Plumbing Problems: Cancer of the Urinary Tract

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MedVet Pittsburgh

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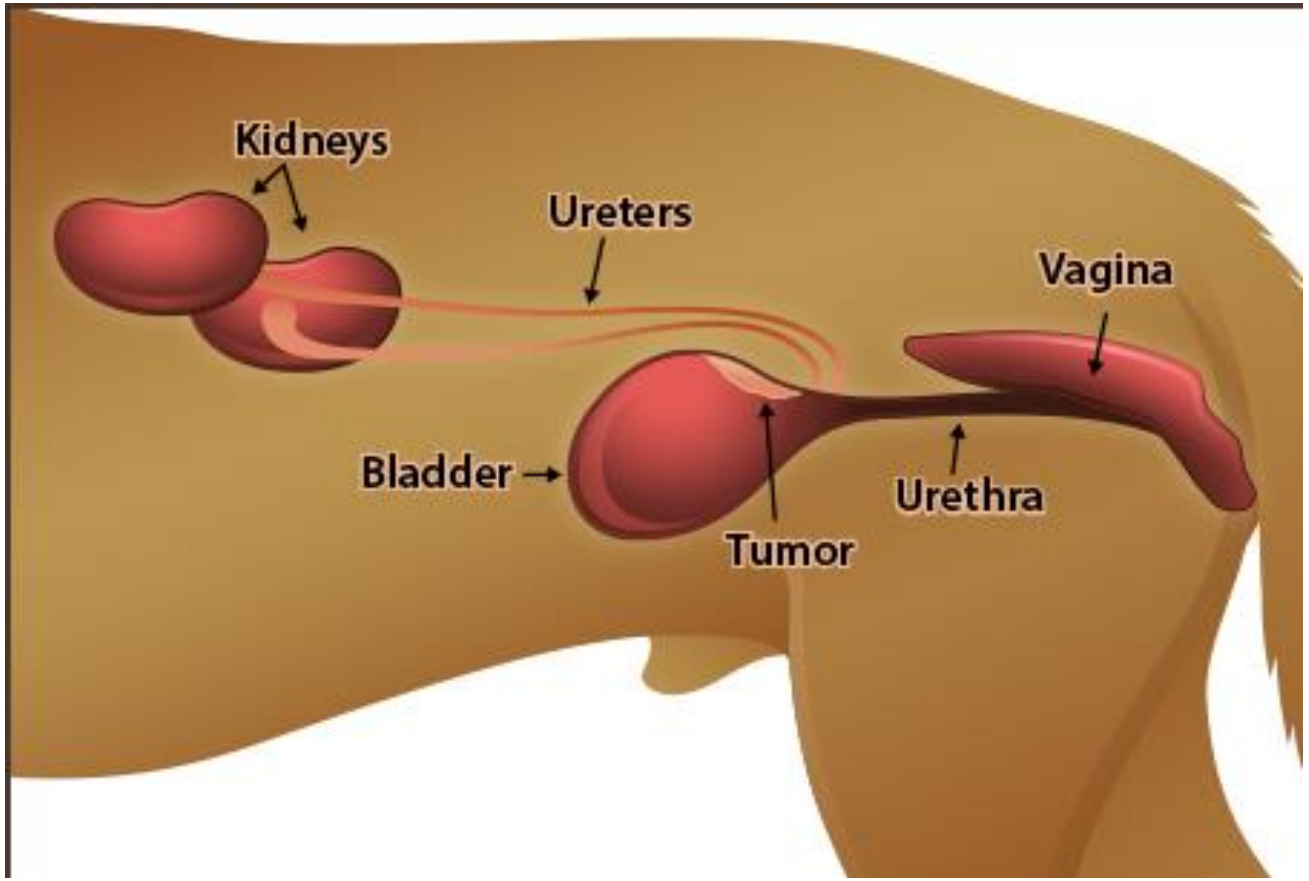
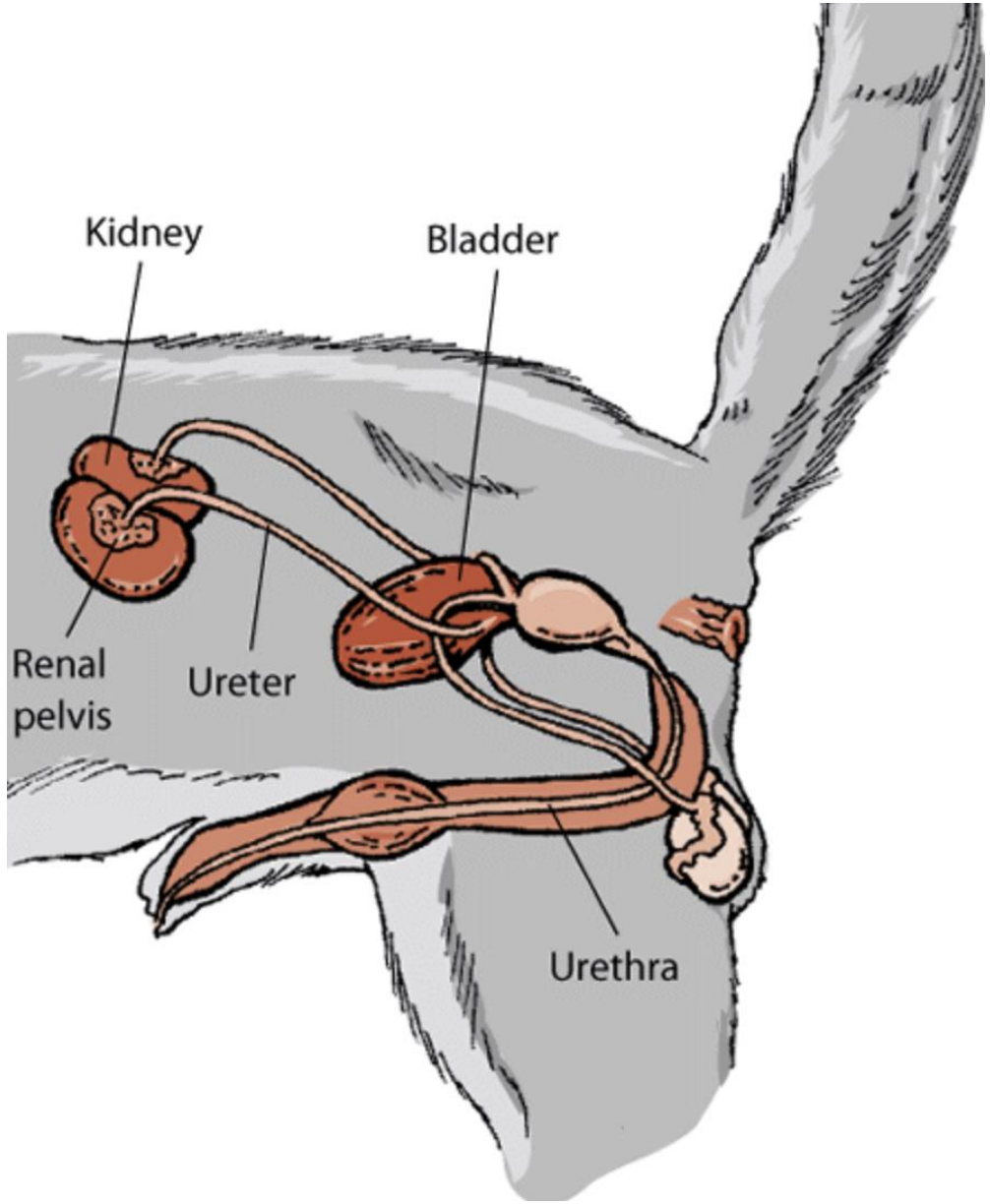
Oncology Terminology

- Median survival time – MST
- Progression free survival – PFS
- Disease free interval - DFI
- Progression free interval – PFI
- Response -RECIST –*r*esponse *e*valuation *c*riteria *i*n *s*olid *t*umors
  - CR – complete response/remission – 100 % resolution of tumor
  - PR – partial response >30% decrease in tumor size
  - PD – progressive disease >20% increase in tumor size
  - SD – stable disease - <20% increase and <30% decrease in size

Urinary Tract Anatomy





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Kidney Tumors – Histologic Types

Renal cell carcinoma

- Tubular, tubular and papillary, clear cell
- Adenocarcinoma
- Transitional cell
- Cystadenocarcinoma

Nephroblastoma

Lymphoma

Cats >> Dogs

Sarcomas

- Hemangiosarcoma
- Leiomyosarcoma
- Osteosarcoma
- Spindle cell sarcoma

Metastatic

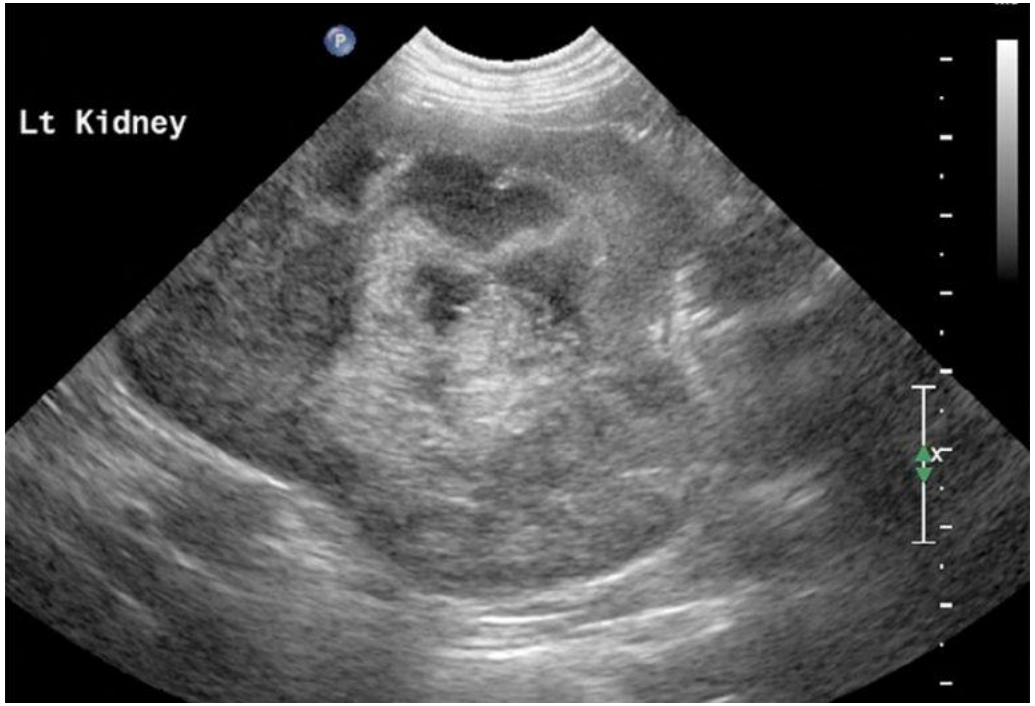
- Local invasion – adrenal or TCC
- Hemangiosarcoma
- Melanoma
- Osteosarcoma

Kidney Tumors – Clinical Signs

- PU/PD
- Vomiting
- Weight loss
- Inappetence
- Hematuria
- Abdominal pain –sarcomas
- Hypertrophic osteopathy

