Hematuria

CPD, University of Manitoba

November 10, 2017

Sabeer Rehsia, MD, BSc, FRCSC

Conflict of interest

- None

Objectives

- Define microscopic and macroscopic hematuria
- Review common causes of hematuria
- Outline the investigations and workup
- Most important “benign” causes of hematuria
- Most important malignant causes of hematuria

Outline

- **Hematuria**
  - Definitions: macroscopic, microscopic, pseudo
  - Relevance
- Asymptomatic Microscopic Hematuria
- Macroscopic hematuria
- Investigations
- Common causes
  - Benign
  - Malignant

Hematuria

- Macroscopic hematuria: visible blood in urine
- Microscopic hematuria: >2-3 RBCs/hpf x 2 microscopic analysis
  - NO recent exercise, menses, sexual activity or instrumentation
- Pseudohematuria: arising from outside the urinary system
  - Menstruation, inflammation from phimosis or balanitis, medications

Hematuria

- Prevalence of hematuria up to 16% of the population
- Hematuria is considered a urologic malignancy until ruled out

Hematuria

- Urologic malignancy
  - 23% in gross hematuria
  - 5% in microscopic hematuria
- In patients with gross hematuria, 8% will have no cause identified
- In adults with microscopic hematuria, 43% will NOT have a identifiable cause

Outline

- Hematuria
  - Definitions: macroscopic, microscopic, pseudo
  - Relevance
- **Asymptomatic Microscopic Hematuria**
- Macroscopic hematuria
- Investigations
- Common causes
  - Benign
  - Malignant

Asymptomatic Microscopic Hematuria

- Based off CUA/AUA guidelines
- Microscopic hematuria: >2-3 RBCs/hpf on at least 2 microscopic urinalysis samples
- Microscopic hematuria in the context of a patient taking an anti-coagulant still needs to be worked up
- When to refer to nephrology: dysmorphic RBCs, proteinuria, cellular casts and/or renal insufficiency

Asymptomatic Microscopic Hematuria

- Most common causes:
  - BPH
  - Infection
  - Calculi
- Always have to think about malignancy

Asymptomatic Microscopic Hematuria

- EVERYONE requires upper tract imaging and cytology
  - Imaging = CUA recommends U/S as first choice for investigation
  - One urine cytology

Asymptomatic Microscopic Hematuria (AUA Guidelines)

Table 1: Common Risk Factors for Urinary Tract Malignancy in Patients with Microhematuria
Male gender
Age (> 35 years)
Past or current smoking
Occupational or other exposure to chemicals or dyes (benzenes or aromatic amines)
Analgesic abuse
History of gross hematuria
History of urologic disorder or disease
History of irritative voiding symptoms
History of pelvic irradiation
History of chronic urinary tract infection
History of exposure to known carcinogenic agents or chemotherapy such as alkylating agents
History of chronic indwelling foreign body

Asymptomatic Microscopic Hematuria

- Follow-up required
  - 1-3% of patients may develop urologic malignancy within three years
- After a negative initial work-up, the family doctor should do follow-up (CUA)
  - Urinalysis & urine cytology
  - Frequency: 6, 12, 24, 36 months

Outline

- Hematuria
  - Definitions: macroscopic, microscopic, pseudo
  - Relevance
- Asymptomatic Microscopic Hematuria
- **Macroscopic hematuria**
- Investigations
- Common causes
  - Benign
  - Malignant

Macroscopic Hematuria

- Macroscopic hematuria: visibly bloody urine
- Always significant
- Higher chance of malignancy with 23% of patients having urologic malignancy

Macroscopic Hematuria

- Most common causes:
  - Bladder cancer
  - Infection
  - Calculi
  - Prostate
  - Radiation cystitis

Macroscopic Hematuria

- Investigations required:
  - Imaging
    - CT IVP – gold standard
    - Retrograde pyelogram + U/S OR CT uninfused
  - Three urine cytology samples
- Cystoscopy

Requires a full work-up

Outline

- Hematuria
  - Definitions: macroscopic, microscopic, pseudo
  - Relevance
- Asymptomatic Microscopic Hematuria
- Macroscopic hematuria
- **Investigations**
- Common causes
  - Benign
  - Malignant

Investigations

- Ultrasound – part of w/o for asymptomatic microscopic hematuria
- CT IVP (urogram) – four phases to imaging
- Retrograde pyelogram – cystoscopy with contrast
- Cystoscopy – direct visualization of bladder

Outline

- Hematuria
  - Definitions: macroscopic, microscopic, pseudo
  - Relevance
- Asymptomatic Microscopic Hematuria
- Macroscopic hematuria
- Investigations
- **Common causes**
  - Benign
  - Malignant

Hematuria

- Differential diagnosis:
  - Malignancy
    - Kidney, urothelial (includes bladder), prostate
  - Prostate
  - Bladder (cystitis)
  - Urethral stricture
  - Calculi
  - Infection
  - Trauma
  - Tuberculosis
  - Thrombosis
- Pseudohematuria

Hematuria

- Medications that cause hematuria:
  - Sulfamethoxazole
  - Nitrofurantoin
  - Ibuprofen
  - Phenytoin
  - Methyldopa
  - Chloroquine
  - Levodopa
  - Rifampin

BENIGN CAUSES

Outline

1. Urolithiasis
2. Benign prostatic hypertrophy
3. Radiation cystitis

1. Urolithiasis

- Stone in the urinary system

- Lifetime prevalence
  - Overall 1 in 11
  - Males ~10.6%
  - Females ~7.1%

- Recurrence rates are 7-10% per year
- Rare <20yrs, but peaks in 40s-60s
- Peaks during summer months

