Analysis of a Urinalysis: Treating Urothelial Carcinomas

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Urothelial Tumors

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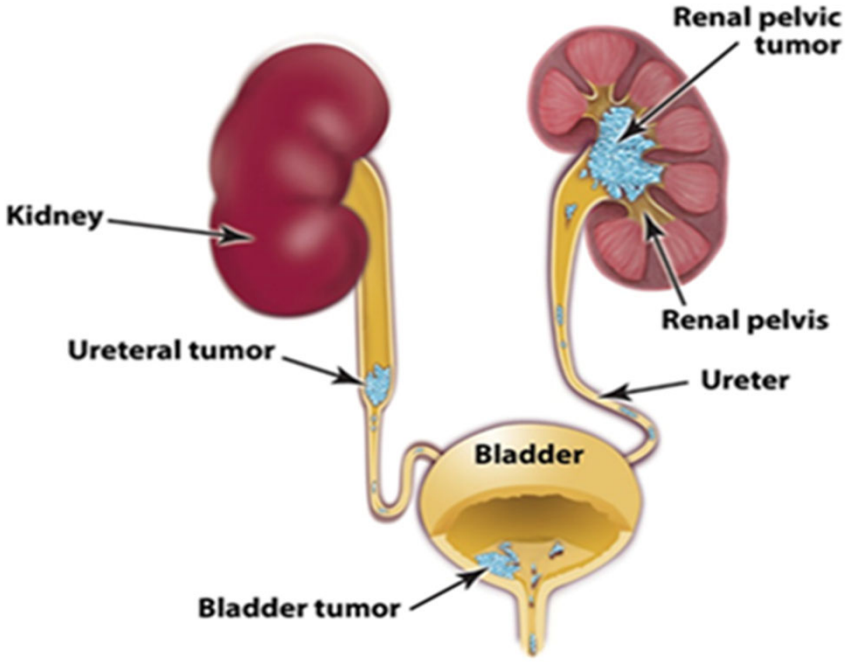
Urinary Tract

- Bladder
  - Trigone
- Urethra
- Prostate
- Ureter
- Kidney



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Etiology

- Older flea/tick products
- Lawn chemicals
- Obesity
- Sex
  - Female >> Male
  - Neutered>> Intact
- Breed

Breed	Odds Ratio (compared with mixed breed dogs)
Scottish Terrier	21.12
Eskimo dog	6.58
Sheltie	6.05
Westie	5.84
Keeshond	4.26
Samoyed	3.43
Beagle	3.09
Dalmation	2.43

Scottish Terriers- Specific Risk Factors

- Increased Risk
  - Exposure to lawn herbicides /insecticides

- Lower Risk
  - Vegetables 3x/week
  - Carrots most frequent treat

- No change
  - Topical flea prevention

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Bladder

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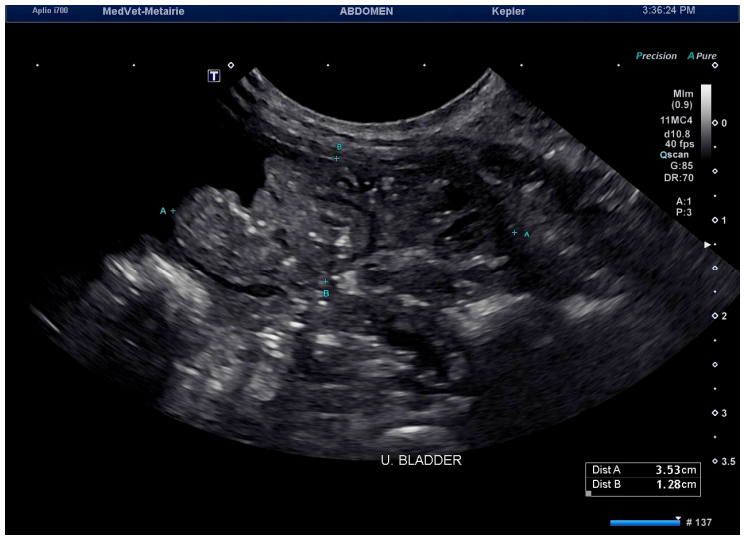
General overview

Transitional Cell Carcinoma

- Most common neoplasm of urinary tract
- 2% canine malignant tumors



Other Neoplastic Lesions

- Other Carcinomas
  - SCC
  - Aca
  - Undifferentiated Ca
- Lymphoma
- Mesenchymal tumors
  - Rhabdomyosarcoma
  - Leiomyosarcoma
  - HSA
  - Fibroma
  - Others