Kidney Tumors – Diagnostics/Staging

- Diagnostics depend on clinical signs
- Urinalysis
- Abdominal radiographs
- Ultrasound
- CBC, serum chemistry
- Thoracic radiographs
- CT



Kidney Tumors - Laboratory Changes

- Urinalysis
  - Hematuria (57%)
  - Pyuria
  - Proteinuria
- CBC
  - Leukocytosis
  - Anemia
  - Polycythemia n-3, all carcinomas
- Chemistry – non specific
  - ↑ BUN ~20%
  - ↑ Creatinine ~20%
  - ↓Albumin ~20%
  - ↑ ALP ~20%

Renal Carcinoma

- Renal adenocarcinoma (renal cell carcinoma) – 70% of cases
- Cystadenocarcinoma -
  - German Shephards, often bilateral
  - Nodular dermatofibrosis
  - Autosomal dominant trait due to mutation in the BHD gene as in familial human disease– genetic testing available
- Metastatic – adrenal tumors (invasion), hemangiosarcoma

Renal Carcinoma

- Renal cell carcinoma
  - Tubular, tubular and papillary, clear cell
  - Adenocarcinoma
  - Transitional cell
  - No difference in prognosis

- Nephrectomy - MST 16 months

  Bryan et al JVIM 2006

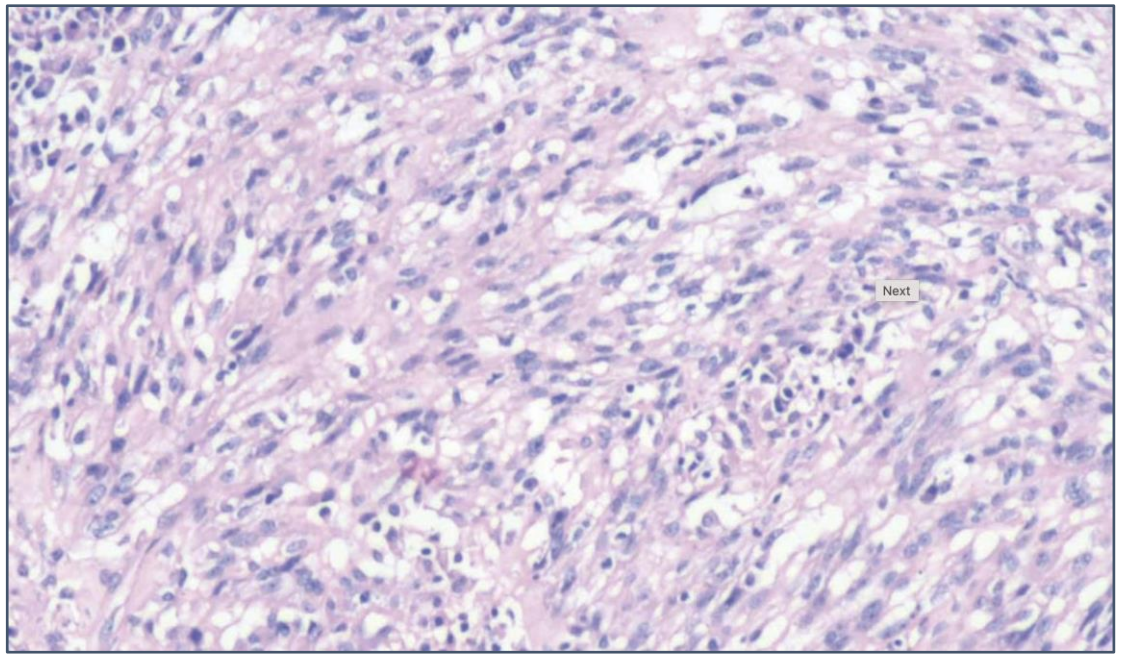
- Prognostic factors
  - Mitotic index (MI) <30 =15 months
  - Mitotic index (MI) >30 = 4 months
  - COX -2 expression also prognostic

  Carvalho et al VCO 2017

Renal Sarcoma

- Hemangiosarcoma
- Leiomyosarcoma
- Osteosarcoma
- Spindle cell sarcoma

- Nephrectomy - MST 9 months



Nephroblastoma

- Uncommon renal tumor- 5 of 82
  - 10 cases in the literature
- All ages represented - 3 mos to >12 years
- Contain epithelial, mesenchymal, and blastemal components
  - Better prognosis with epithelial, not anaplastic
- Nephrectomy - MST 6 months
- Good outcomes possible
  - Case reports >19 months and > 25 months

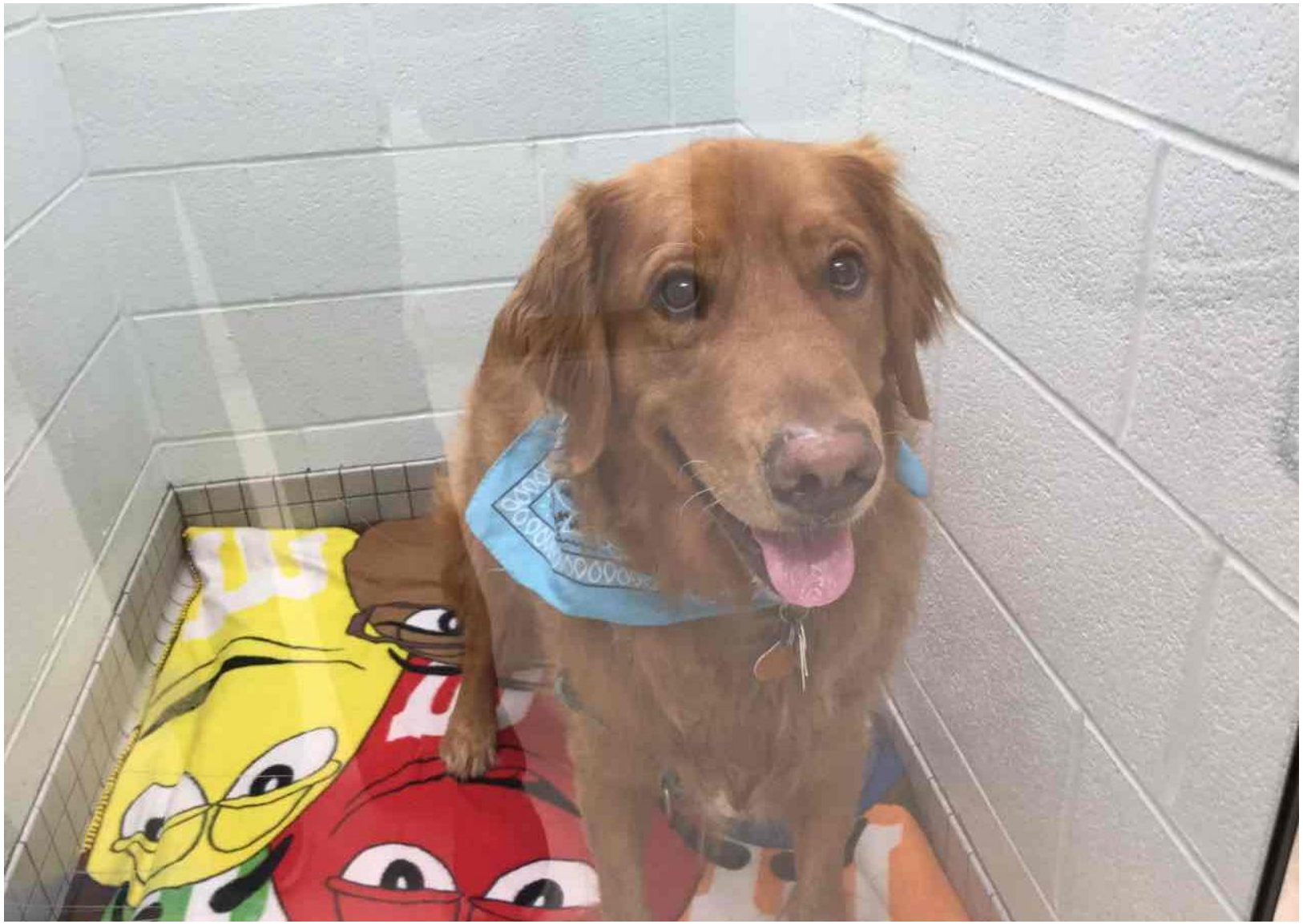
Nephroblastoma

- Metastatic risk - spleen, lymph nodes, liver, lungs, gingiva[1]
  - 1 of 5 at diagnosis
  - 75% overall (3/4 one lost to follow up)
- Chemotherapy?
  - Doxorubicin, vinblastine, cyclophosphamide, actinomycin-D

Chen B et al. J Vet Diagn Invest. May 2018;30(3):430-43

Mason

- 4-year-old MC Golden retriever
- 8 cm mass palpated on annual exam



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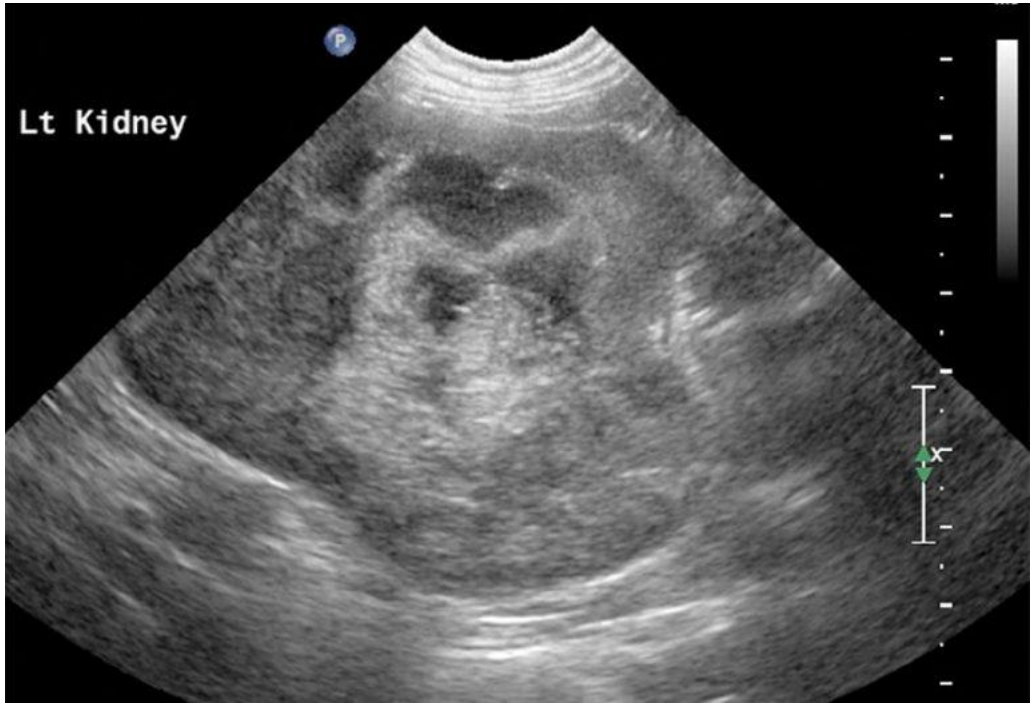
Mason

