Welcome
We're so glad you're here!

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Updates in Diagnosing and Treating Bladder Cancer

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Agenda

- Risk factors
- Expected behavior
- Diagnostic work-up
- Treatment
- Prognosis
- TCC in cats

PUVTH = Purdue University Veterinary Teaching Hospital

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Risk Factors

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Risk Factors

- Age (9-11yrs)
- Female sex (1.71:1 to 1.95:1)
- History of spay/neuter
- Obesity
- Breed
  - Scotties (18-20x), Westies, Shelties, Beagles, Fox Terriers
- Chemical exposure
  - Older generation topical flea control
  - Lawn chemicals

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Expected Behavior

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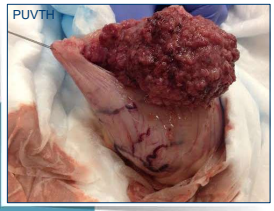
Transitional Cell Carcinoma (TCC)

- Most common urinary tract tumor in dogs
  - "*Urothelial carcinoma*" = TCC
- Arises from epithelial cells lining urinary tract
  - Bladder, ureter, urethra, prostatic ducts, renal pelvis
  - Trigone and proximal urethra most common
- Two types
  - Superficial - more common in people
  - Muscle invasive – more common in dogs
- High metastatic rate
  - ~20% @ diagnosis
  - ~50% @ death



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Clinical Signs – Primary Tumor

- ***Hematuria*** – bloody urine
- ***Stranguria*** – straining to urinate
- ***Pollakiuria*** – frequent urination
- ***Dysuria*** – painful urination

UTI
Cystitis
Stones
Cancer

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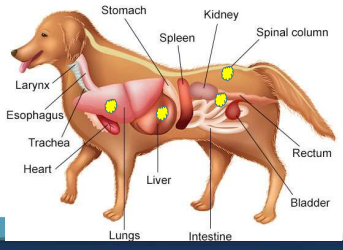
Clinical Signs - Metastasis



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Diagnostic Work-Up

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Diagnostic Work-Up

- PE – ALWAYS include digital rectal examination:
  - 56% have urethral involvement
  - 29% males have prostatic involvement
- Blood work usually unremarkable
  - Exception – renal azotemia secondary to obstruction of ureters at level of trigone
- Rule out infection (UA/UCS)
  - If possible, image bladder first to make sure no mass prior to cystocentesis
    - If mass present, obtain mid-stream free catch

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Suspect Tumor? Say "NO" to Cystocentesis

J Am Vet Med Assoc. 2013 Feb 15;242(4):499-506. doi: 10.2460/javma.242.4.499.

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

Higuchi T[1], Burcham GN, Childress MO, Rohleder JJ, Bonney PL, Ramos-Vara JA, Knapp DW.

- 24 of 544 (4.4%) TCC cases had evidence of TCC in abdominal wall
- 20/24 dogs had known potential tumor seeding events
- Poor response to medical treatment once SQ masses clinical detectable
  - Major factor leading to euthanasia
- Extravesical TCC from surgical seeding in humans also responds poorly to treatment

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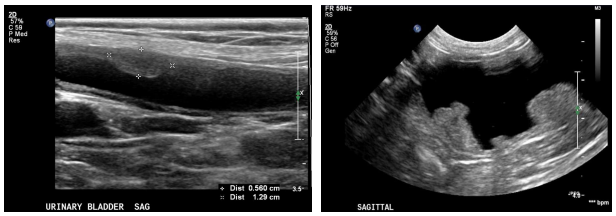
Diagnostic Work-Up: Imaging



TCC Ultrasound Images; PUVTH

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If Suspect TCC….

- Two steps:
  1. Confirm TCC
  2. Determine extent of disease (“staging”) to rule in/out metastasis

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Step 1 – Confirm TCC

- Gold standard = **histopathology**
  - Catheter biopsy
  - Cystoscopy
  - Surgical biopsy
  - Percu[illegible]ous biopsy?