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Presentation

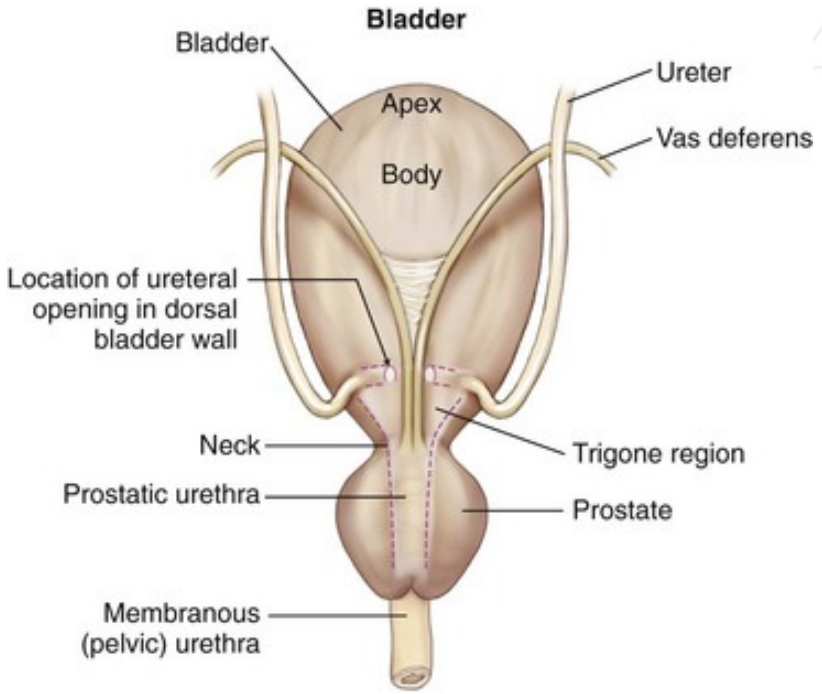
Older dogs

Location- Trigone of the bladder

- 56% have urethral involvement
- 29% of male dogs have prostatic involvement

Clinical Signs

- Hematuria, dysuria, pollakiuria



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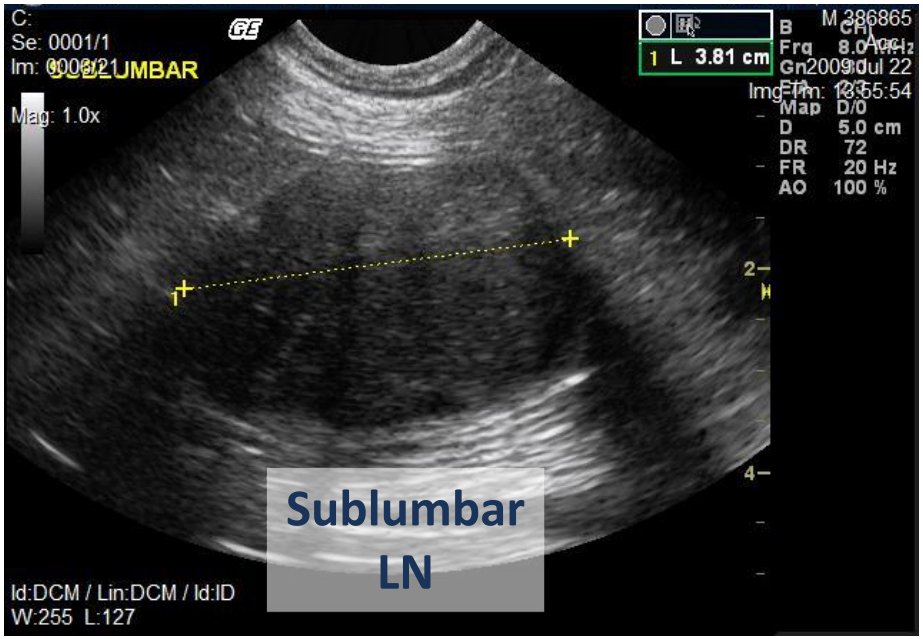
Physical exam findings

- Bladder mass/distended bladder on abdominal palpation
- Rectal exam findings:
  - Thickening of urethra/trigone region of bladder
  - Sublumbar LN enlargement
  - Prostatomegaly



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TCC vs Cystitis?

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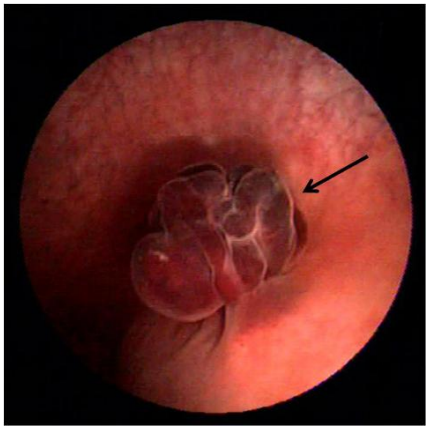
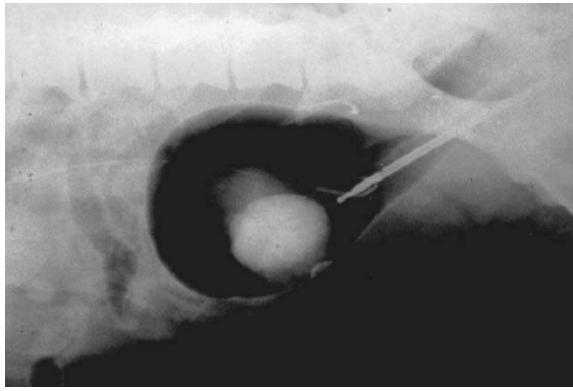
Differential Diagnosis