Urolithiasis

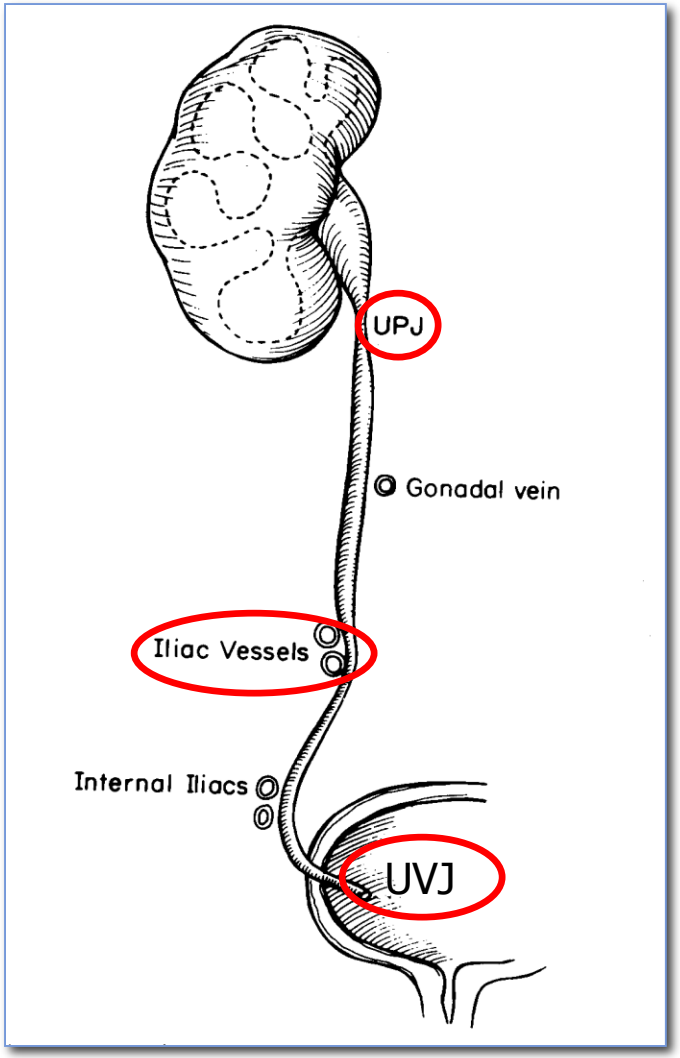
- Etiology:
  - Lifestyle – dehydration, high sodium diet, high oxalate diet, carbonated drinks
  - Disease state – obesity, DM, HTN, gout, IBD
  - UTIs
  - Sedentary lifestyle
  - Anatomic obstruction
  - Medications – vitamin C, vitamin D, furosemide

Urolithiasis

- Calcium oxalate – most common renal & bladder stone
- Calcium phosphate – more common in certain disease states
- Uric acid – radiolucent
- Struvite – caused by infection

Gross or microscopic hematuria present in 90% of cases

Urolithiasis



Urolithiasis

- Evaluation:
  - KUB x-ray
  - Ultrasound
  - CT KUB
  - Urinalysis
- Treatment depends on several factors
  - Most stones <5mm will pass spontaneously

2. BPH

- Extremely common
  - 70% of 70 year old males
- BPH occurs in the transition zone of the prostate
  - Increase in prostate stroma
  - Increase in number of a-1 receptors in prostate stroma
- Bladder outlet obstruction can occur from BPH
  - Degree of BOO does NOT correlate with size of prostate

BPH

- LUTS = decreased force of stream, hesitancy, intermittent stream, PV dribbling, nocturia
- With progressive BOO, bladder can become overworked and lead to symptoms of OAB
- With severe & prolonged BPH, the bladder may decompensate and have ineffective contractions, leading to retention

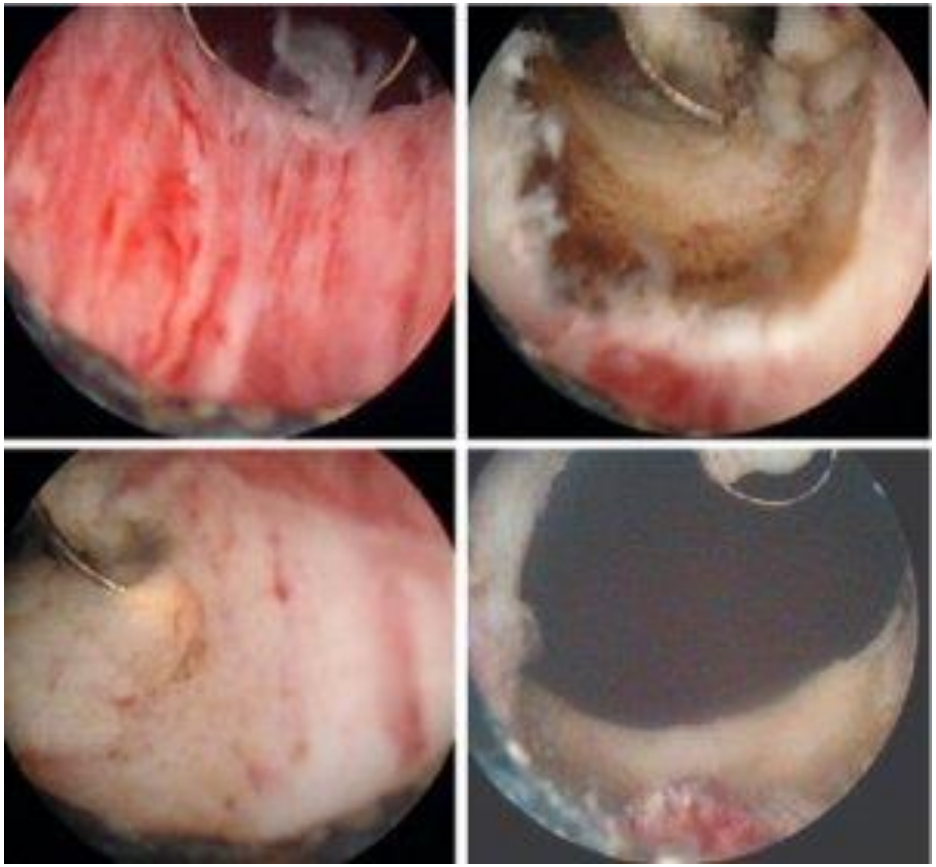
BPH

- Complications:
  - Hematuria 2.5%
  - Acute urinary retention 2-5%
  - Incontinence 5%
  - UTIs <1%
  - Bladder calculi <1%
  - Upper tract deterioration 2.5%
  - Bladder decompensation

BPH

- Medical treatment
  - Alpha-blocker
  - 5a-reductase inhibitor – helps to reduce recurrent BPH-related hematuria
- Surgical treatment
  - TURP
  - Open/simple prostatectomy

BPH



3. Radiation Cystitis

- Damage to the urinary bladder as a complication from pelvic radiation therapy of malignant tumors
  - Inflammatory response to radiation, followed by healing
  - Leads to ischemic tissue damage due to necrosis of vascular endothelium