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Urinary Catheter Biopsy

- Transurethral traumatic catheterization
  - Red rubber and syringe with digital pressure applied rectally
  - Sedation helpful
- Female dogs more challenging, requires sedation or anesthesia
- Goal is to get chunks of tumor
  - If unsuccessful, can submit fluid samples for cytological analysis
    - Recommend “spin down” and fixation on glass slides

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Cystoscopy

- Benefits of cystoscopy:
  - Minimally invasive
  - Visualize of extent of disease
  - Usually diagnostic:
    - 96% female dogs
    - 65% male dogs
- Limitations:
  - Requires anesthesia
  - Significant debulking not possible
    - Can only remove superficial component of disease
  - May not be possible in small dogs due to size of scopes

Cystoscopy; PUVTH

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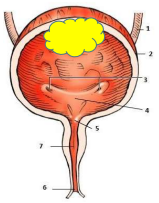
Surgical Biopsies

- Good option for masses in head of bladder (rare)
  - Chance of removal with surgery
- Can debulk trigonal tumors but margins will not be complete
- Take steps to minimize seeding risk:
  - Avoid urine spilling into abdomen
  - Change surgical tools/packs and gloves when closing the SQ and skin



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Urine Tests for TCC

- What if histopathology is not an option?
  - Dog too small to scope (or it's a cat)
  - Co-morbidities/high-risk anesthesia
  - Owners cannot afford cystoscopy or surgery but want an answer
- Urine based tests:
  - Urine cytology
  - V-BTA test
  - CADET BRAF test

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Urine Cytology

- Often suggestive of cystitis:
  - RBCs
  - WBCs
  - Bacteria
- Non-neoplastic, reactive transitional cells can appear like TCC
  - Use caution when interpreting in-house
  - Always recommend pathology review
- If sample has low cellularity, try spinning down urine and making sediment slides

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Polymedco V-BTA Test (Bladder Tumor Antigen)

- Rapid latex agglutination test
- Quantitative detection of bladder tumor analytes in urine
- Advantages
  - Non-invasive
  - Need small amount of urine
  - Highly sensitive (90%) = few false negatives
- Limitations
  - Low specificity (78%)
    - False positives with 4+ protein, 4+ glucosuria, >30-40 RBC or WBC per hpf

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ANTECH CADET® *BRAF* Test

- Urine assay
- Detects specific genomic signature in cancer cells within urine of dogs with TCC

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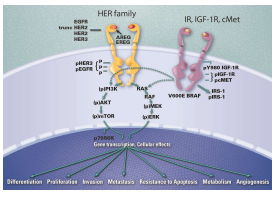
BRAF Mutation in Human Cancer

- 2002 Cancer Genome Project discovered high frequency of BRAF gene mutations in human melanoma
  - Acquired mutation: **BRAF V600E**
  - Leads to activated version of BRAF enzyme
- In humans, present in:
  - ~70% melanoma
  - ~8% of all human cancers



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BRAF Mutation in Canine Cancer

- Two studies looking at canine melanoma (n=29) – none harbored BRAF V600E mutation
- But, canine TCC does!
  - Complete transcriptome of 4 canine TCC tumors was sequenced
  - All 4 samples harbored somatic mutation homologous to human BRAF(V600E) mutation
  - Identical mutation present in ~85% of canine TCC tumor samples (n=66)

Mol Cancer Res. 2015 Jun;13(6):993-1002. doi: 10.1158/1541-7786.MCR-14-0689. Epub 2015 Mar 12.

Homologous Mutation to Human BRAF V600E Is Common in Naturally Occurring Canine Bladder Cancer--Evidence for a Relevant Model System and Urine-Based Diagnostic Test.

Decker B[1], Parker HG[2], Dhawan D[3], Kwon EM[2], Karlins E[2], Davis BW[2], Ramos-Vara JA[4], Bonney PL[3], McNiel EA[5], Knapp DW[6], Ostrander EA[7].