- Other neoplasia
- Chronic bacterial cystitis
- Polypoid cystitis
- Fibroepithelial polyp
- Granulomatous cystitis/urethritis
- Gossypiboma
- Calculi
- Inflammatory pseudotumor



Cystoscopy: Urethral Polyp
University of Florida Small Animal Hospital



Double-contrast cystogram: Fibroma
Withrow & Vail: Small Animal Clinical Oncology

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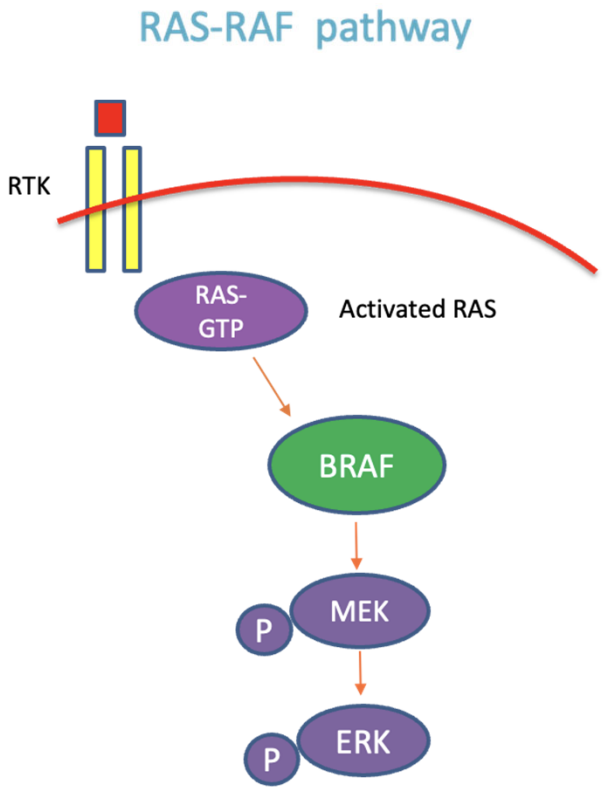
Diagnosis

- Definitive diagnosis = histopathology with Uroplakin III IHC
  - Cystotomy, Cystoscopy, Traumatic catheterization
- Cytology
  - Neoplastic cells in 30% of urine
  - Difficult to distinguish from reactive epithelial cells associated with inflammation
- Screening test – V-BTA (bladder tumor antigen)
  - Sensitive, but many false positives
    - hematuria, proteinuria, glucosuria
- BRAF – Digital PCR
  - Sensitivity 85%, Specificity 100%
  - BRAF+ (FISH) Sensitivity to 95%

What is BRAF?

- BRAF gene provides instructions to make a protein
- This protein is part of RAS/MAPK pathway
- RAS/MAPK regulates
  - Cell proliferation
  - Differentiation
  - Migration
  - Apoptosis
- Oncogene
- Somatic mutation



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BRAF in human oncology

- Nucleotide substitution resulting in a change of amino acid at codon 600
- Noted to occur in:
  - Melanomas
  - Colorectal cancer
  - Thyroid cancer
  - Ovarian cancer
  - Hairy cell leukemia
  - Rare in bladder tumors
- Development of BRAF inhibitors

BRAF in veterinary oncology

- Nucleotide substitution resulting in a change in amino acid at codon 595
- Highest penetrance rates (87%) in urothelial carcinoma
- Vemurafenib (BRAF inhibitor)
- Variable effect on cellular proliferation in vitro with transitional cell carcinoma

Cadet BRAF

Urine sample: 40 mls of urine into preservative within 15 minutes of collection

Can have multiple collections into the same sample cup

Report the % of copies of mutant BRAF genes (generally heterozygous) – fractional abundance

CADET BRAF

BRAF Mutation Status	DETECTED	

This is an updated and/or corrected result(s).

Comment:

Result is diagnostic for transitional cell carcinoma/urothelial carcinoma.

The University of Wisconsin-Madison has a clinical study to determine whether household chemicals are linked to TCC / UC in dogs. Please provide the attached information link to owners of dogs with bladder cancer, so they can decide if they want to enroll in the study. The University of Wisconsin-Madison will handle all recruitment, consenting, and sample collection once owners contact them. For more information go to: https://Environmental risk for bladder cancer.pdf

Volume of urine received	50	ml
Fract. abundance of BRAF mutation	16	%
% of cells with BRAF mutation	up to 32	%

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.