- Can be very difficult to manage

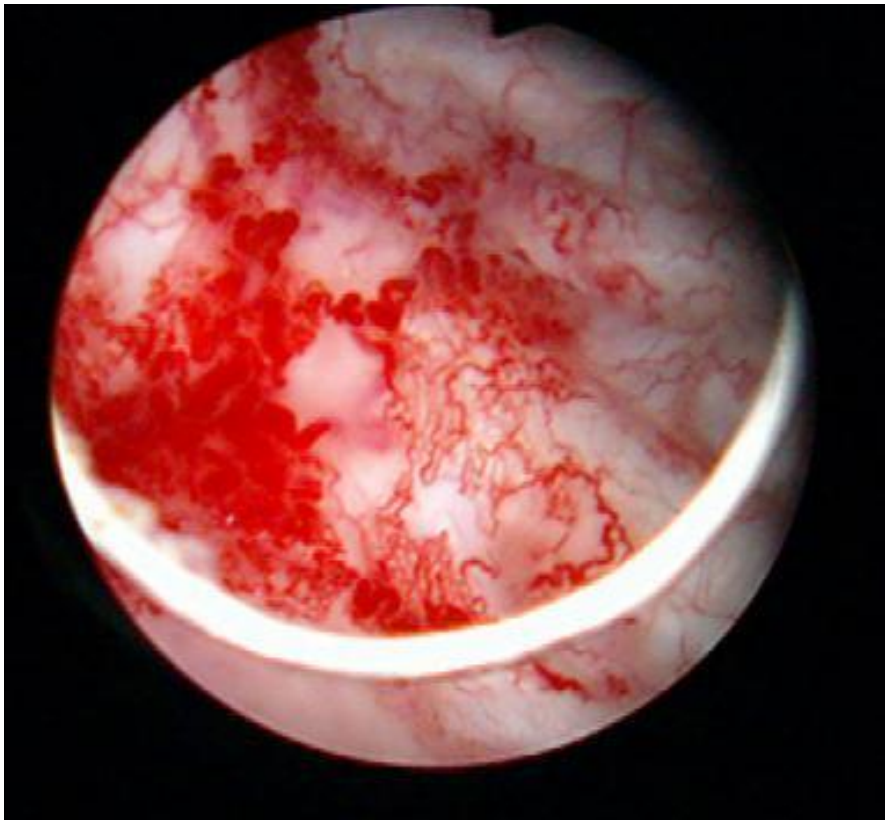
Radiation Cystitis

- Prevalence of up to 9% in patients treated with pelvic radiation for prostate cancer
  - Dependent on dosage of radiation
- Standard hematuria work-up required even if patient has had radiation in the past
  - 2-4x increase in incidence of bladder cancer
  - Usually high-grade & locally advanced at time of diagnosis

Radiation Cystitis

- Treatments:
  - Continuous bladder irrigation (3-way catheter)
  - Cystoscopoy & fulguration
  - Alum irrigation
  - Formalin
  - Hyperbaric oxygen

Radiation Cystitis



MALIGNANT CAUSES

Outline

1. Bladder cancer
2. Upper tract urothelial cancer
3. Renal cysts
4. Kidney cancer

1. Bladder Cancer

- The bladder is the most common site of cancer in the urinary system
- Most common type → urothelial carcinoma (transitional cell carcinoma)
- Fourth leading cause of cancer death in males
- 3x more common in men

Bladder Cancer

- Incidence increases with age (median age ~70yrs)
- Overall mortality from bladder cancer decreasing despite rising incidence
- Higher 5yr survival among men

Bladder Cancer

- Risk factors:
  - Smoking
  - Chemical exposure – aniline dyes, acrolein, aromatic amines
  - Radiation
  - Chemotherapy – cyclophosphamide

Bladder Cancer

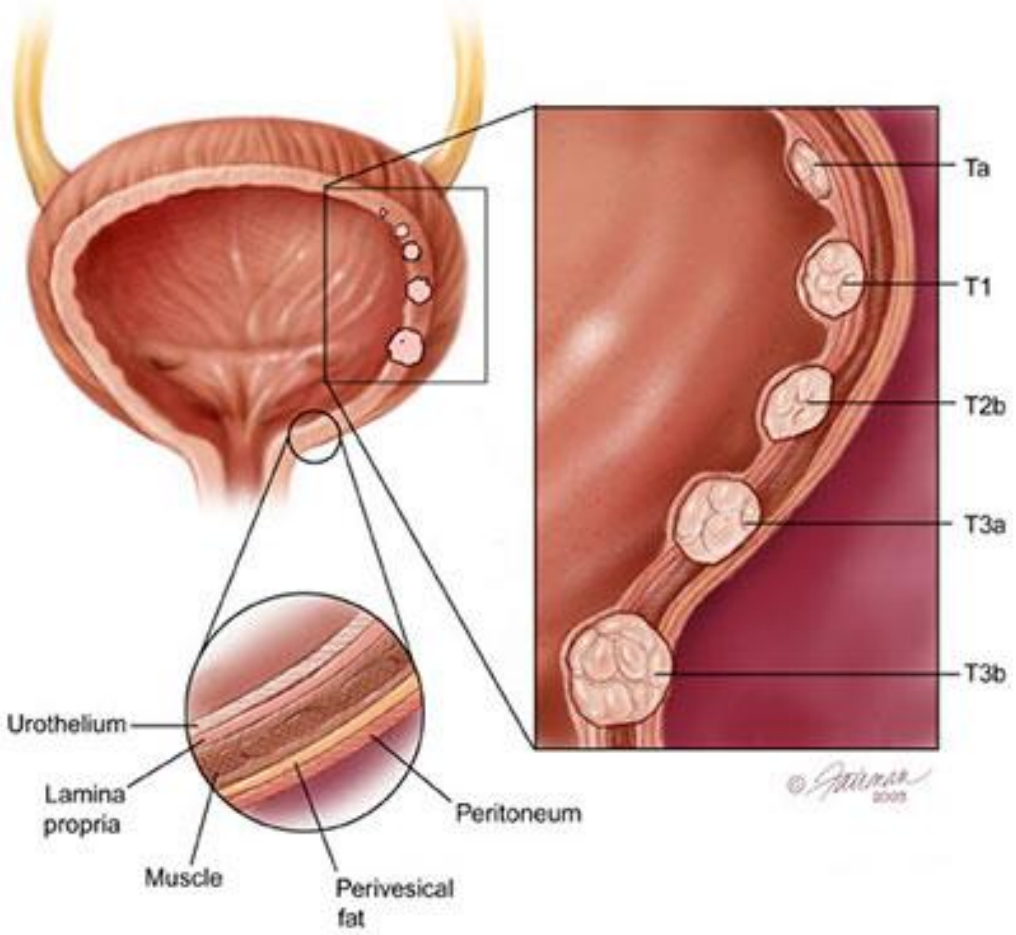
- Grading system:
  - PUNLMP (well differentiated)
  - Low grade
  - High grade