- Abdominal radiograph –
  - Mass in left kidney
- Abdominal ultrasound –mass isolated to left kidney, no metastasis
- Thoracic radiographs – normal



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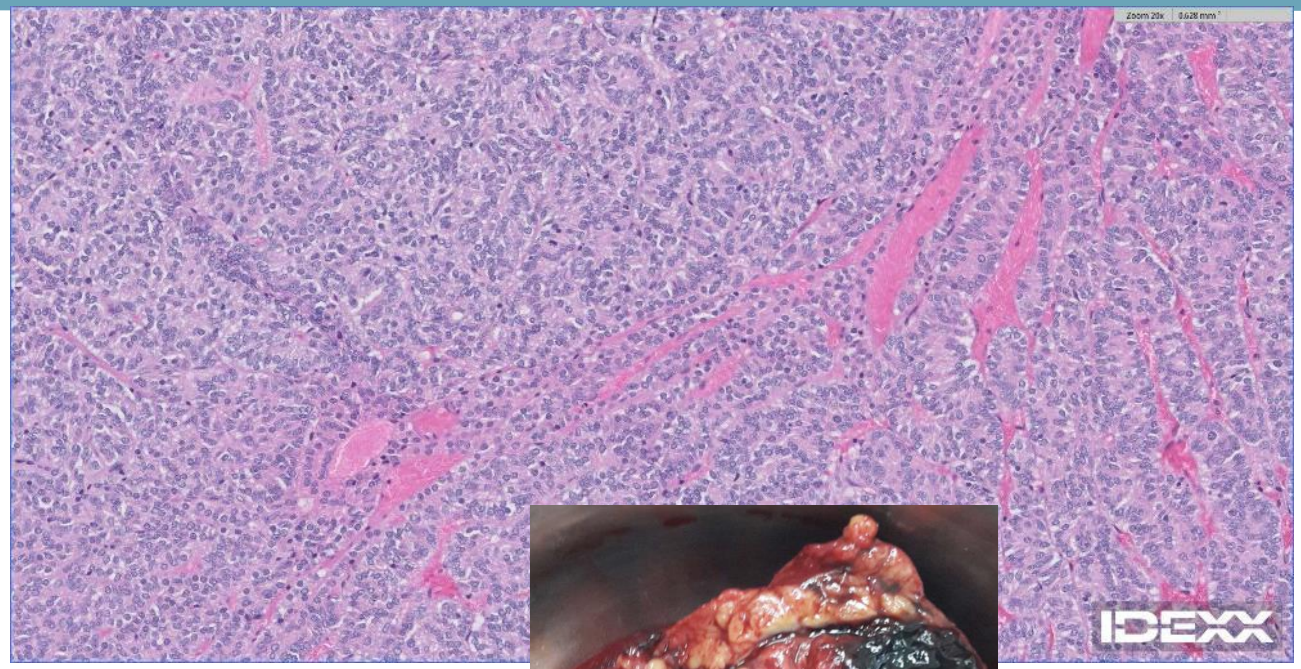
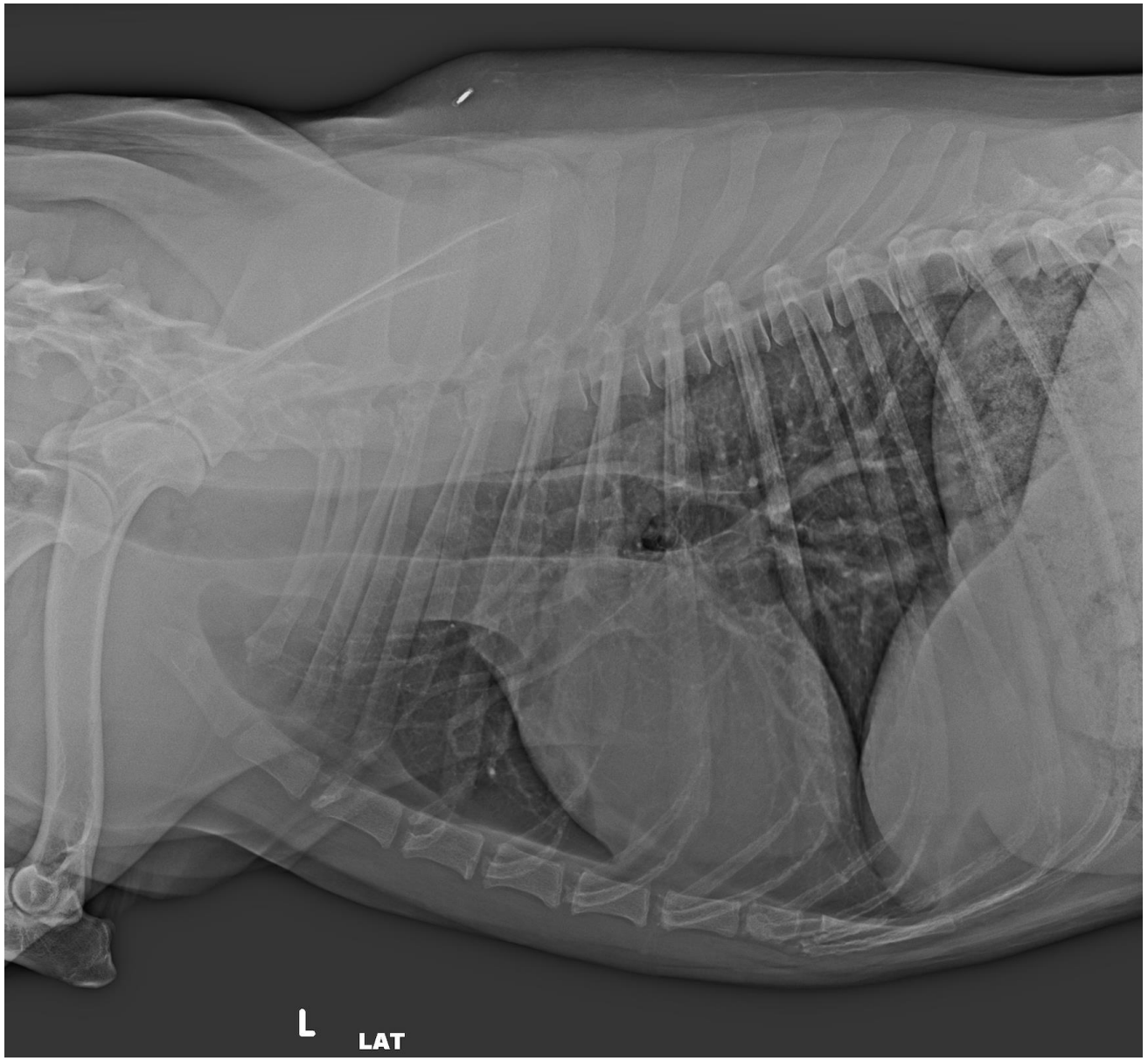
Mason

- Left nephrectomy
- Nephroblastoma
  - Mitotic index 22/10 hpf
  - 30-40% necrosis
- Discussed chemotherapy
  - Minimal data – rare tumor
  - Extrapolated from humans
- Received doxorubicin x 5



Mason

- Latest staging evaluation
  - Jan 2021 – 18 mos
  - No tumor on US or thoracic radiographs
- Had new MCT – low grade
- Doing great!



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Bladder Tumors

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Bladder Tumors

- Transitional cell carcinoma (TCC)
- Squamous cell carcinoma
- Adenocarcinoma
- Leiomyosarcoma
- Rhabdomyosarcoma
- Nephroblastoma
- Lymphoma
- Hemangiosarcoma

Transitional Cell Carcinoma - Breeds

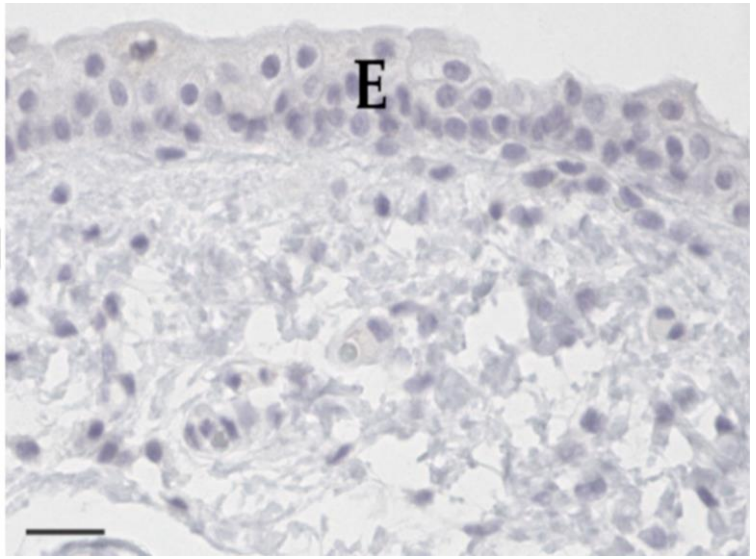
- **Scotties!** 18-20x risk compared to other breeds
- West Highland white terriers
- Beagles
- Shelties
- Wire Hair Fox terriers

Transitional Cell Carcinoma- Other Risk Factors

- Older dogs -95% >6 years
- Female > male
- Chemical exposure
  - Urban or industrial areas
  - Insecticide/herbicide exposure
    - Phenoxy herbicides
    - Older topical flea and tick (NOT fipronil or imidacloprid)
- Obesity
- Green leafy and red/yellow vegetables may be associated with *decreased* risk in Scottish terriers