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Staging Diagnostics

CBC, Chemistry, UA +/- urine culture

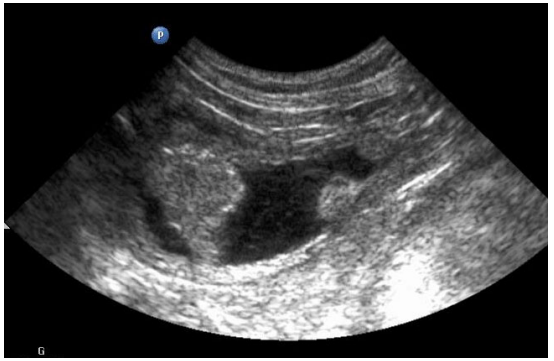
- Avoid cystocentesis
- E. coli and Staphylococcus sp. most common in tumor and non-tumor bearing dogs

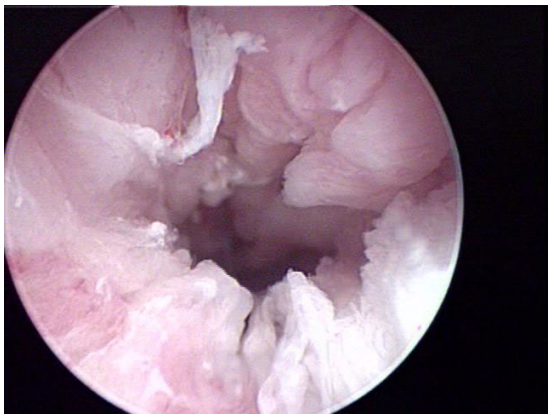
Abdominal ultrasound

Thoracic radiographs

Urinary tract imaging

- Cystoscopy/Urethroscopy





WHO Staging

TNM	Defined
T_{is}	CA in situ
T_0	No evidence primary tumor
T_1	Superficial papillary tumor
T_2 **78%**	Tumor invading bladder wall (with induration – thickening or firm mass)
T_3 **20%**	Tumor invading neighboring organs (prostate, uterus, vagina, pelvic canal)
N_0	No regional LN metastasis
N_1	Regional LN metastasis
N_2	Regional and juxtaregional LN metastasis
M_0	No distant metastasis
M_1	Distant metastasis

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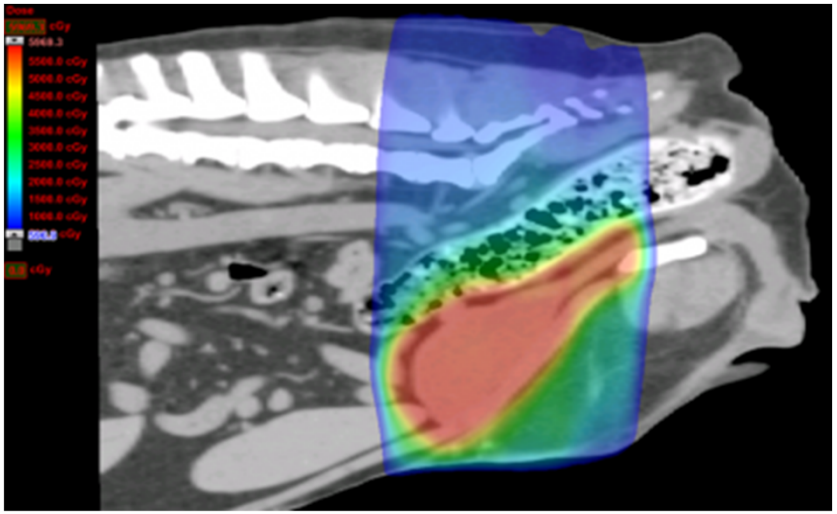
Metastatic Rates and Pattern

- Metastasis at diagnosis
  - Nodal 16% and distant 14%
- Metastasis at necropsy
  - 42% LN and 58% distant; 33% of total dogs had both LN and distant
  - Most common distant site: lungs (50%) followed by bone (9 - 14%)
- Abdominal wall via seeding: surgical or non-surgical procedures
  - Aggressive and poorly responsive to medical therapy

Treatment

- Local and Metastatic Control
  - Medical
  - Surgical
  - Radiation Therapy
  - Palliative Therapy



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Medical- NSAIDs

Piroxicam

- First studied
- 0.3 mg/kg PO SID
- 6% CR, 12% PR, 53% SD, 29% PD
- Overall response rate 17.6%
- Median survival time 181 days (range 28-720+ days)
- D/C if vomiting, melena, or anorexia occurs

Deracoxib (Deramax)

- 3 mg/kg PO SID
- 0% CR, 17% PR, 71% SD, 12% PD
- Overall response rate 17%
- Median survival time 323 days; Median progression free interval 133 days
- Mild GI toxicity (20%), 4% renal/hepatic toxicity

Medical- NSAIDs

Firocoxib (Previcox)

- Combined study with cisplatin but arm with firocoxib alone
- 20% partial remission/overall response rate
- Median survival time 152 days
- Median progression free interval 105 days

What about carprofen and meloxicam?