Bladder Cancer

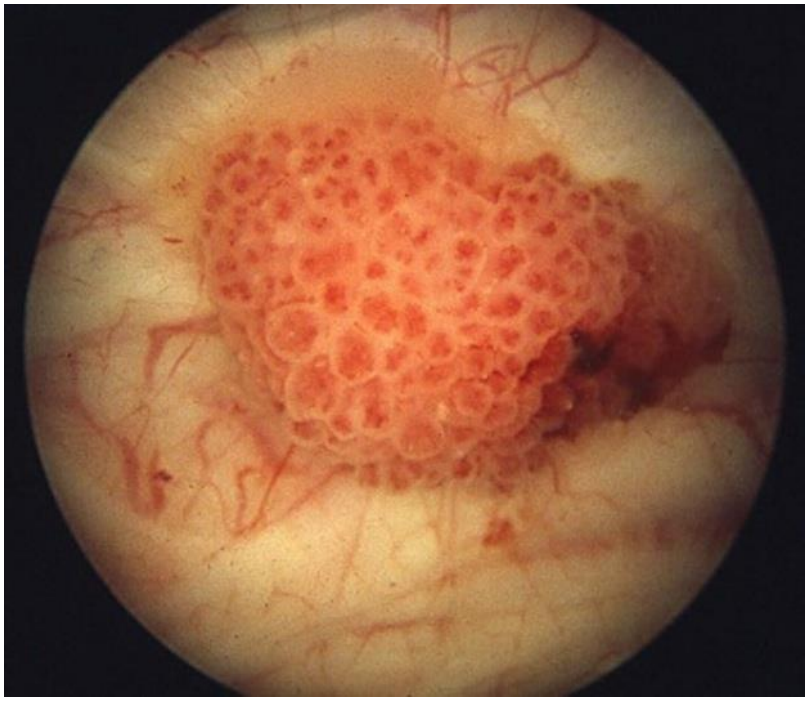
- Ta = noninvasive papillary
- Tis = carcinoma in situ (high-grade superficial)
- T1 = lamina propria invasion

- T2 = muscle invasion
- T3 = fat invasion
- T4 = local invasion

Bladder Cancer

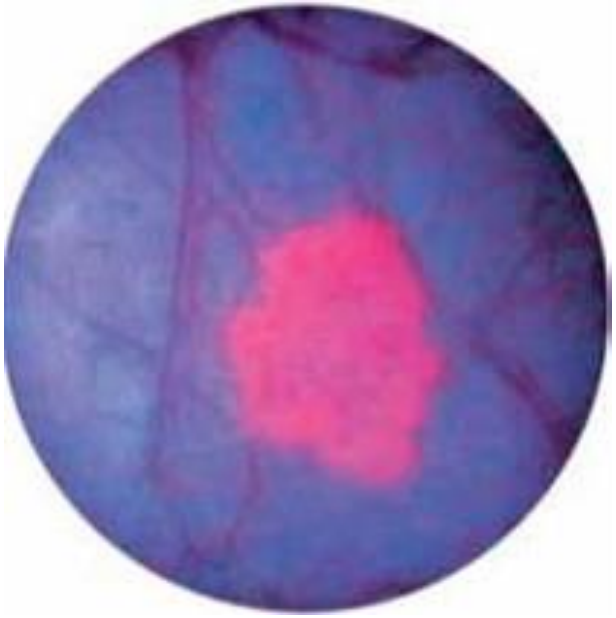


Bladder Cancer



Bladder Cancer

Blue Light Cystoscopy

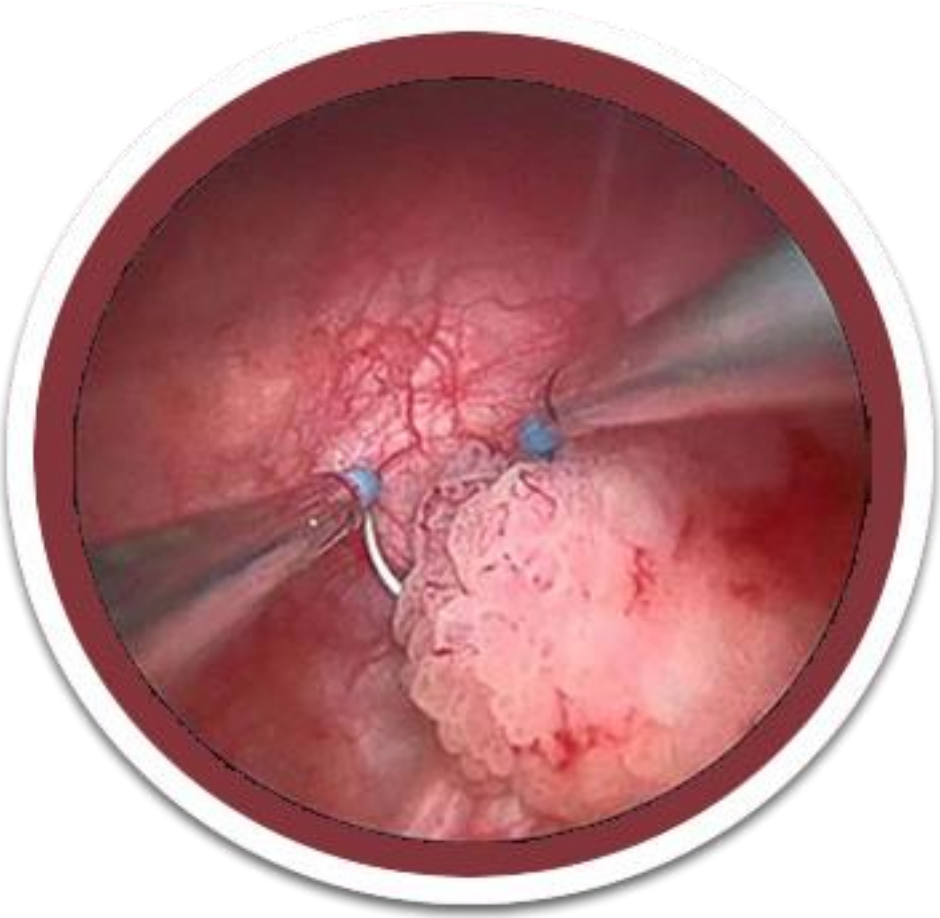


Bladder Cancer

- Diagnosis:
  - Urine cytology x 3
  - Cystoscopy
  - Imaging – CT scan, U/S

- Treatment:
  - Transurethral resection of bladder tumor

Bladder Cancer



Bladder Cancer

- Treatment of superficial disease (Ta-T1):
  - Bladder tumor resection
  - BCG
- Treatment of muscle invasive (T2<):
  - Radical cystectomy
  - Partial cystectomy
  - TURBT + chemotherapy+ radiation
- Palliative care