Transitional Cell Carcinoma

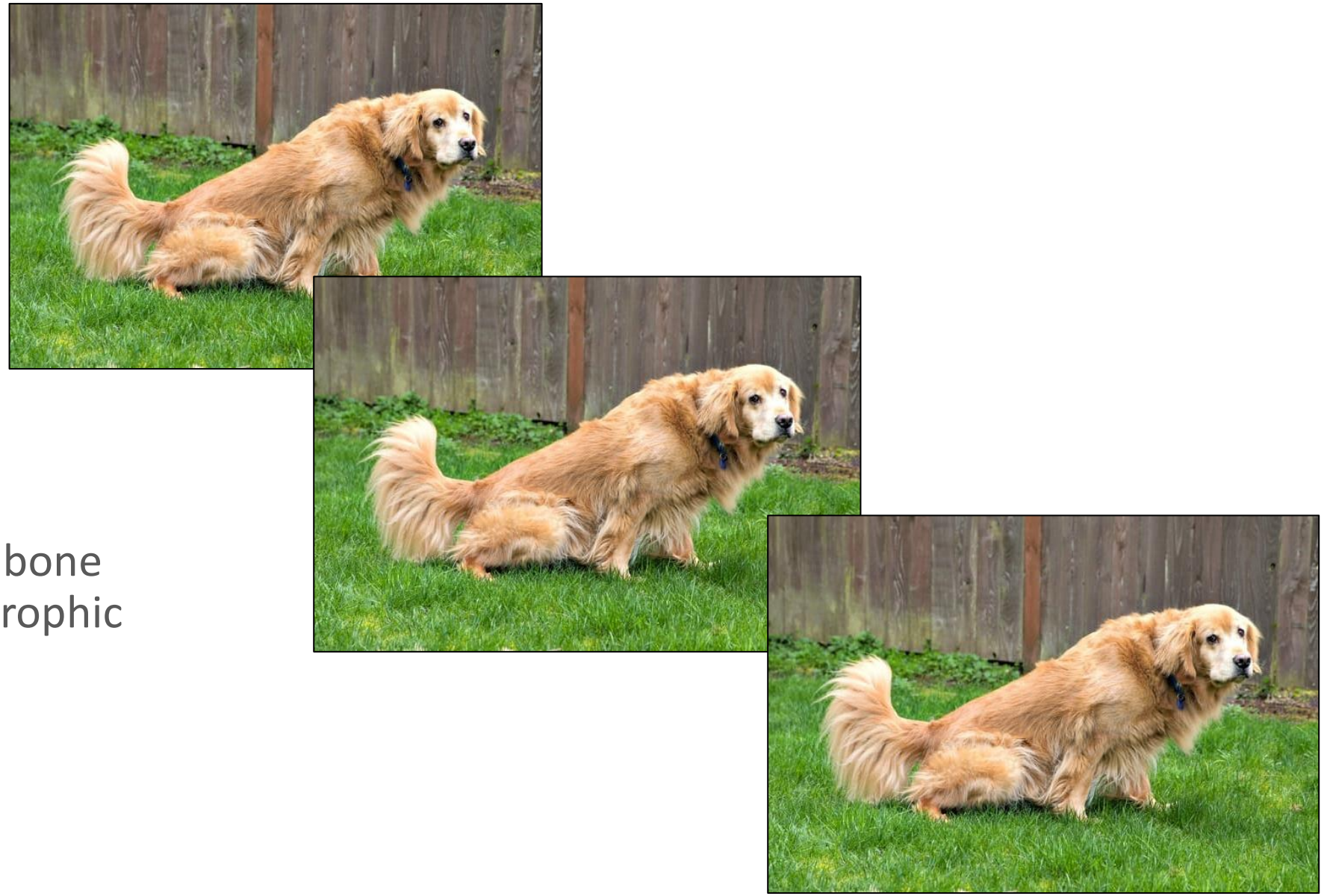
- Transitional epithelial cells lining bladder
- Bladder, prostate, urethra
- Trigone location most common
- Local extension
  - Urethra
  - Ureters
  - Abdominal structures – thorough bladder wall or iatrogenic seeding
- Metastasis
  - Lymph nodes
  - Vertebrae
  - Lungs



Grassinger et al, Vet Sci 2019

Clinical Signs

- Hematuria
- Pollakiuria
- Stranguria
- Dysuria
- Incontinence
- Pain/lameness from bone metastasis or hypertrophic osteopathy



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Common History/Presentation

Pet presents with urinary tract signs:

→ UA → RBC, WBC, +/- bacteria → treated symptomatically antibiotics

→ Pet improves, then relapses

→ UA, culture, treat symptomatically

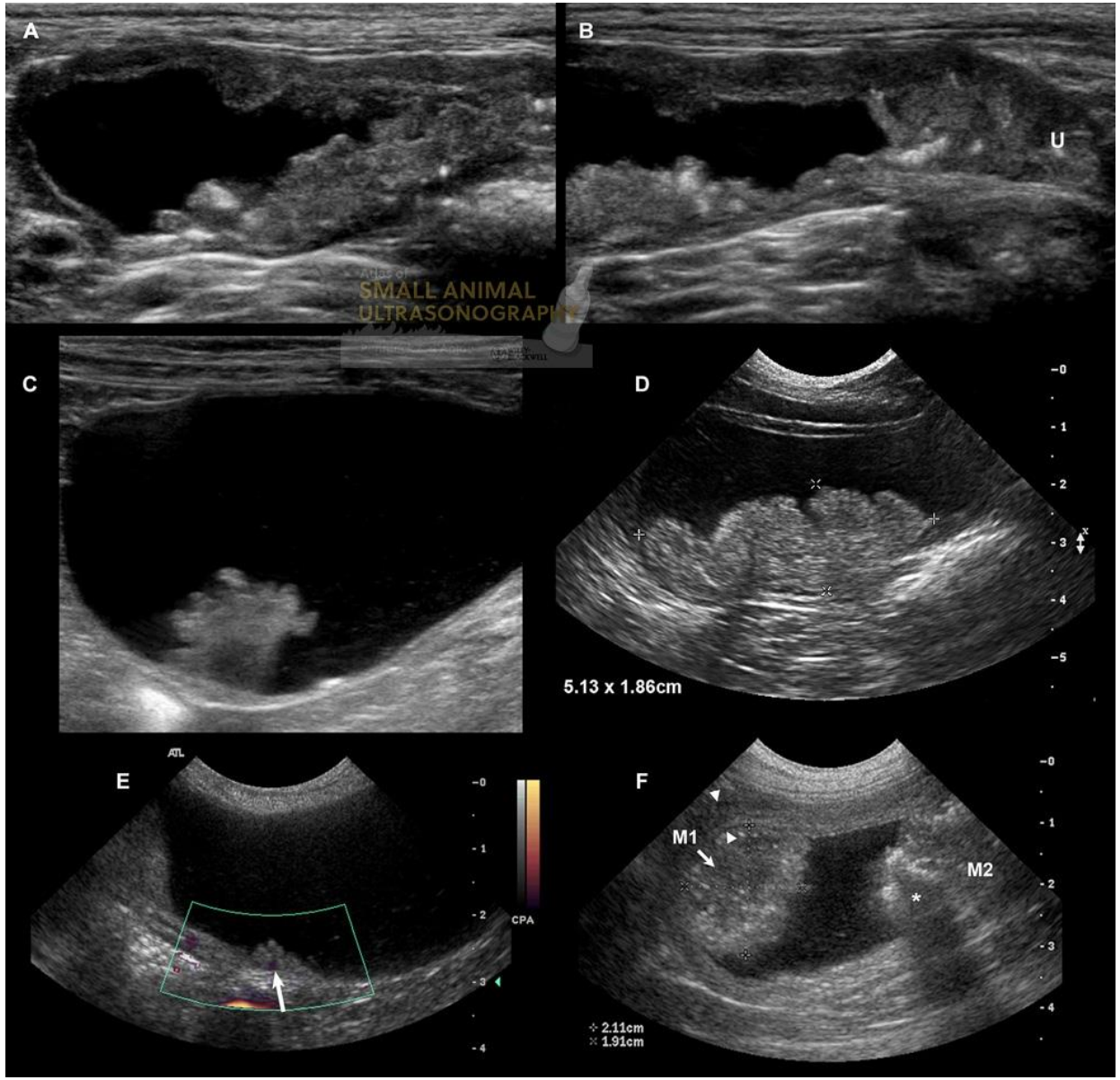
Meanwhile tumor is progressing, eventually US or referral

Often advanced at time of diagnosis

Diagnostics – First Line

- Physical exam
  - **Rectal** – thickened urethra, enlarged prostate, enlarged lymph nodes
  - Firm bladder or mass
- Urinalysis
  - US guided cystocentesis or mid stream free catch
  - Hematuria +/- pyuria, bacturia
- Bloodwork?
  - Usually normal unless ureteral obstruction → post renal azotemia
- Abdominal radiographs? - tumor rarely evident

Diagnostics- Ultrasound



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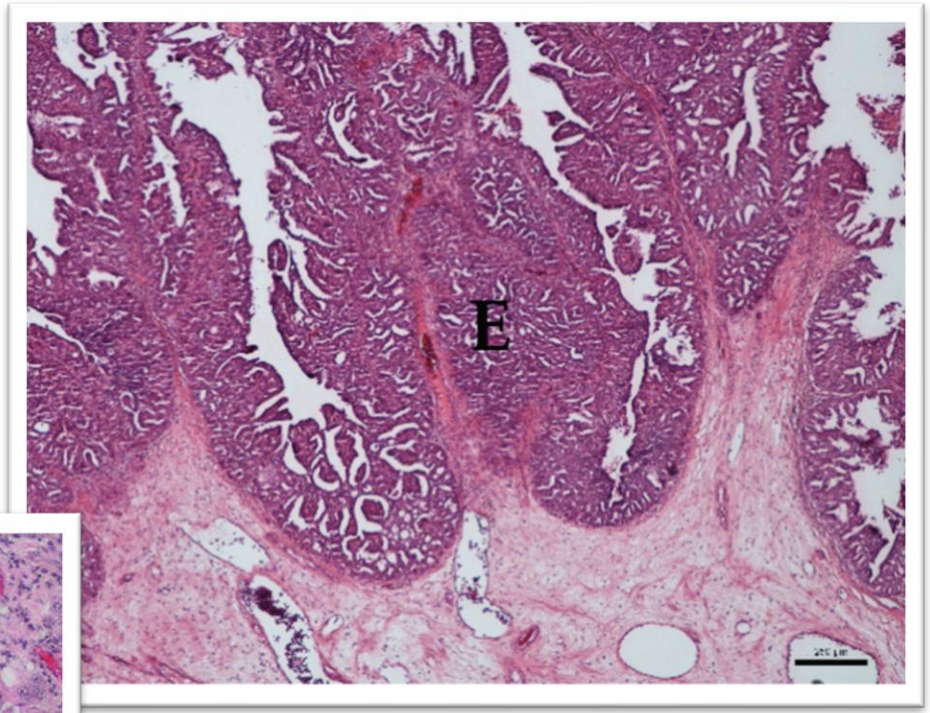
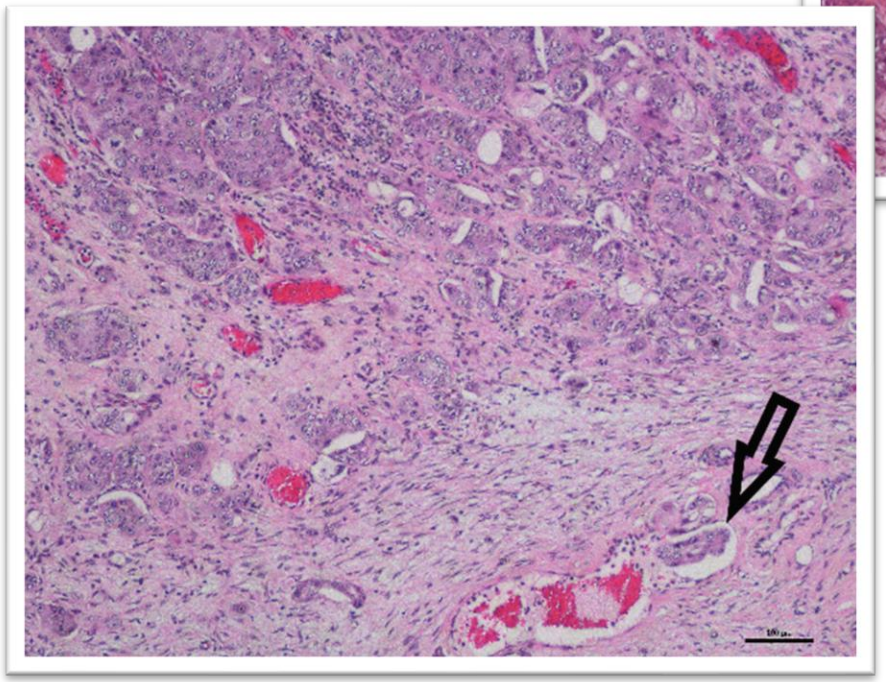
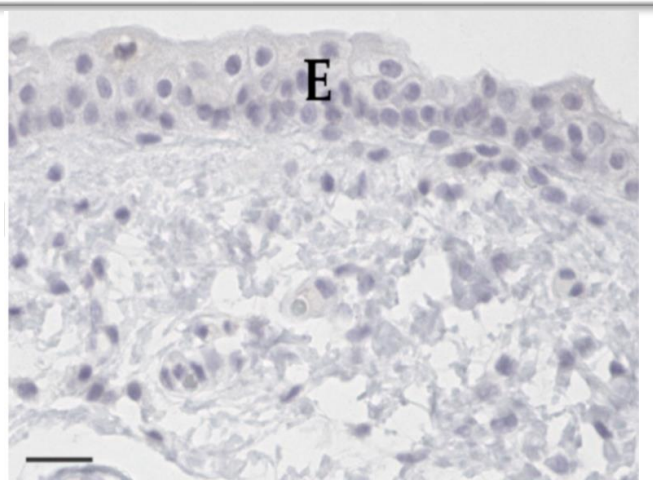
Diagnostics - Histopathology