- No studies evaluating the use of these NSAIDs as single agent in transitional cell carcinoma to date

Medical- Intravenous Chemotherapy

Mitoxantrone

- 5 mg/m^2 every 3 weeks IV
- Two studies with mitoxantrone and piroxicam
  - Henry et al. 2% clinical remission, 33% partial remission, 46% stable disease
  - Median progression free interval 194 days
  - Median survival time 350 days
  - Allstadt et al. 8% partial remission, 69% stable disease
  - Median progression free interval 106 days

Vinblastine

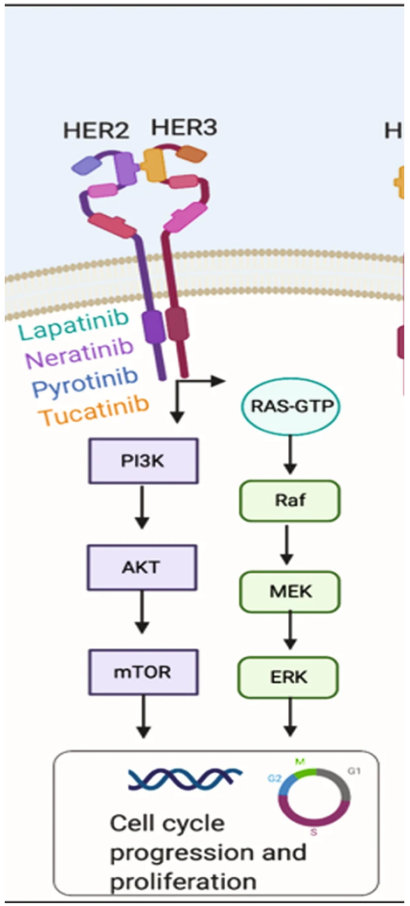
- 2 mg/m^2 every 2 weeks IV
- Vinblastine alone – 22% partial remission, 70% stable disease, 3.7% progressive disease
  - Median progression free interval 143 days
  - When adding in piroxicam AFTER vinblastine median survival time 531 days
- Vinblastine and piroxicam – 58% partial remission, 33% stable disease, 8.3% progressive disease
  - Median progression free interval 199 days; Median survival time 299 days

Medical- Oral chemotherapy

- Metronomic chlorambucil +/- NSAID daily
- 29/31 dogs failed other therapy
- 3% partial remission, 67% stable disease, 30% progressive disease
- Median progression free interval 119 days; median survival after starting chlorambucil 221 days

Medical- Oral chemotherapy

- Lapatinib: Dual inhibitor of EGFR and HER2 tyrosine kinases
- Non-randomized, clinical trial comparing 44 dogs who received Lapatinib and piroxicam to 42 dogs who received piroxicam alone



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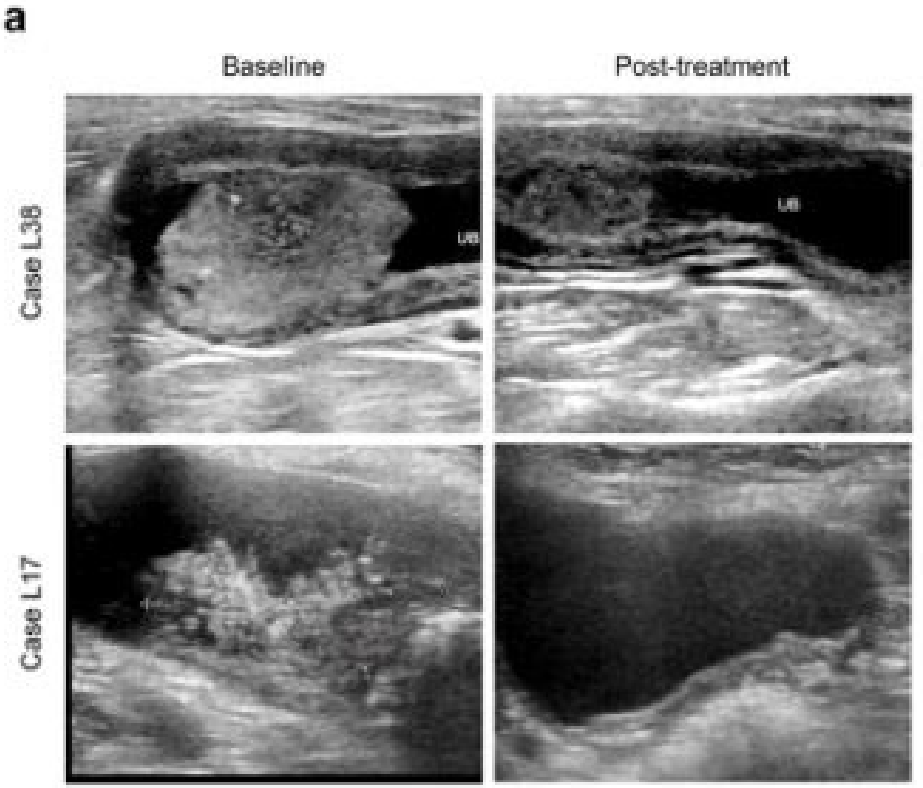
Medical- Oral chemotherapy