2. Upper Tract Urothelial Carcinoma

- UTUC → includes urothelial cancer of the ureter, renal pelvis, or renal calyces
- About 90% of upper urinary tract cancers are urothelial cancer
- UTUC accounts for ~5% of urothelial tumors

Upper Tract Urothelial Carcinoma

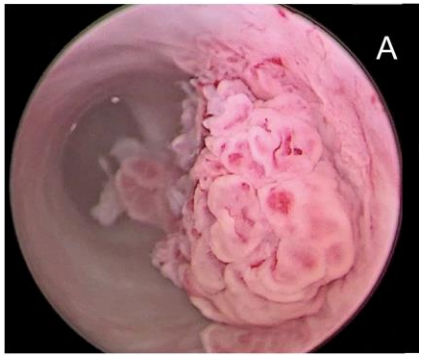
- Most common age of presentation is 50-70yrs
- Most common presenting symptom of UTUC is hematuria
- Second most common symptom is flank pain
- Filling defect is most common finding on imaging

Upper Tract Urothelial Carcinoma

- Risk Factors:
  - Smoking
  - Cyclophosphamide
  - Radiation
  - Papillary necrosis
  - Chronic UTIs
  - Occupational exposure
  - Lynch syndrome
  - History of urothelial carcinoma of bladder

Upper Tract Urothelial Carcinoma

Upper Tract Urothelial Carcinoma



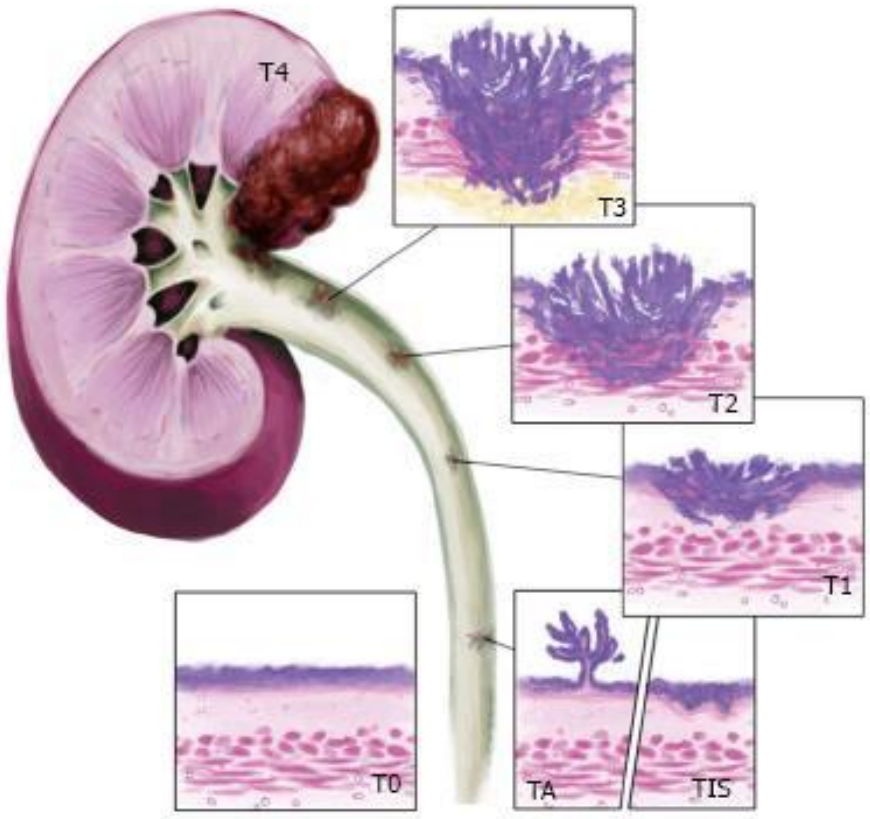
Upper Tract Urothelial Carcinoma

- Investigations:
  - Urine cytology x 3
  - Cystoscopy
  - Upper tract imaging – CT IVP preferred, retrograde pyelogram

Upper Tract Urothelial Carcinoma

- Prognostic factors:
  - Stage – most important
  - Grade
  - Associated carcinoma in situ
  - Lymphovascular invasion