- Gold standard
  - Traumatic catheterization
  - Cystoscopy
  - Surgical biopsy

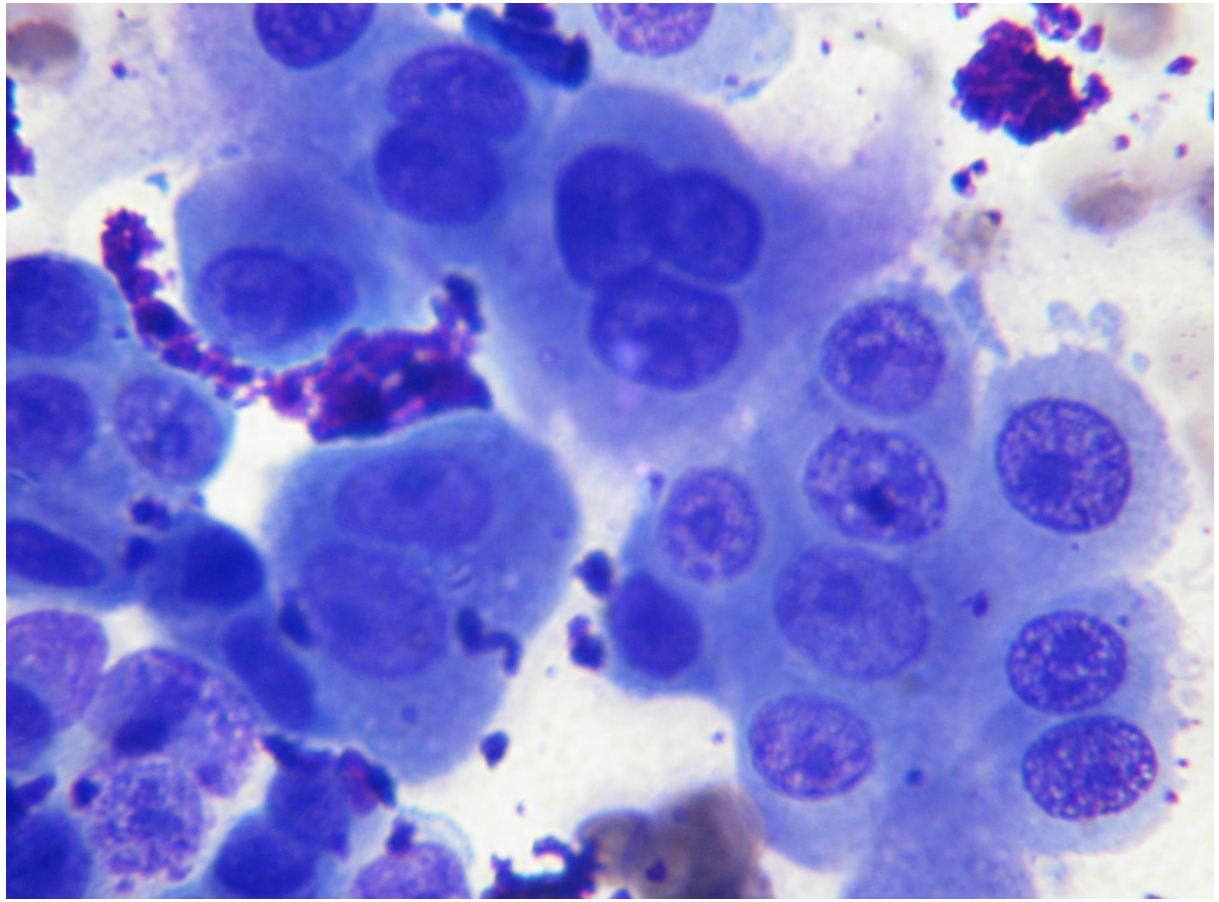






Diagnostics– Traumatic Catheterization

- Suction biopsy or catheter biopsy
  - Polypropylene catheter and syringe
  - Requires sedation in female dog
  - Ideally obtain pieces of tumor
  - In very diseased bladder, rupture is possible though not common



Cystoscopy

- Cystoscopy + biopsy
  - Minimally invasive
  - Female - diagnostic in ~95%
  - Male - diagnostic in 57-65%
  - Limited options in small dogs
  - Requires anesthesia

Surgical iopsy

- Most invasive/expensive option
- +/- therapeutic
- Reasonable option if apical lesion that appears removable
- Potential debulking of trigonal lesions
- Avoid seeding abdomen
  - Pack off bladder to avoid urine contaminating peritoneum
  - Change pack/instruments to close abdominal wall

TCC - Fine Needle Aspirate?

- US guided aspirate not recommended due to risk of tumor seeding of abdominal wall
- Carcinomatosis reported in cats
  - Risk is relatively low, but better methods to obtain a diagnosis

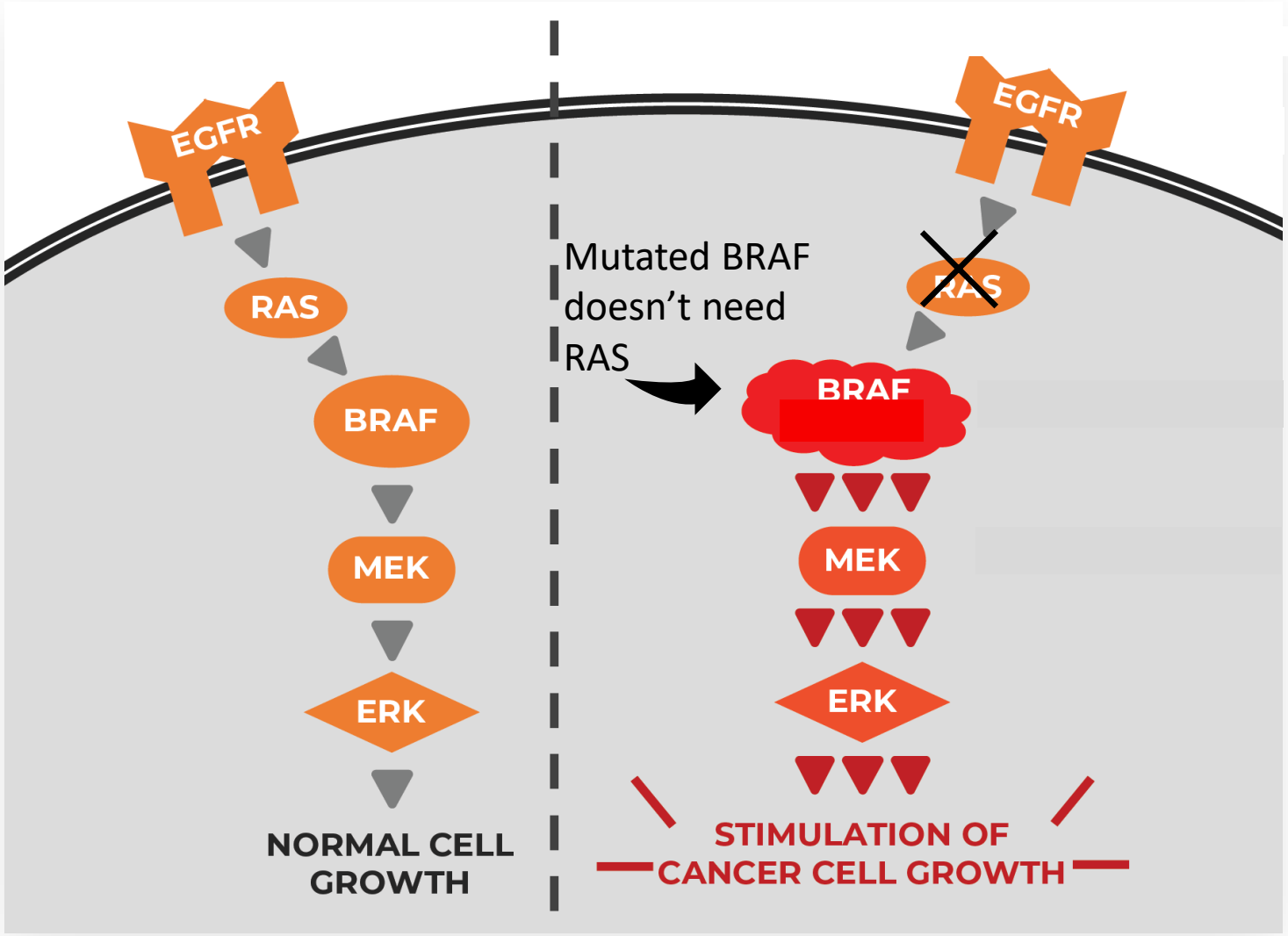
CADET® BRAF ASSAY

- Non invasive! - Urine test
- Acquired point mutation in proto-oncogene BRAF V585e
- 100% specific for TCC – no false positives!
- 85% sensitive
- BRAF-Plus 95% sensitive – now no additional charge
- Not affected by blood, WBC, bacteria in urine
- Antech

CADET® BRAF Test

- Normally, receptor on cell binds its ligand, then activates a pathway including BRAF, leading to cell proliferation

- Acquired point mutation →
- BRAF activated without upstream signaling resulting in uncontrolled proliferation



