Case Studies in Renal & Urologic Impairments

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AAIM October 2015

RiverSource Insurance

Normal Lab Values for Case #1

Serum Creatinine

- Female 0.6 – 1.3 mg/dl (53 -115 umol/L)
- Male 0.7 – 1.5 mg/dL (62 – 133 umol/L)

Blood urea Nitrogen

- Female 9 – 26 mg/dl (3.2 – 9.3 mmol/L)
- Male 9 – 27 mg/dL (3.2 – 9.6 mmol/L)

Case #1: 62 year old NSF for $625,000 permanent life

She has an abnormal urinalysis on the paramedical exam (10/27/2014)

Serum Creatinine 0.8 mg/dL (71 umol/L)

Blood Urea Nitrogen [BUN] 18 mg/dL (6.57 mmol/L)

BP 132/78, P 64; Height 62", Weight 106 pounds

RESULT NAME	NORMAL	ABNORMAL	REFERENCE/CUTOFF	UNITS
URINALYSIS				
GLUCOSE	NEGATIVE		0.00 - 0.15*	(GM%)
PROTEIN		48 H	0 - 20*	(MG%)
LEUKOCYTE SCREEN	NEGATIVE		NEGATIVE	
HEMOGLOBIN SCREEN		POSITIVE	NEGATIVE	
WHITE BLOOD CELLS	1		0 - 10*	(/HPF)
RED BLOOD CELLS	TOO NUMEROUS TO COUNT		0 - 2*	(/HPF)
GRANULAR CASTS	0		0 - 5*	(/40LPF)
HYALINE CASTS	0		0 - 5*	(/40LPF)
SPECIFIC GRAVITY	1.033		1.002 - 1.035*	
URINE TEMPERATURE		90.0 L	90.5 - 99.6	(FAHR.)
CREATININE	206.6		10 - 300*	(MG/DL)
PROT/CREATININE RATIO		230 H	0 - 200*	(MG/GMCR)
MISCELLANEOUS URINE TESTS				
COTININE(NIC)	0.00		< 0.25*	(MCG/ML)
DIURETIC AGENTS (DIU)	NEGATIVE		< 1500	(NG/ML)
URINE ADULTERANT RESULTS				
URINE TEMPERATURE		90.0 L	90.5 - 99.6	(FAHR.)
CREATININE	206.6		10 - 300*	(MG/DL)

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Case #1: 62 year old NSF for $625,000 permanent life

She has an abnormal urinalysis on the paramedical exam

Medical records show she had been taking care of her ill husband and therefore hadn't been to a doctor in years until 9/24/2014, just one month prior to applying for life insurance. She saw a new PCP who did a physical, bloodwork, sent her for a colonoscopy and a mammogram. Her only complaint was the stress of caring for a husband with dementia. Her other tests included:

- Normal CBC
- Normal "comprehensive metabolic panel" [kidney, liver, calcium]
- Normal lipids
- Urinalysis: Yellow, clear; specific gravity 1.020; Blood 2+; protein negative; Leukocytes trace; WBC 6-10 [ref range 0 – 10]; RBC 15-25 [ref range 0– 3].

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Hematuria

Discussion Questions

What are your concerns from an underwriting perspective?

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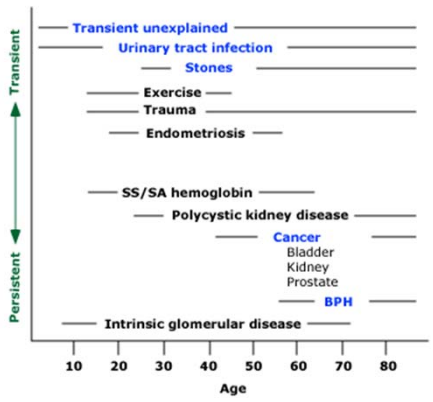
Major causes of hematuria by age and duration



Schematic representation of the major causes of hematuria in relation to the age at which they usually occur (horizontal axis), transience or persistence (vertical axis), and frequency (blue implies more frequent).
BPH: benign prostatic hyperplasia.