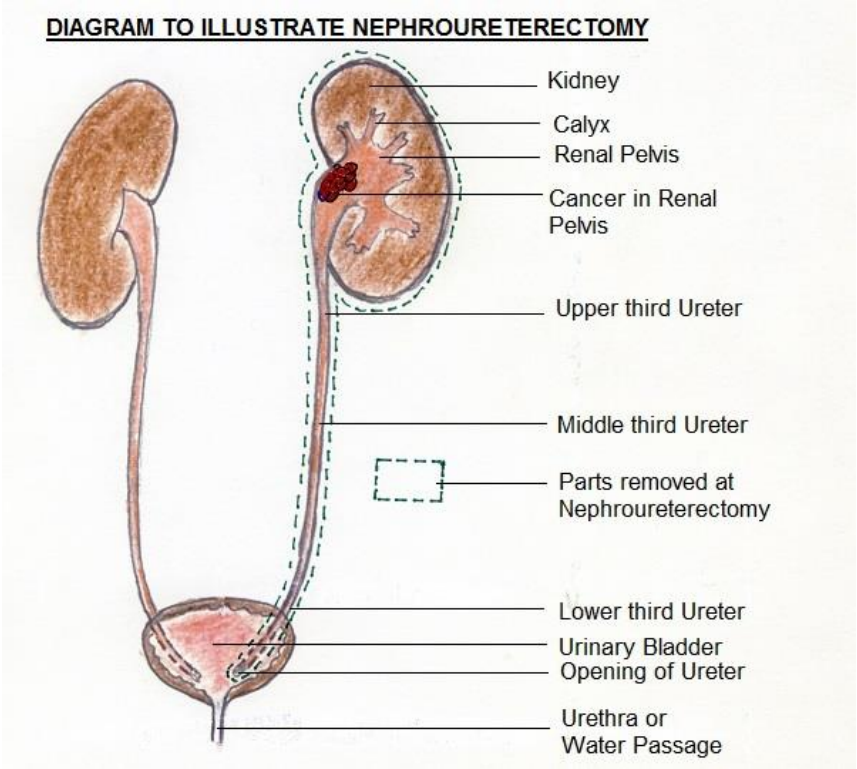
Upper Tract Urothelial Carcinoma

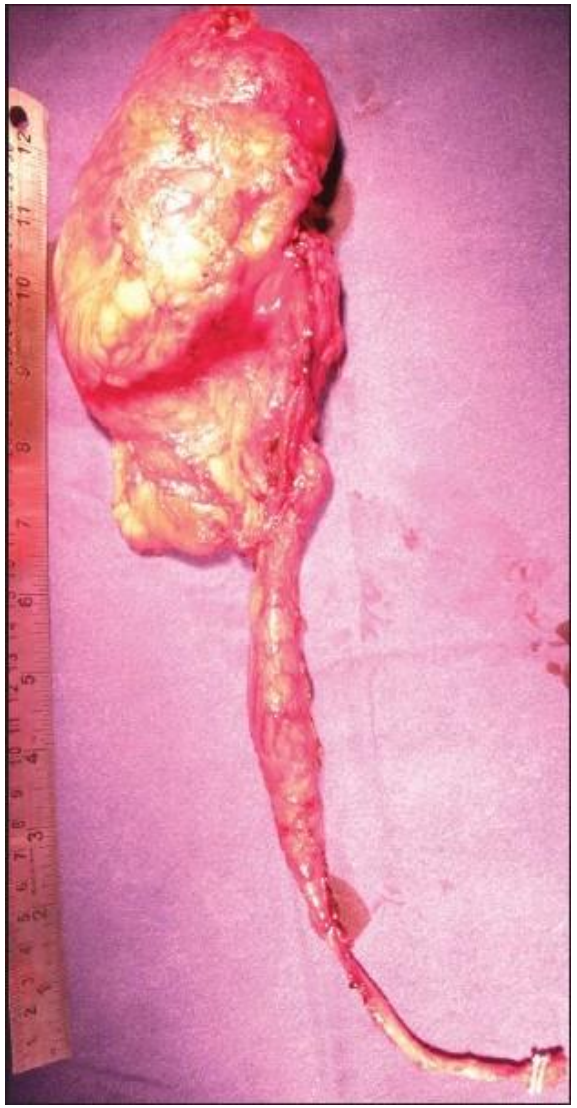


Upper Tract Urothelial Carcinoma

- Treatment:
  - Endoscopic
  - Segmental ureterectomy
  - Nephroureterectomy (gold standard)

Upper Tract Urothelial Carcinoma

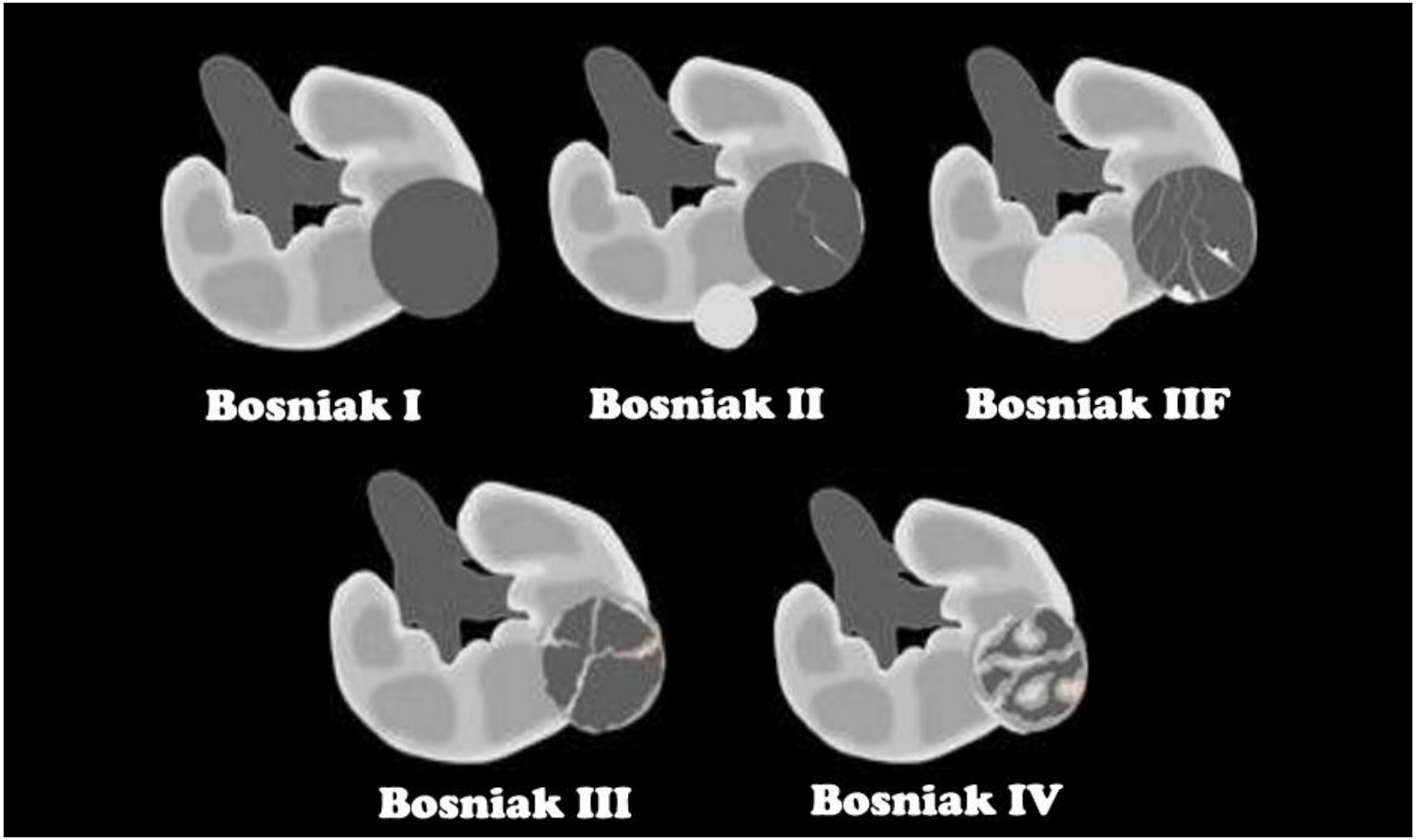




3. Renal Cysts

- Renal masses are often found incidentally
- Estimated that up to 1/3rd of individuals >60yrs old will be diagnosed with at least one simple renal cyst
- More common in men