- L+P: 2% complete remission, 52% partial remission, 34% stable disease, 12% progressive disease
- P: 9% partial remission, 67% stable disease, 24% progressive disease
- Median PFS 193d (L+P) vs 90d (P)
- Median overall survival- 435d (L+P) vs 216d (P)



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Surgical

- Indications for surgery:
  1) Obtain tissue for diagnosis
  2) Removal of tumor if located away from the trigone
  3) Maintain or restore urine flow
- Concerns regarding surgical approach
  1) Crucial to avoid seeding the tumor
  2) Field Effect- the concern that the entire urothelium has undergone widespread preneoplastic change

Radiation Therapy- Intensity-Modulated and Image-guided RT (IM/IGRT)

- IMRT is a type of radiation therapy in which the intensity of the radiation beam is adapted to match the precise contours of a tumor and minimize the damage to surrounding tissue
- IGRT is the use of imaging during radiation therapy to improve precision and accuracy of treatment delivery
- Three groups of dogs:

  1) Treated with mitoxantrone less than 1 month before RT

  2) Treated with mitoxantrone longer than 1 month before RT with stable disease

  3) IMRT as a salvage after failing mitoxantrone +/- surgery

Radiation Therapy- IM/IGRT

- Administer 57 total Gy in 20 daily fractions (Monday-Friday)
- Median event free survival 260 days
- Median overall survival 510 days
- Overall survival affected by severity of clinical signs, prostate involvement, and lymph node irradiation
- Rate of locoregional progression after IM/IGRT 59% (27/46)
- 61% developed bone marrow toxicity
- Acute side effects in 65% (colitis, dermatitis, genitourinary)
- Late side effects
  - 31% urinary incontinence
  - 6% urethral obstruction

Radiation Therapy: Whole pelvic irradiation with simultaneous boost volumetric modulated arc radiotherapy

- 12 dogs separated into 2 groups by stage (group 1: confined to the urinary tract vs group 2: metastasis to lymph node)
- 36-42 GY in 6 fractions
- All dogs received piroxicam and carboplatin as a radiosensitizer
- Treatment was well tolerated with no high-grade side effects
- Median OST for group 1 was 1,230d vs group 2 at 150d

Radiation Therapy- Palliative

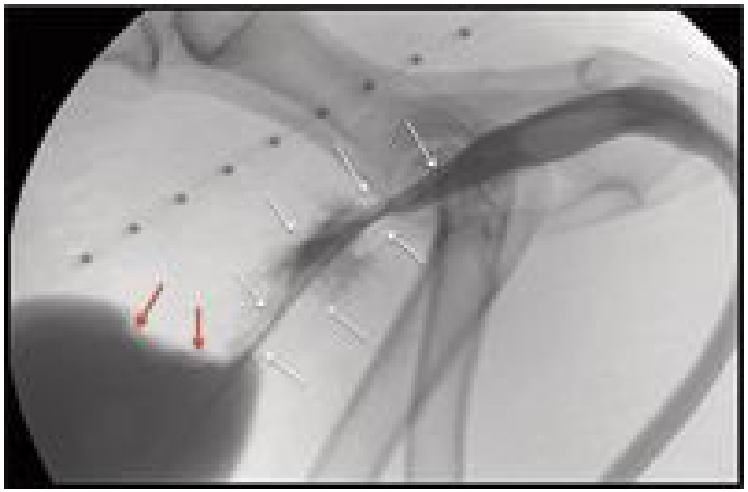
- 13 dogs total bladder and urethra – 6 first line, 7 as rescue
- 10 fractions x 2.7 Gy (Monday-Friday)
- 1 clinical remission, 7 partial remission, 5 stable disease = overall response rate 61.5%
- All first line therapy dogs went on to receive mitoxantrone chemo
- 3 dogs had relief of urethral obstruction 3-8 days after starting RT
- 1 dog with unilateral ureteral obstruction reversed 6 weeks after completing RT

Radiation Therapy- Palliative

- Median survival for all patients = 179 days (50-767 days)
  - Median survival in first line group = 156 days
  - Median survival in rescue group = 270 days (includes other treatments they received)
  - Median treatment survival between groups was similar (150 days for first line vs. 147 days for rescue)
- Acute side effects were grade 1-2
  - Perianal dermatitis, colitis, cystitis, vaginitis
- No significant late side effects

Non-Surgical Therapy

- Laser Ablation
- Intra-arterial chemotherapy
- Urethral Stent
  - Dr. Ralph will be discussing this in more detail