National Cancer Institute

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CADET®BRAF Test

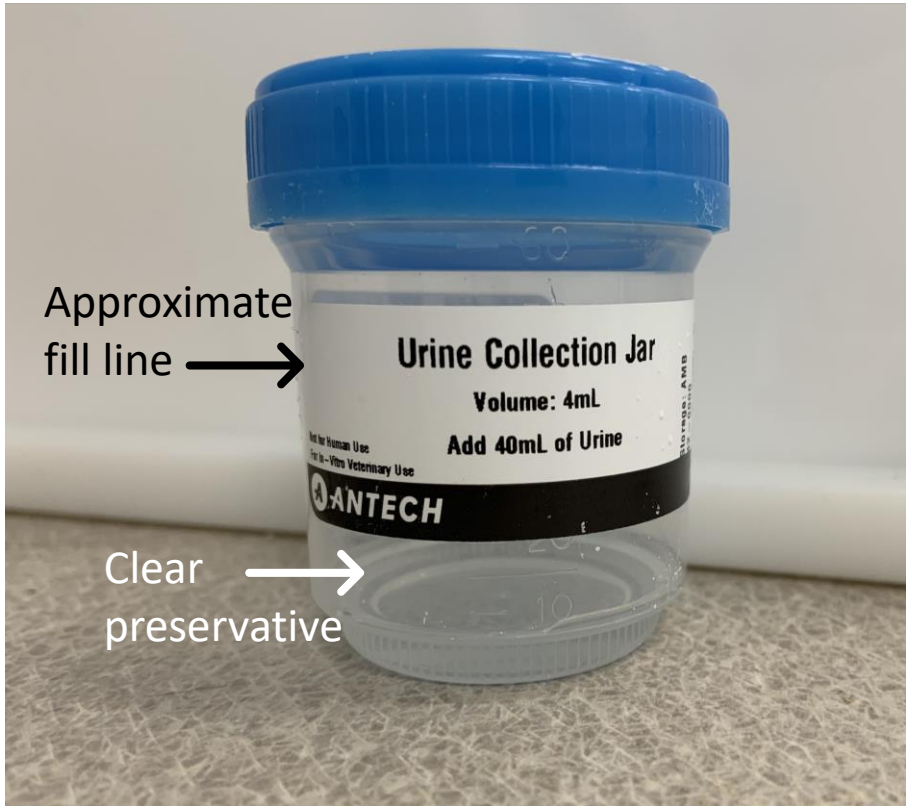
40 ml of voided urine

Urine to be added to vial with preservative within 15 minutes

Can be collected over several days

No refrigeration

Mutation detected vs undetected



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If mutation is not detected

- Antech will run BRAF+ at no additional charge
  - Detects additional genomic signatures
  - Increases sensitivity from 85% to 95%

- Negative after BRAF+?
  - Either not TCC or one of the 5% of false negative results

- If still highly suspect TCC
  - Biopsy by other methods

CADET®BRAF Test

Indications

- Bladder mass
- Recurrent or complicated UTI without mass or stones
- Screening predisposed breeds after age 6
- NOT to monitor response to therapy/relapse

Advantages

- Confirms TCC
- Affordable
- Non-invasive

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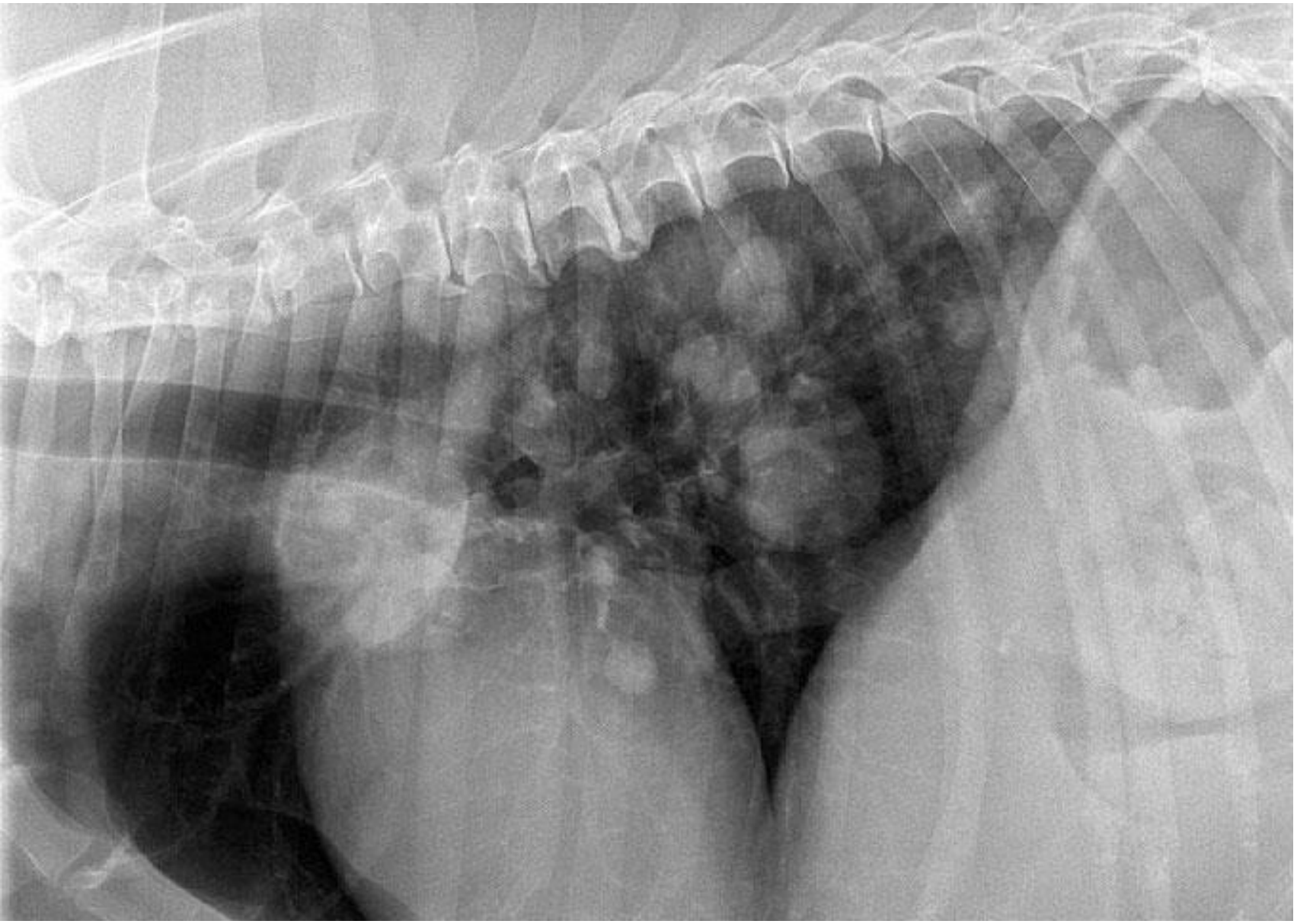
CADET®BRAF Test as screening test

- Can we intervene earlier for better outcome?
- Can we use for monitoring response to treatment?



Staging - Metastasis

- 10-20% at diagnosis
- 50% at time of death
- Iliac lymph nodes
- Lumbar vertebrae
- Lungs
- Other abdominal organs

Staging

- Establish prognosis
- Determine appropriate treatment options
- Baseline for monitoring response to therapy

Ripey et al 2016

- Abdominal ultrasound
- Abdominal radiographs
  - Vertebral changes
  - Iliac sublumbar lymphadenopathy
- CT?
  - Best modality to find small metastatic lesions
  - $
  - Prior to surgery

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TCC - NSAIDS

- COX-2 overexpressed in most TCC. Other mechanisms proposed apoptosis, immunomodulatory effects, antiangiogenic effects
- Piroxicam: median survival time (MST) 6 mos
  - Piroxicam has the most data
  - Up to 10-30%d/c for gi toxicity
- Deracoxib: MST - >10 mos
  - Dose used relatively high for deracoxib 3 mg/kg/day,
  - n=24 – 19% GI toxicity, one azotemic
- No head-to-head studies with different NSAIDS

TCC - Chemotherapy

- Many agents have been evaluated
  - Mitoxantrone
  - Carboplatin/cisplatin
  - Doxorubicin
  - Vinblastine
  - Palladia

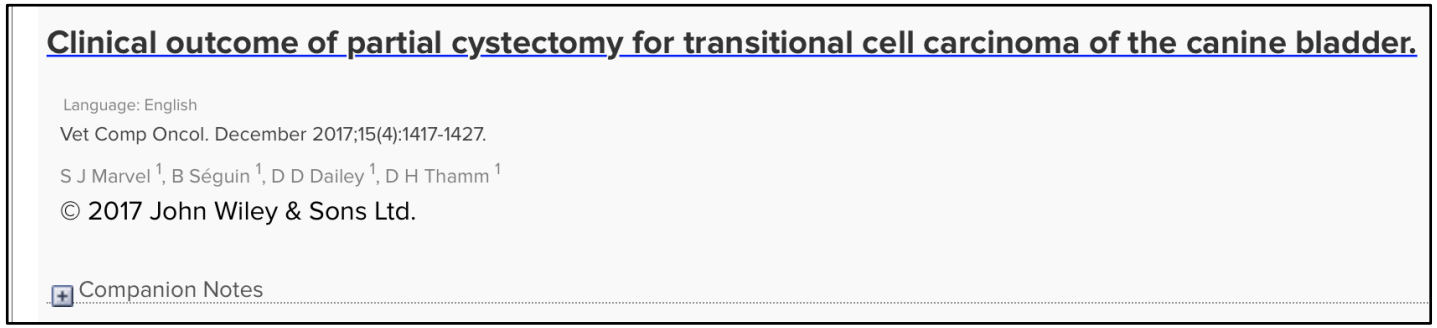
TCC – Chemotherapy Prognosis

- Remission rate:
  - 20-30% response rate – most partial responses
  - Additional 20-30% stable disease
  - Complete remission very rare
- Response duration – 6 months
- Chemotherapy + piroxicam – 1 year
- Location important
  - Prostatic, trigone, urethra involvement worse
  - Apical better

Ideal to diagnose while quality of life is still good!

TCC Surgical Management

- Non-trigonal location
  - Full thickness excision
  - Piroxicam
  - +/- chemotherapy



Clinical outcome of partial cystectomy for transitional cell carcinoma of the canine bladder.

Language: English

Vet Comp Oncol. December 2017;15(4):1417-1427.

S J Marvel [1], B Séguin [1], D D Dailey [1], D H Thamm [1]

Companion Notes

- Best outcome with surgery, daily piroxicam, +/- chemotherapy
  - MST 772 days
- Overall PFI , MST
- Can develop tumors in other areas of the bladder - “field effect”

Characterization and treatment of transitional cell carcinoma of the abdominal wall in dogs: 24 cases (1985-2010).

J Am Vet Med Assoc. February 2013;242(4):499-506.