Renal Cysts



Renal Cysts

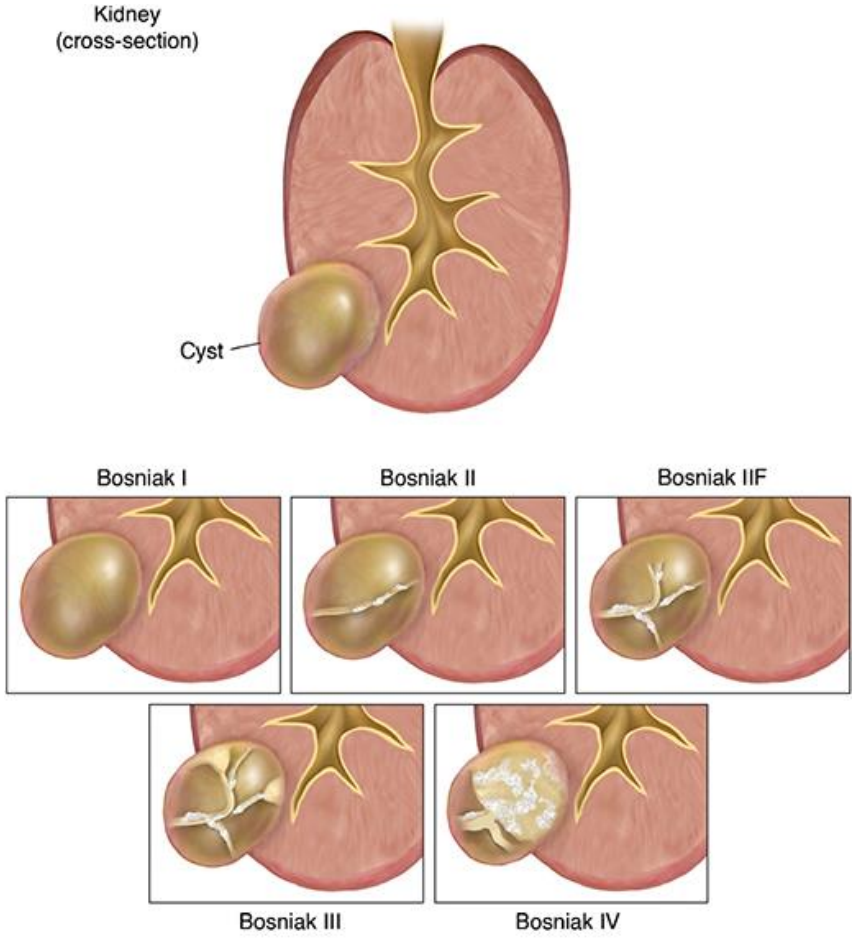
CUA guideline on the management of cystic renal lesions

Table 1. The Bosniak classification and management recommendations

Bosniak classification – key findings	Recommendations
Bosniak category I (simple renal cyst) • Usually round or oval shape • Anechoic with posterior enhancement on US • Regular contour with clear interface with renal parenchyma • No septa, calcification or enhancement	• No followup required
Bosniak category II • Thin septum (<1 mm) • Fine calcification (often small, linear, parietal, or septal) • Small hypderdense cyst (<3 cm; >20 HU) • No perceived contrast enhancement	• No followup required
Bosniak category IIF • Cyst unequivocally categorized as category II or III cysts • Multiple thin septa or a slightly thickened, but smooth septa • Calcifications – thick or nodular • No perceived contrast enhancement • Large hyperdense cysts (≥3 cm)	• Followup recommended • Imaging at 6 months and 12 months after diagnosis and then annually for at least 5 years if no progression.
Bosniak category III • Uniform wall thickening and/or nodularity • Irregular, thickened, and/or calcified septa • Contrast-enhancing sept	• Surgical excision is suggested • Conservative management and RFA in select cases
Bosniak category IV • Wall-thickening • Gross, irregular, and nodular septal thickening • Solid contrast-enhancing component, independent of septa	• Malignant until proven otherwise • Surgical excision is suggested • Potential role for pretreatment RTB (of solid component) to confirm malignancy • RFA and conservative management in select cases

US: ultrasound; RFA: radiofrequency ablation; RTB: renal tumour biopsy.

Renal Cysts



Source: Khaled M. Elsayes, Sandra A. A. Oldham: *Introduction to Diagnostic Radiology*: www.accessmedicine.com

Renal Cysts

- Treatment:
  - Bosniak I – II require no intervention or follow-up
  - Bosniak IIF – regular follow-up
  - Bosniak III-IV – observation or excision

Renal Cysts

- Other benign renal tumors:
  - Pseudotumor
  - Renal cyst
  - Oncocytoma
  - Angiomyolipoma
  - Cystic nephroma

4. Kidney Cancer

- 2-3% of adult malignancies
- Mostly sporadic, 4% familial
- Mostly incidental finding
- Renal cell carcinoma is most common
  - Most common age of presentation is 60-70yrs

Kidney Cancer

- Risk factors for RCC:
  - Smoking
  - Obesity
  - HTN
  - Horseshoe kidney
  - Acquired renal cysts from CKD

Kidney Cancer

- 50% of RCC found incidentally
- Gross hematuria
- Flank pain
- Paraneoplastic syndrome
  - HTN, elevated ESR, anemia, cachexia, fever, hypercalcemia, Stauffer syndrome
- Constitutional symptoms for metastatic disease