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Prostate

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Presentation

Older castrated male dogs

Urinary or fecal signs

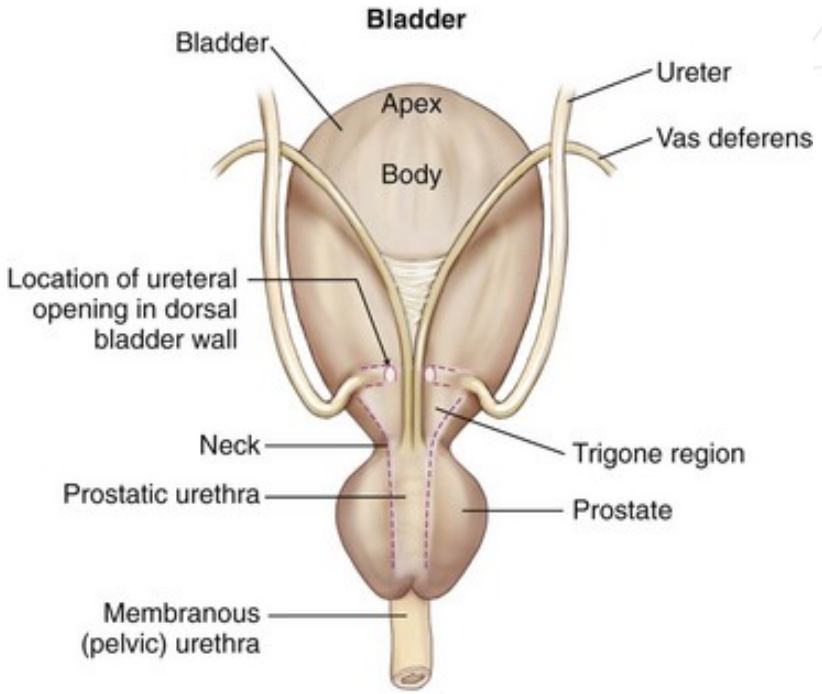
- Hematuria, stranguria
- Tenesmus, flattened, or “ribbon-like” stool shape

Urinary tract obstruction

- Azotemia → Renal failure

Bone metastasis

- Pain, gait abnormalities, lameness, straining to defecate



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Prostatic tumor types

- Adenocarcinomas*
- Others:
  - FSA
  - Leiomyosarcoma
  - OSA
  - LSA
  - HSA
- Benign tumors rare

Breeds

- Increased risk:
  - Bouvier des Flandres
  - Doberman
  - Sheltie
  - Scottie
  - Beagle
- Decreased risk:
  - American cocker spaniel
  - Dachshund

Prostatic Tumors

Occurs in both castrated & intact dogs

- Increased risk in castrated male dogs

Arise from urothelial or ductular origin

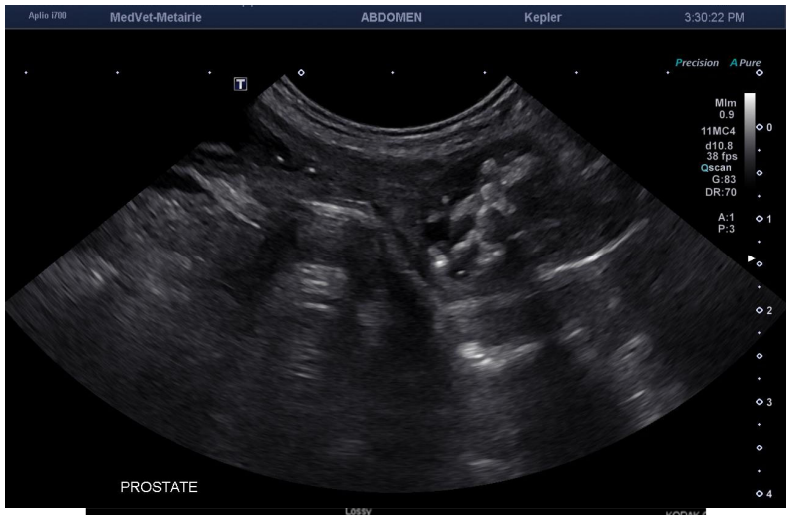
- NOT acinar (like in people)
- NOT androgen dependent

Etiology unknown

- Prostatic intraepithelial neoplasia (PIN) is a precursor in people & is likely uncommon in dogs
  - PIN in < 3% of dogs with prostate tumors in 2 large studies

Staging Diagnostics

- Typically palpable on rectal exam
- CBC, Chemistry, UA +/- urine culture
  - Avoid cystocentesis
- Abdominal ultrasound
- Thoracic and abdominal radiographs
  - Especially lumbar and pelvic bones



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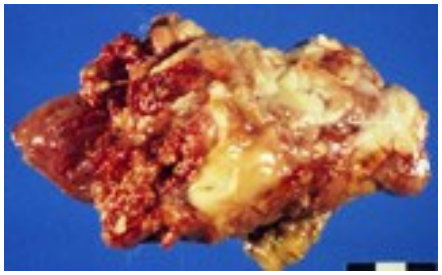
Diagnosis