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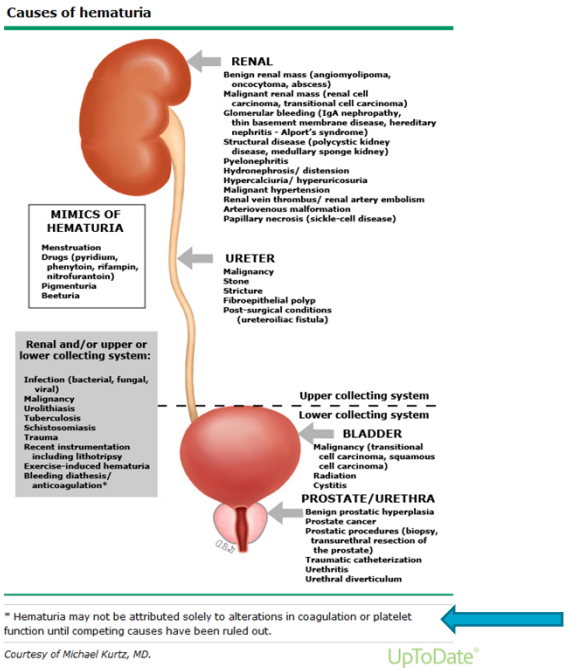
Feldman A et al. Etiology and evaluation of hematuria in adults. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2015. Reproduced with permission from UpToDate.



Feldman A et al. Etiology and evaluation of hematuria in adults. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2015. Reproduced with permission from UpToDate.

Historical Clues to Etiology of Hematuria

You may or may not have this information……

- Pyuria and dysuria – UTI (and bladder cancer)
- Symptoms of prostatic obstruction in older men - BPH
- Recent URI – post-infectious GN, IgA nephropathy
- Unilateral flank pain – ureteral obstruction (stones, malignancy)
- Recent vigorous exercise – exercise-induced hematuria
- History of a bleeding disorder
- Family history of renal disease, such as PCKD, hereditary nephritis (Alport Syndrome)
- Known history of sickle cell disease
- Medications that cause nephritis

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Risk Factors for Urinary Tract Malignancy in Microscopic Hematuria

American Urological Association (AUA) Guideline 2012

- History of gross hematuria
- Male gender
- Age > 35 years
- Past or current smoking
- Occupational or other exposure to chemicals or dyes [benzenes, aromatic amines]
- History of urologic disease or disorder [e.g. chronic cystitis, chronic UTI]
- History of irritative voiding symptoms
- History of pelvic irradiation
- History of exposure to known carcinogenic agents or chemotherapy such as alkylating agents
- History of chronic indwelling foreign body

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Hematuria

Discussion Questions

For this applicant, are there any clues as to the etiology of the hematuria?

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Case #1: 62 year old NSF for $625,000 permanent life

Applicant sees a urologist after your company declines to offer insurance

The urologist sends a letter to your company with the following explanation:

I have evaluated Mrs Catherine [redacted] for hematuria and the only abnormality I can find is that she has multiple small stones in her kidneys. These are non-obstructive, but could be the source of the blood. I can not find anything else that could be causing the hematuria. She is to return to see me in a year.

Sincerely,

Are you content with the explanation?

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Case #1: 62 year old NSF for $625,000 permanent life

Urology records [EMR format]

Proposed insured is seen 1/2/2015 by the urologist, who notes:

Chief complaint: "I have blood in my urine", she did not see the blood, denies any history of blood clots in her urine.

- Within the HPI: Denies dysuria, difficulty voiding, unintentional weight loss. "She is not having any pain".
- "Patient reports abdominal pain. Denies nausea, vomiting or change in bowels"

Contained within this initial urology consult is the following:

PAST DATA REVIEWED:

Source Of History: Patient
X-Ray Review: C.T. Abdomen/Pelvis: Reviewed Films. Discussed With Patient. HS KIDNEY

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Case #1: 62 year old NSF for $625,000 permanent life

Urology records

Urinalysis from 1/2/2015 urology consult:

- Specimen clear, yellow; large amount of blood, leukocyte esterase negative, protein negative, specific gravity 1.015 (no microscopic done)