Kidney Cancer

Classification	Definition
T—Primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 7.0 cm or less in greatest dimension, limited to the kidney
T1a	Tumor less than 4.0 cm in greatest dimension, limited to the kidney
T1b	Tumor 4.0–7.0 cm in greatest dimension, limited to the kidney
T2	Tumor more than 7.0 cm in greatest dimension, limited to the kidney
T2a	Tumor >7 cm but ≤10 cm in greatest dimension, limited to kidney
T2b	Tumor >10 cm in greatest dimension, limited to kidney
T3	Tumor extends into major veins or perinephric tissues but not into ipsilateral adrenal gland or beyond Gerota's fascia
T3a	Tumor invades renal vein or its segmental branches or perirenal fat or renal sinus fat but not beyond Gerota's fascia
T3b	Tumor grossly extends into vena cava below the diaphragm
T3c	Tumor grossly extends into vena cava above diaphragm or into the wall of the vena cava
T4	Tumor invades beyond Gerota's fascia including contiguous extension into ipsilateral adrenal gland
N—Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph nodes
M—Distant metastases	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

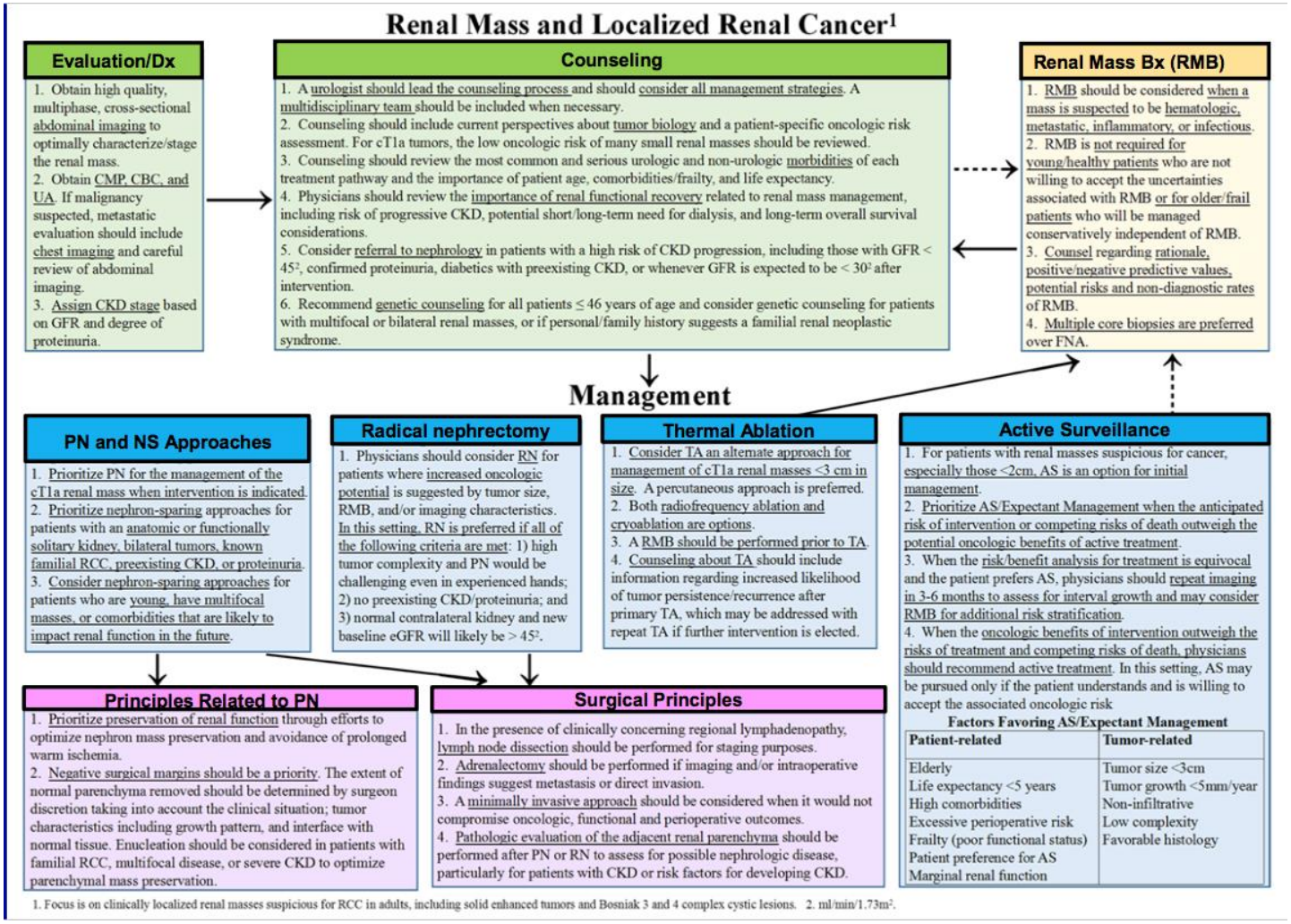
Kidney Cancer

CUA GUIDELINES

Canadian guidelines for the management of small renal masses (SRM)

- Small renal masses: defined as enhancing tumors <4cm in diameter, with image characteristics consistent with stage T1aN0Mo RCC
  - About 20-25% of SRMs are benign

Kidney Cancer



Hematuria

- Thank you

References

- Wolloin, T. Laroche, B. Psooy, K. Canadian Guidelines for the management of asymptomaic microscopic hematuria
- Rodney Davis, Steven Jones et al. AUA Guideline: Diagnosis, management and follow up of Asymptomaic microscopic hematuria in adults
- Wein, A. Kavoussi, L. Partin, A. Peters, Craig. Campbell-Walsh Urology. (10th ed.) 2012. Ch 4. GU Imaging. Elsvier.
- American Urological Association Guideline: management of benign prostatic hyperplasia. AUA education and research, Inc. (www. Auanet.org)
- McConnell JD et al for the MTOPS research group: The long term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign progression of BPH. NEJM 349:285, 2003
- Wieder, J. Pocket Guide to Urology. 5 th ed. 2015. pp. 267-272
- Wein, A. Kavoussi, L. Partin, A. Peters, Craig. Campbell-Walsh Urology. (10th ed.) 2012. Ch 53. Urothelial tumors of the upper urinary tract and ureter. Elsvier.
- Richard, P. Violette, P. et al. CUA Guideline on the management of cystic renal lesions 2017. (www.cua.org)
- Jewitt, M. Rendon, R et al. Canadian Guidelines for the management of small renal masses. 2015. (www.cua.org)
- American Urological Association Guideline: Renal Mass and Localized Renal Cancer. 2017. (www.auanet.org)