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CADET® *BRAF* Test Advantages

- Non-invasive; need 30-40mL
- High sensitivity (85%)
- High specificity (100%) – results not affected by:
  - Red or white blood cells
  - Protein
  - Bacteria
  - Other cancer types

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CADET® *BRAF*-PLUS Test

- Additional genomic signatures now identified
- Can be added on samples in which TCC is suspected but *BRAF* mutation is undetected on standard CADET *BRAF* test
- Increases sensitivity from 85% → >95%

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CADET® *BRAF* Test – When to Use

- Dog with urinary signs and bladder mass found on imaging
- Early diagnosis in dogs with recurrent or complicated UTIs without bladder mass on imaging
- Early diagnosis in high-risk dog breeds over age of 6
- To monitor treatment success?
  - Chemotherapy success by decreased levels of BRAF mutation detection
  - Recurrence after surgery

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Summary of CADET Urine Testing

- **Convenient:** non-invasive urine sample
- **Sensitive:** permits early detection of TCC; identifies 95% of TCC
- **Specific:** not affected by blood, protein, sugars, bacteria
- **Affordable:** allows to diagnose quickly vs. months of UA/UCS, antibiotics ($$)
- **Rapid:** Results available 3-5 business days

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Step 2 – Stage the Disease

- TCC has a moderate-high metastatic rate:
  - ~20% @ diagnosis
  - ~50% @ time of death
- Importance of staging:
  - Determining prognosis
  - Choosing appropriate course of treatment
  - Establishing a baseline set of tumor measurements
    - Will help determine if subsequent treatment is successful
  - Anticipating which future symptoms may arise

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Step 2 – Stage the Disease

- TCC is staged using Tumor, Node, Metastasis WHO Classification:
  - T= Primary Tumor:
    - T1= Superficial papillary tumor
    - T2*= Tumor invading the urinary bladder wall
    - T3*= Tumor invading into adjacent organs
  - N= Node:
    - N0= No evidence of regional lymph node metastasis
    - N1= Regional lymph node involvement
    - N2= Regional and juxta-regional lymph node involvement
  - M= Metastasis:
    - M0= No metastasis
    - M1= Evidence of distant metastasis

* = most dogs

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Staging Diagnostics

- Full staging
  - CBC, chemistry
  - Imaging
    - Abdominal ultrasound and chest x-rays
    - Full body CT scan
      - Recommend obtaining ultrasound images of bladder at same time for monitoring purposes

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Table 2 Sites of metastases identified in 137 dogs with transitional cell carcinoma undergoing necropsy at Purdue University between 2005 and 2013 with comparison with published autopsy findings from humans (Wallmeroth et al. 1999)

Location of metastases	Number of dogs with metastasis in that location (% of 137 dogs undergoing necropsy)	Number of humans with metastases in that location (% of 308 humans undergoing autopsy)
Any metastases	92 (67)	214 (69)
Any nodal metastases	57 (42)	180 (58)
Regional nodes (abdominal, pelvic inguinal nodes)[a]	40 (29)	158 (51)
Thoracic nodes[b]	17 (12)	80 (26)
Other nodes	1 (1)	8 (3)
Any distant metastases	80 (58)	147 (48)
Lung	69 (50)	96 (31)
Bone	15 (11)	71 (23)
Liver	10 (7)	103 (33)
Kidney[c]	10 (7)	30 (10)
Adrenal gland	8 (6)	28 (10)
Skin	8 (6)	4 (1.5)
Spleen	6 (4)	11 (3.6)
Gastrointestinal[d]	3 (2)	45 (15)
Heart	5 (4)	13 (4)
Brain	2 (1.5)	8 (2.5)

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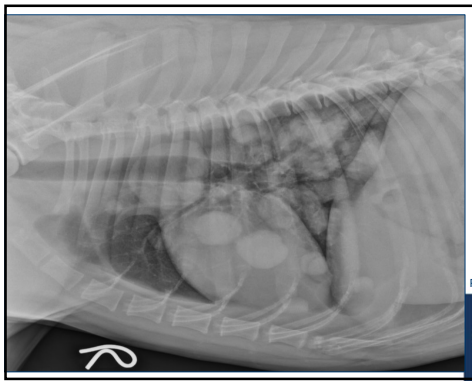

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Treatment Options

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Treatment

- Treatment goal = slow disease while palliating symptoms
- Need to address local disease AND metastatic disease (or risk for)
  - Most dogs (~60%) are euthanized d/t primary tumor
  - 14% euthanized d/t metastatic disease
  - 25% euthanized for something else (including resistant UTI)
- Local therapy mainstays: surgery, radiation, chemotherapy, NSAID
- Delay metastasis: chemotherapy