- Biopsy – gold standard
  - Surgical
  - Percutaneous biopsy
    - Risk of seeding, urethral trauma, hemorrhage
- Cytology – most common
  - Traumatic catheterization
  - Prostatic massage/wash
  - US-guided FNA (*risk of seeding)*
- Prostate specific antigen (PSA)
  - Not useful in dogs
- BRAF – Digital PCR
  - Sensitivity 85%, Specificity 100%
  - BRAF+ (FISH) Sensitivity to 95%

Metastatic Rate and Patterns

- Most dogs diagnosed with advanced disease
- Locally invasive with a high risk of metastasis
  - 1 necropsy study showed 80% had metastasis, most commonly to lung & lymph node
- Tendency to metastasize to bone
  - 22-42% develop skeletal metastasis predominantly to lumbar vertebrae & pelvis



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Prostate Tumors - Treatment

- Surgery (prostatectomy)
  - Dogs with early-stage disease still confined within the capsule
- Radiation
  - Study of 10 dogs treated with intraop-orthovoltage therapy. Nine were prescribed 20 to 30 Gy to the prostate, with an MST of 114 days, although the range extended to 750 days
  - IMRT in 21 dogs with genitourinary carcinomas – 54-58Gy in 20 fractions
    - 10 had prostatic carcinomas – 317 day event free survival, OST for ALL dogs was 654 days. Need more investigation into RT for control
    - 20% of dogs had manageable grade 3 toxicity (including urethral, ureteral, and rectal stricture)

Prostate Tumors- Treatment

- Chemotherapy
  - Injectable
    - Carboplatin +/- gemcitabine IV q3wks, mitoxantrone IV q3wks, vinblastine IV q1-2wks
  - Metronomic (oral)
    - Chlorambucil 4 mg/m2 PO SID + NSAIDs
- NSAIDs
  - Survival benefit in dogs treated with piroxicam or carprofen (MST 6.9 months) vs. untreated dogs (0.7 months)

Feline Bladder Tumors

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General overview

- 2nd most common urinary tract tumor
- Incidence rate is very low
- Carcinomas, malignant & benign mesenchymal tumors, lymphoma

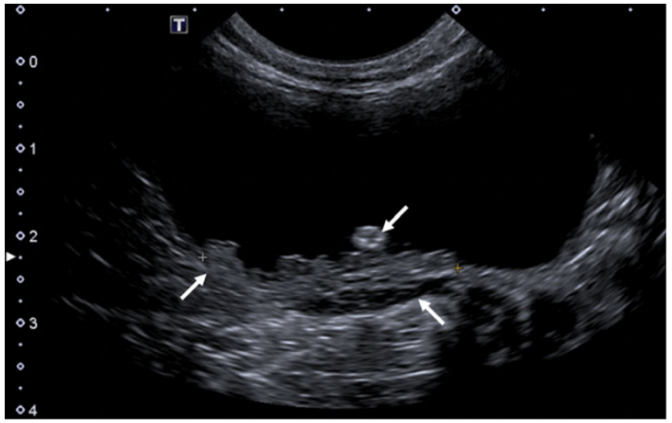
- TCC
  - Hematuria, stranguria, pollakiuria
  - Concurrent UTI common (75%)
  - Treatment = surgery, chemotherapy, NSAID
  - MST 261 days

Lower urinary tract transitional cell carcinoma in cats: Clinical findings, treatments, and outcomes in 118 cases

- Study Population
  - Median age 15 years old
  - 65% domestic shorthair
- Previous history
  - Chronic UTI in 23.7%
  - Feline idiopathic cystitis in 14.4%
- Presenting complaint
  - Hematuria, Pollakiuria, Stranguria
  - Urethral obstruction at time of diagnosis in 10.2% of cases

Lower urinary tract transitional cell carcinoma in cats

- Diagnostic results
  - CBC: Anemia
  - Chemistry: Azotemia
  - Urinalysis: UTI
- Abdominal ultrasound
  - Location- trigone in 27.1% followed by ventral bladder wall in 23.7%
- Staging
  - 12.7% metastatic rate at time of diagnosis
  - Regional LN > lungs > carcinomatosis



Hamlin et al. Vet Rad US 2019.

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Lower urinary tract transitional cell carcinoma in cats

- Treatment- 62% received therapy
  - NSAIDs- piroxicam, meloxicam, robenacoxib
  - Chemotherapy- mitoxantrone >> vinblastine, doxorubicin, others
  - Surgery- partial cystectomy

- Survival
  - Median PFS 113 days
  - Time to recurrence post-surgery 205 days
  - Overall MST 155 days
    - Untreated cats- 46 days
    - Medical management alone –176 days
    - Partial cystectomy with or without other treatment- 294 days