The diagnosis is microscopic hematuria and urine cytology and cystoscopy are ordered

- Cystoscopy is negative
- Urine cytology negative
- Urinalysis 1/8/2015 - clear, yellow, large amount of blood (no microscopic done)

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Case #1: 62 year old NSF for $625,000 permanent life

Urology records, CT scan referred to by urologist

[redacted]

CLINICAL HISTORY: PAIN/GROSS HEMATURIA/LEFT FLANK PAIN

CT STONE STUDY

FINDINGS:
There is no evidence of free air or fluid within the abdomen or pelvis. Numerous pelvic phleboliths are present. The patient has a horseshoe kidney which is fused at the lower pole moiety. It is somewhat eccentric in the abdomen with much of the left kidney overlying the spine. Within the left upper pole, there is a 1-2 mm stone. No right renal stones are apparent. I cannot appreciate any ureteral dilatation or hydronephrotic change. I cannot however follow the ureters in their entirety.

Incidental note is made of small dependent gallstones.

IMPRESSION:
1. **Horseshoe kidney with 1-2 mm left moiety stone.**
2. **Incidental note is made of multiple gallstones.**

Are you content with this work-up? What is the work-up for unexplained, asymptomatic microhematuria?

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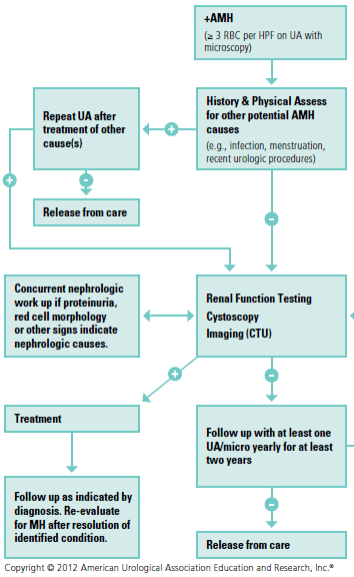
Diagnosis, Evaluation and Follow-up of AMH



In the 2012 AUA GLs, the definition of AMH changed to "≥ 3 RBC per HPF on a properly collected urinary specimen in the absence of an obvious benign cause."

Cytology & molecular markers are not recommended as part of a routine work-up for AMH. Some would advocate bladder washings for cytology in those with significant RFs or a high index of suspicion for bladder cancer.

*The threshold for re-evaluation should take into account patient risk factors for urological pathological conditions such as malignancy.

One More Thing to Consider

From a "Hematuria Clinic" website in New York*:

Blood in urine in women can sometimes originate from vaginal bleeding, uterine bleeding or menstrual period. Sometimes rectal bleeding can be confused with hematuria.

> It is important to distinguish whether the blood if from genital or urinary tract as the causes, evaluation and treatments are different.

*http://www.newyorkurologyspecialists.com/hematuria/common-causes-blood-urine-women/

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Case # 2: 55 year old male with microscopic hematuria; applying for $500,000 permanent life 10/2015

Former smoker, 1.5 PPD x 30 years; quit 7 years ago

Saw PMD 3 years prior to life insurance application for intermittent dysuria of 2 months duration, no gross hematuria.

- September 2012 Physical exam unremarkable
- UA with 25 RBC/HPF, WBC 7/HPF; urine culture negative; STD evaluation negative
- Treated with Ciprofloxacin

Returned 6 months later with similar complaints, wasn't sure if prior antibiotic helped or not. March 2013:

- UA 20 RBC/HPF, 2 WBC/HPF; urine culture negative
- Referred to urologist who diagnosed him with a low grade NMIBC

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Bladder Cancer

Discussion Questions

What is the epidemiology & the most common presentation of bladder cancer?

What are the important prognostic factors for bladder cancer?

What is the treatment & appropriate follow up of bladder cancer?

What is the mortality from bladder cancer?