DOI: 10.2460/javma.242.4.499

Takashi Higuchi [1], Grant N Burcham, Michael O Childress, Jacob J Rohleder, Patty L Bonney, José A Ramos-Vara, Deborah W Knapp

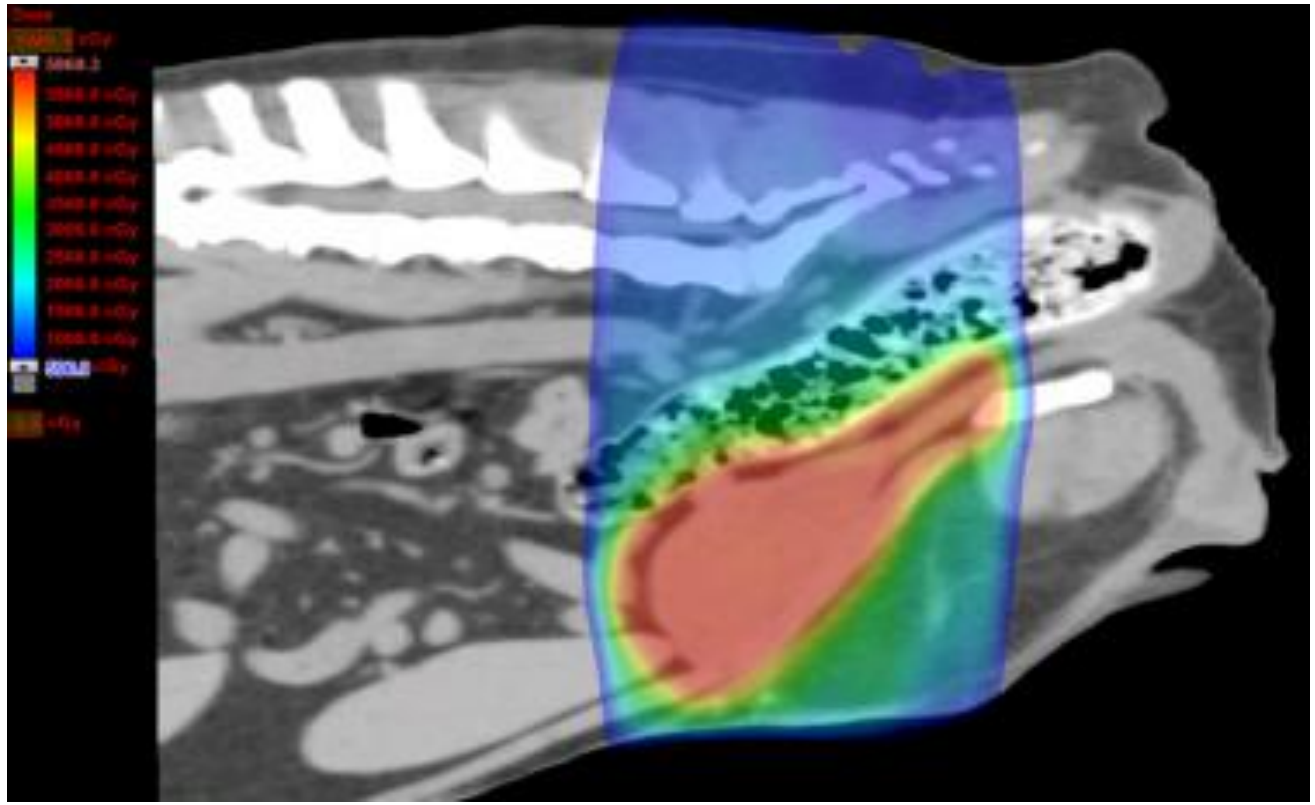
- 18 dogs had undergone a cystotomy (18/177 – 10.2%)
- 6 - no cystotomy (3/367 – 1.6%)
- No response to treatment
- MST 64 d (0-324 d)

TCC – Radiation Therapy

- IMRT – Intensity modulated radiation therapy
- Radiation field changes shape with multiple fields around patient
- Creates conformal field around tumor
- On board imaging – CT to confirm location of tumor/bladder

TCC- Radiation IMRT

- High dose to tumor/target
- Rapid dose drop off to critical structures
- Ideal to have on board imaging



NCSU website

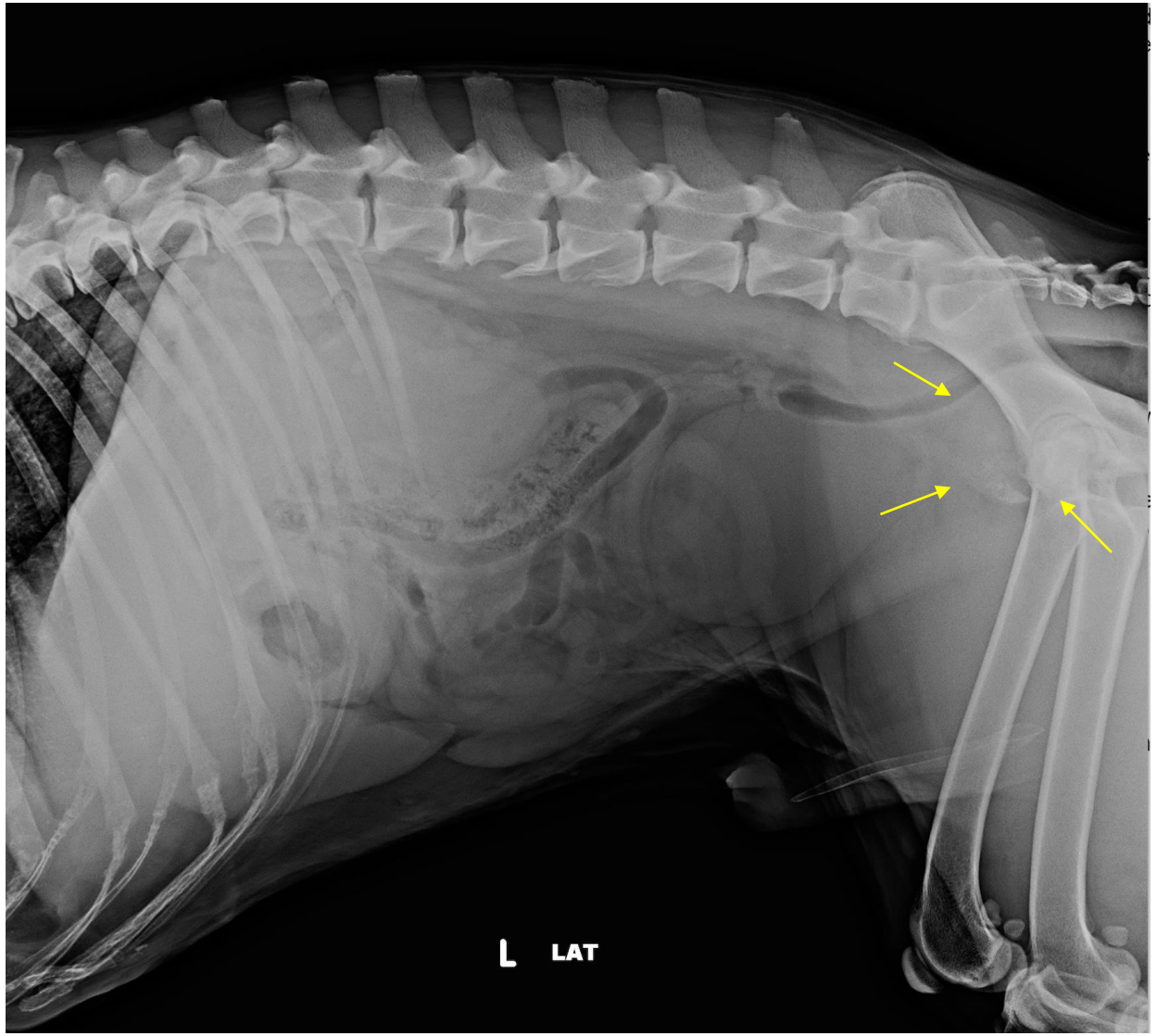
TCC – Radiation Therapy IMRT

- n=20, 10 prostate, 8 bladder, 2 urethra
- 20 fractions M-F
- 7/20 tumor recurrence
  - 5 local disease
  - 2 iliac LN – treated
- 60% improved clinical signs, 30% stable
- Progression free survival – 330 days
- Median survival time 654 days
- 19% late complications – urethral and rectal strictures

Nolan et al. JVIM 2012

Prostate Tumors

- Most are TCC vs adenocarcinoma
- Dysuria
- Dyschezia
- Rectal exam
- Often visible on radiographs
  - Mineralization consistent with cancer
- No standard of care



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Prostate tumors – Medical Management

- Prognosis guarded – MST ~ 6 months
- 30-50% have metastatic disease at diagnosis
  - Dogs with metastasis do worse than dogs without
- Incidental findings typically do better
- NSAID + chemotherapy > NSAID

Evaluation of Mitoxantrone with Piroxicam as First Line Therapy for Carcinomas of the Prostate in Dogs

Int J Appl Res Vet Med. 2013;11(1):16-24. 29 Refs

Trina N Hazzah [1], Philip H Kass, Edwin M Brodsky, Amanda K Elpiner, Michelle L Silver, Nicole J Buote, Gerald S Post

Hide author information

[1] The Veterinary Cancer Center (formerly Veterinary Oncology and Hematology Center), Norwalk CT, USA (Work performed at this facility).

Outcome and prognostic factors in medically treated canine prostatic carcinomas: A multi-institutional study.

Language: English

Vet Comp Oncol. December 2018;16(4):450-458.

DOI: 10.1111/vco.12400

S Ravicini [1], S J Baines [1], A Taylor [2], I Amores-Fuster [3], S L Mason [4], E Treggiari [1]

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Prostate tumors - Surgery

Total prostatectomy as a treatment for prostatic carcinoma in 25 dogs.

Language: English

Vet Surg. April 2018;47(3):367-377.

DOI: 10.1111/vsu.12768

Tristram C Bennett [1], Brad M Matz [2], Ralph A Henderson [2], Rodney C Straw [3], Julius M Liptak [4], Laura E Selmic [5], Francesco Collivignarelli [6], Paolo Buracco [7]

- n=25
- 15 TCC, 8 adenocarcinoma
- 8 of 25 incontinent
- MST – 231 days (24-1255 d)
- Shorter if extracapsular extension

Prostatic Carcinoma – Radiation/IMRT

- Limited data
- Overall MST – 563 days
- Event free survival 220 days
- Incidental finding better than symptomatic 581 vs 220 days
- Dogs with metastasis did worse
- Late toxicity - stricture

Definitive-intent intensity-modulated radiation therapy for treatment of canine prostatic carcinoma: A multi-institutional retrospective study.

Language: English
Vet Comp Oncol. September 2020;18(3):381-388.
DOI: 10.1111/vco.12561

Jillian Z Walz [1], Noopur Desai [1], Nathaniel Van Asselt [2], Valerie J Poirier [3], Katherine Hansen [4], Laura Selmic [1]

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End Stage

Cause

- Urethral/ureteral obstruction
- Metastasis
  - Pain
  - Decline in activity/weight/appetite
- Renal failure

Options

- Urethral stenting
- Cystostomy tube
- Palliative RT

Nemo

- 10-year-old MC Jack Russell Terrier
- Urinated twice in the house
- Drinking more
- Possibly stranguric
- Had new dog in the family?