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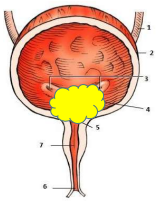
Surgery

- Most lesions are not resectable due to either:
  - Trigonal location
  - Urethral or prostatic involvement
  - Presence of multiple bladder tumors; "field effect"
- Recommended for non-metastatic apical bladder masses
  - Goal 1-2cm margins around tumor
  - Take precautions to avoid seeding
  - Active surveillance after (~60% recur)
- Surgical diversion – rarely done due to morbidity
  - Transurethral resection
  - Ureterocolonic anastomosis
  - Resection of bladder neck and proximal urethra



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Surgery – Partial Cystectomy

Vet Comp Oncol. 2017 Dec;15(4):1417-1427. doi: 10.1111/vco.12286. Epub 2017 Feb 20.

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

Marvel SJ[1], Séguin B[1,2], Dailey DD[1], Thamm DH[1,2].

- N = 37 dogs
- All underwent partial cystectomy +/- medical therapies
- PFI 235 days
- MST 348 days
  - MST for dogs that had cystectomy, piroxicam +/- chemo MST 772 days
- Conclusion: Dogs with non-trigonal bladder TCC treated with full thickness partial cystectomy and daily piroxicam (+/− chemotherapy) may have improved outcome

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Radiation Therapy

- Efficacy and recommended use for TCC is still evolving
  - Expensive ($3000-9000)
  - Logistics – not readily available
- Types of external beam radiation:
  - Palliative radiation ("hypofractionated")
  - Definitive radiation ("hyperfractionated" or "IMRT")
  - Stereotactic radiation

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Chemotherapy

- Current mainstay of treatment = systemic medical treatment
  - Chemotherapy and/or NSAID
- Not usually curative; majority stable disease and some partial remission
- Most protocols well tolerated:
  - ~60-70% no side effects
  - ~30% mild side effects
  - ~<10% severe, life-threatening side effects

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Chemotherapy

Bladder Cancer. 2016 Apr 27;2(2):241-250.

A Nonselective Cyclooxygenase Inhibitor Enhances the Activity of Vinblastine in a Naturally-Occurring Canine Model of Invasive Urothelial Carcinoma.

Knapp DW[1], Rupp-Czerniak A[2], Ramos-Vara JA[2], Naughton JF[3], Fulkerson CM[4], Honkisz SI[4]

Vinblastine + piroxicam
- N = 24 dogs
- RR = 58.3%
- PFI 199 days

Clin Cancer Res. 2003 Feb;9(2):906-11.

Clinical evaluation of mitoxantrone and piroxicam in a canine model of human invasive urinary bladder carcinoma.

Henry CJ[1], McCaw DL, Turnquist SE, Tyler JW, Bravo L, Sheafor S, Straw RC, Darnell WS, Madewell BR, Jorgensen L, Scott MA, Higginbotham ML, Chun R

Mitoxantrone + piroxicam
- N = 48 dogs
- RR = 35.4% (recent study only 8%)
- PFI 194 days

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Metronomic Chemotherapy

J Am Vet Med Assoc. 2013 Jun 1;242(11):1534-8. doi: 10.2460/javma.242.11.1534.

Metronomic administration of chlorambucil for treatment of dogs with urinary bladder transitional cell carcinoma.

Schrempp DR[1], Childress MO, Stewart JC, Leach TN, Tan KM, Abbo AH, de Gortari AE, Bonney PL, Knapp DW.

- Metronomic = frequent (i.e. daily), low dose, oral chemotherapy
  - No direct cytotoxic activity but rather anti-angiogenic + immunomodulatory
  - Better at tumor stabilization vs. shrinkage
- N = 31 dogs (29/31 had failed other therapy)
  - RR = 3% but 67% stable disease
  - MST 7 months with minimal toxicity

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COX Inhibition

- COX-2 overexpressed in canine TCC
- Piroxicam (0.3mg/kg PO once daily) – 17.7% response rate
  - MST as single agent 195 days
  - Can be used alone or combined with chemotherapy protocols
  - S/E: GI ulceration → melena, vomiting, anorexia, abdominal discomfort
    - Switch to COX-2 inhibitor (i.e. deracoxib, 17% response rate)
- "NSAIDS for all carcinomas!"