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Bladder Cancer

Statistics

Estimated new cases in 2015: 74,000 [SEER]
Estimated deaths in 2015: 16,000 [SEER]
Percentage surviving 5 years: 77.4% [SEER]
Male: Female 3:1
Median age at diagnosis: 69 [M], 71 [F]

- Onset younger in current smokers than never-smokers by 6 years

~75% present as NMIBC, 20% muscle invasive, 5% metastatic

- Of NMIBC, 60% Ta, 30% T1, 10% Tis

In the U.S. & Europe 90% are urothelial carcinoma; SCC (~5%), adenocarcinoma (~2%); small cell carcinoma, mixed histology & metastatic cancers make up the remaining 3%

- SCC comprises ~50 – 75%% of histology of schistosomal related BC

Urothelial carcinoma: 90% originate in bladder, 8% in renal pelvis, 2% in ureter and urethra

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Bladder Cancer

Signs & Symptoms

Bladder cancer is usually symptomatic

"The discovery of incidental bladder cancer at autopsies is virtually non-existent."

From page 258 in: Sexton, WJ et al, "Bladder Cancer: A Review of Non-Muscle Invasive Disease", Cancer Control October 2010, Vol 17, No 4, Pgs 256-268

Most common presentation

- ~75% present with painless hematuria (gross or microscopic); can be intermittent
- 25% will have irritative voiding symptoms (frequency, urgency, dysuria)
  - May signify trigone involvement or CIS

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Bladder Cancer

Discussion Questions

What is the epidemiology & the most common presentation of bladder cancer?

What are the important prognostic factors for bladder cancer?

What is the treatment & appropriate follow up of bladder cancer?

What is the mortality of bladder cancer?

TNM staging system for bladder cancer

Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Ta	Noninvasive papillary carcinoma		
Tis	Carcinoma in situ: "flat tumor"		
T1	Tumor invades subepithelial connective tissue		
T2	Tumor invades muscularis propria		
pT2a	Tumor invades superficial muscularis propria (inner half)		
pT2b	Tumor invades deep muscularis propria (outer half)		
T3	Tumor invades perivesical tissue		
pT3a	Microscopically		
pT3b	Macroscopically (extravesical mass)		
T4	Tumor invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall		
T4a	Tumor invades prostatic stroma, uterus, vagina		
T4b	Tumor invades pelvic wall, abdominal wall		
Regional lymph nodes (N)*			
NX	Lymph nodes cannot be assessed		
N0	No lymph node metastasis		
N1	Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)		
N2	Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node metastasis)		
N3	Lymph node metastasis to the common iliac lymph nodes		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic stage/prognostic groups			
Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a	N0	M0
	T2b	N0	M0
Stage III	T3a	N0	M0
	T3b	N0	M0
	T4a	N0	M0
Stage IV	T4b	N0	M0
	Any T	N1-3	M0
	Any T	Any N	M1

Note: cTNM is the clinical classification, pTNM is the pathologic classification.

* Regional lymph nodes include both primary and secondary drainage regions. All other nodes above the aortic bifurcation are considered distant lymph nodes.

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer New York, Inc.

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Lotan Y, Choueiri TK. Clinical presentation, diagnosis, and staging of bladder cancer. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2014.
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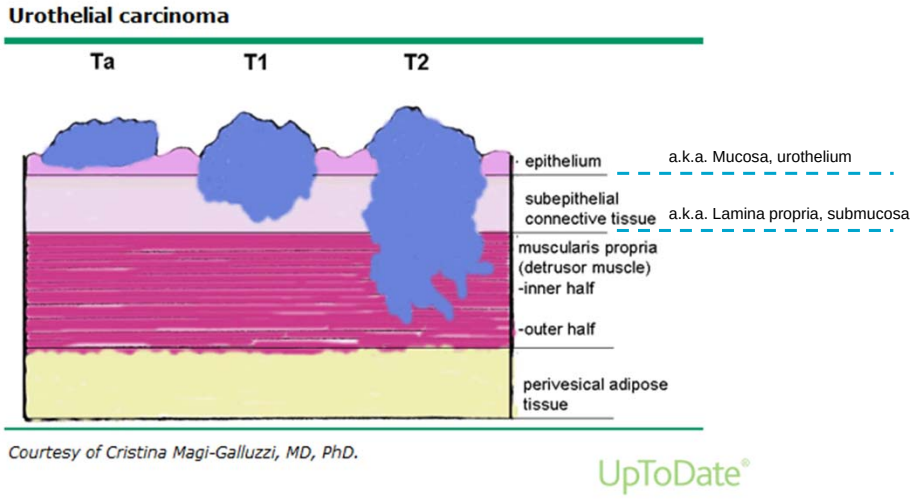
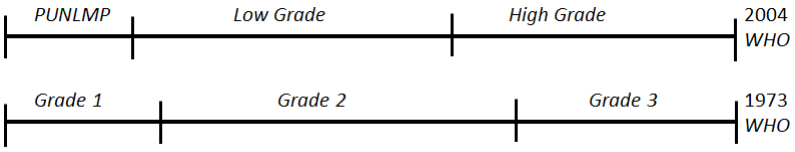