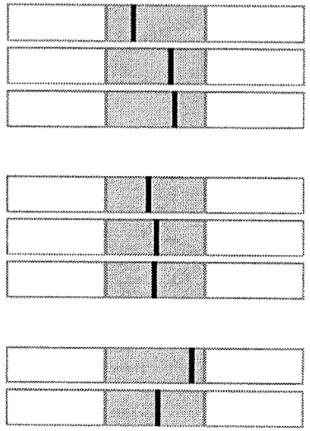
Nemo

- Urinalysis – Normal

Catalyst Dx,ProCyte Dx,SediVue Dx,UA Analyzer

08/11/2020 09:27 AM

WBC	* <1 /HPF	
RBC	* <1 /HPF	
BACr	* None detected	
BACc	* None detected	
sqEPI	* None detected	
nsEPI	* <1 /HPF	
HYA	* None detected	
nhCST	* None detected	
CRY	* None detected	
CaOxDi	* None detected	
STR	* None detected	
BIURAT	* None detected	
BILI	* None detected	
GLU	88	70-143 mg/dL
CREA	1.3	0.5-1.8 mg/dL
BUN	20	7-27 mg/dL
BUN/CREA	15	
TP	6.4	5.2-8.2 g/dL
ALB	3	2.2-3.9 g/dL
GLOB	3.4	2.5-4.5 g/dL
ALB/GLOB	0.9	
ALT	106	10-125 U/L
ALKP	116	23-212 U/L
Collec	Free Catch	



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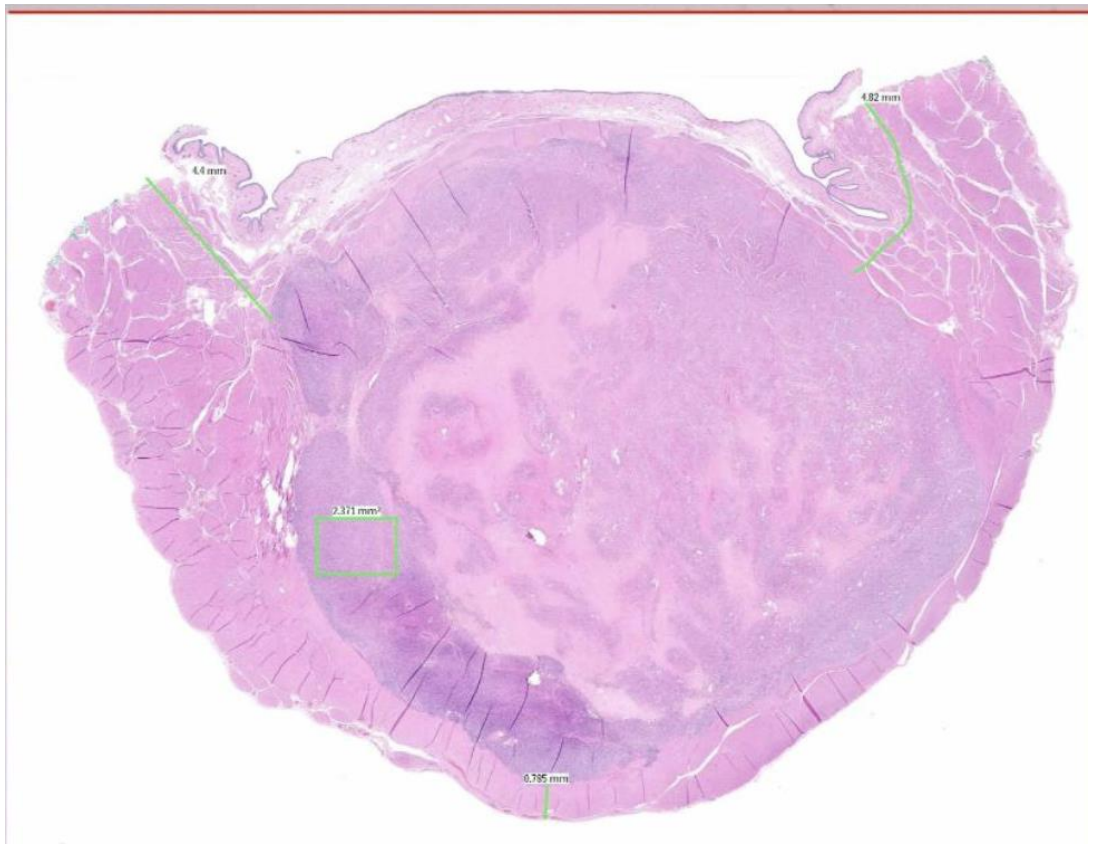
Nemo

- Ultrasound at referral partner– mass in bladder
- US at MedVet
  - Thickening of ventral bladder wall 1.65 x 1.85
  - Normal lymph nodes
- Thoracic radiographs – no evidence of metastatic disease

Nemo -Leiomyosarcoma



- Infiltrating muscular tunic
- Not penetrating mucosa or serosa
- Removed with 4 mm margins

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Nemo

- Doing well 8 months post diagnosis with no adjuvant treatment
- Has had one follow up US, thickening at surgical site, believed to be scar tissue

TCC in Cats

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Clinical signs, treatments, and outcome in cats with transitional cell carcinoma of the urinary bladder: 20 cases (1990-2004).

Language: English
J Am Vet Med Assoc. July 2007;231(1):101-6.
DOI: 10.2460/javma.231.1.101

Heather M Wilson [1], Ruthanne Chun, Victoria S Larson, Ilene D Kurzman, David M Vail

- Median age 15y
- Trigone 50%
- MST ~9 months – all died related to disease
- Variety of treatments –piroxicam, chemotherapy, surgery

TCC in Cats – New Data

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

Language: English
J Vet Intern Med. January 2020;34(1):274-282.
DOI: 10.1111/jvim.15656

Maureen A Griffin [1], William T N Culp [1], Michelle A Giuffrida [1], Peter Ellis [1], Joanne Tuohy [2], James A Perry [3], Allison Gedney [3], Cassie N Lux [4], Milan Milovancev [5], Mandy L Wallace [6], Jonathan Hash [7], Kyle Mathews [7], Juli
Philipp D Mayhew [1], Michele A Steffey [1], Robert B Rebhun [1], Jenna H Burton [1], Michael S Kent [1]

Ultrasound characteristics of feline urinary bladder transitional cell carcinoma are similar to canine urinary bladder transitional cell carcinoma.

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Alessandra N Hamlin [1], Laura E Chadwick [2], Stacey A Fox-Alvarez [3], Eric T Hostnik [1]

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TCC in Cats – US Findings

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- n=20
- More likely to be in body or apex than trigone
- Less likely to involve urethra than dogs

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

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- 11 institutions over 27 years (1991-2018)
- Median age 15y
- Females 53%, 46% male
- Location: trigone 27%, diffuse 8%, remaining 65% - bladder wall

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TCC in Cats - Findings

History & Physical Exam

- Stranguria/Hematuria/Pollakiuria
- Anorexia

- Pain on abdominal palpation 20%
- Thickened bladder/mass 19%

Laboratory Abnormalities

- Anemia (30%)
- BUN (50%)
- Creatinine (30%)
- Hematuria/pyuria/bacturia

TCC in Cats 118 Cases

- Variety of biopsy techniques
- Many treatment modalities
- PFS – 3.7 mos
- MST – 5 mos
- Partial cystectomy – 9.8 mos, other treatments - 5.8 mos
- 1 year survival: 6.7% untreated, 28% cystectomy, 0% other treatment
- NSAIDS – piroxicam, meloxicam

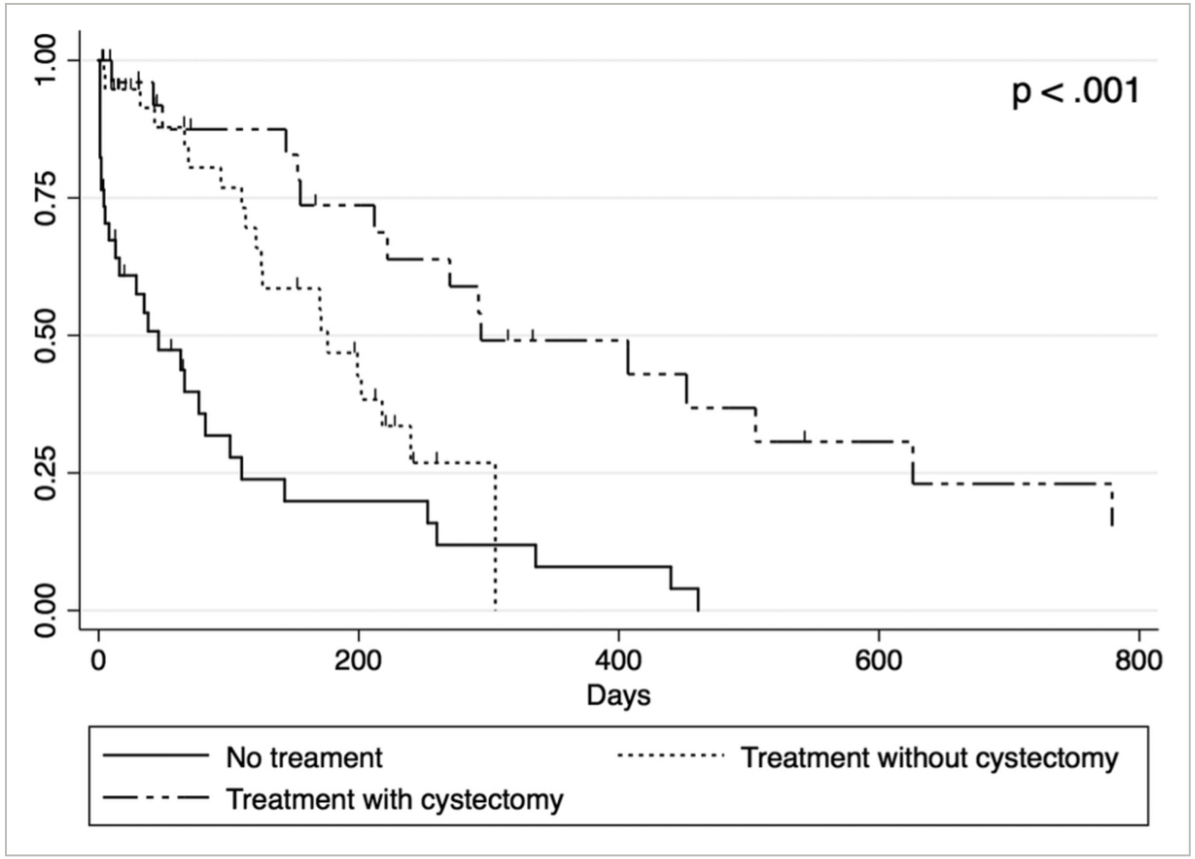

Figure 1 Open in figure viewer | PowerPoint

Kaplan-Meier estimates of survival with different treatment groups. Survival increased significantly ($P < .001$) when comparing cats across the ordered treatment groups: no treatment, treatment without partial cystectomy, treatment with partial cystectomy

Treatment Outcome

- No treatment – 1.5 mos
- Partial cystectomy – 9.8 mos
- Other treatments - 5.8 mos
- 1 year survival:
  - 6.7% untreated
  - 28% cystectomy
  - 0% other treatment
- NSAIDS – piroxicam, meloxicam, robenacoxib
  - 26% adverse effects
    - 46% azotemia
    - 54% GI
  - Associated with improved survival

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TCC in Cats - Summary

- Uncommon compared to dogs
- Old cats - median age 15 y
- Often can palpate firm bladder
- Usually present in advanced state
- Trigone ~50%

Thank you.
Questions?

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