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Treatment Options For Urethral Obstruction from TCC

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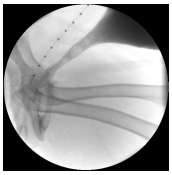
Urethral Stenting

- Majority of cases will have urine flow restored (>90%)
- Complications:
  - Urinary incontinence
  - Urethral penetration
  - Improper placement
  - Persistent stranguria
- MST 2.6 – 5 months post placement (longer if chemo/NSAID to follow)
  - Tumor can grow into stent resulting in obstruction
  - Stent migration
  - Recurrent UTIs
  - Warn owners – stranguria will continue



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Laser Ablation

- CO_2 laser ablation
  - Did not extend survival time vs. chemotherapy alone
- Ultrasound-guided diode laser ablation
  - MST 380 days
  - Complications - stranguria, hematuria, stenosis ,spread of TCC within the lower urinary tract, spread to the urethrostomy site, urethral perforation, bacterial cystitis

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Cystostomy Tube

- Surgically placed cystotomy tube to bypass trigone and urethra
- Complications common (50%):
  - Recurrent and resistant UTI
  - Urine leakage around the tube
  - Fistula formation
  - Inflammation
  - Inadvertent removal/displacement

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Other Types of Palliative Therapy

- Pain management for bone metastasis
  - Aminobisphosphonate – i.e. once monthly IV infusions of:
    - Pamidronate
    - Zoledronate – more potent, shorter infusion
  - Radiation therapy
- Supportive medications PRN
  - Antibiotics if concurrent UTI, stool softeners, fluids for renal failure, etc

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How Does TCC "Win"?

- Local disease = primary challenge
  - Urethral obstruction
  - Ureteral obstruction → hydronephrosis → renal failure
  - Recurrent UTIs
    - 55% will have a UTI during treatment
    - Most common: *Staphylococcus* 23.9%, *E.coli* 19.8%
    - Risk factors: female > male, urethral involvement
- Metastatic disease can also become life-limiting
  - Widespread metastasis
  - Painful lesions (i.e. skeletal metastasis)

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Prognosis

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Prognosis

- Fair to guarded
- Remission rates <20% w/single agent; 35-60% with combined
  - Best results typically seen in dogs sequentially receiving multiple protocols
- Survival times
  - Highly variable depending on TNM stage of dz, vascular invasion, location of tumor, therapy pursued, owner's expectations
  - Usually <1 year unless early detection or non-metastatic apical tumor removed w/surgery

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What about Cats?

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TCC in Cats

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

Maureen A. Griffin, William T. N. Culp, Michelle A. Giuffrida, Peter Ellis, Joanne Tuohy, James A. Perry, Allison Gedney, Cassie N. Lux, Milan Milovancev, Mandy L. Wallace, Jonathan Hash ... See all authors

First published: 13 November 2019 | https://doi.org/10.1111/jvim.15656 | Citations: 2

BRAF CADET TEST NOT APPLICABLE FOR CATS

- N = 118 cats with TCC
  - Median age at diagnosis 15 years
- Trigone affected most commonly 27%; (different vs. dogs)
- At diagnosis – 21% had metastasis
- Therapy pursued in 62% – piroxicam, chemo, surgery
- MST 113 days

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Take Home Points

- TCC should be a ddx for older dogs with recurrent/severe urinary signs
- If possible, ultrasound bladder before cystocentesis
  - If mass present, AVOID cystocentesis, do free catch
- Although histopathology gold standard, consider new BRAF CADET test for diagnosis esp. for financially limited owners
- Staging is important
- Remember local disease and metastatic potential in treatment plan
  - Surgery, radiation, chemotherapy, NSAIDs

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Thank You

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Acknowledgements

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- Sentinel Biomedical
- Antech
- Purdue University

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