy has shown great promise as a treatment option
4. Several different chemotherapeutic agents have been used for the treatment of iUC.
   - Roughly 75% of dogs can have good quality of life and extended survival times of over a year
5. Concurrent urinary tract infections are common.
   - It is important to continually screen and treat if detected as the clinical signs may improve dramatically

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Questions