Magi-Galluzzi C, Zhou M.. Pathology of bladder neoplasms. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2015.

Urothelium, basement membrane and lamina propria are known collectively as the mucous membrane

Comparison of Grading Classification Systems for Papillary Neoplasms

Comparison of Neoplasm Grading Systems	
World Health Organization 1973	**WHO/ISUP 1998 Concensus; 2004 WHO**
Papilloma	Papilloma
TCC (Transitional Cell Carcinoma) Grade 1	Papillary Urothelial Neoplasm of Low Malignant Potential
TCC (Transitional Cell Carcinoma) Grade 1	Urothelial Carcinoma, Low-Grade
TCC (Transitional Cell Carcinoma) Grade 2	Urothelial Carcinoma, Low-Grade or High-Grade
TCC (Transitional Cell Carcinoma) Grade 3	Urothelial Carcinoma, High-Grade



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Bladder Cancer Risk Stratification (EUA)

Risk Group Stratification	Characteristics
Low risk tumors	Primary, solitary, Ta, G1*, < 3 cm, no CIS
Intermediate risk tumors	All tumors in between the category of low- and high-risk
High risk tumors	Any of the following: • T1 tumor • G3* (HG) tumor • CIS • Multiple and recurrent and large (> 3 cm) TaG1G2 tumors (all conditions must be presented in this point)

* See slide: Grading Systems

Babjuk M, Böhle A, et al. Guidelines on Non-muscle -invasive Bladder Cancer (Ta, T1 and Cis), European Association of Urology 2015, pg. 16

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Non-Muscle Invasive Bladder Cancer

Carcinoma in Situ (CIS a.k.a. TIS) ☹

Carcinoma in situ

- Flat, high grade, non-invasive urothelial carcinoma; comprises 10% of all cases of bladder cancer
- Can be missed at cystoscopy or considered an inflammatory lesion if not biopsied
- 50% of the time is multifocal; 20 – 30% is an isolated lesion (primary)
- Can occur in the bladder, upper tracts, prostatic ducts, prostatic urethra
- Without treatment, 54% will progress to muscle invasive disease

Classification of CIS into clinical type

- Primary: isolated CIS w/no previous or concurrent papillary tumors and no prior CIS
- Secondary: CIS detected at follow up on individuals w/a previous tumor that was not CIS
- Concurrent: CIS detected in the presence of any other urothelial tumor in the bladder

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Case # 2: 55 year old male with microscopic hematuria; applying for $500,000 permanent life 10/2015

The APS from the urologist at the time of underwriting

DATE OF ADMISSION: 7/15/2013

HISTORY OF PRESENT ILLNESS
This is a [redacted] male who is admitted to [redacted] Hospital for transurethral resection of recurrent transitional cell carcinoma of the bladder. This gentleman's first transitional carcinoma was resected on 4/15/2013, low grade, noninvasive but somewhat bulky tumor involving the anterior wall of the bladder near the bladder neck and prostate junction. Biopsy of the base of this tumor was negative for muscular invasion.

The patient has done well postoperatively and on his routine post three month bladder tumor checkup, he was found to have a residual tumor at the site of the previous tumor. He is then brought in for resection of this lesion.

(Please refer to previous record for details).

APS does not contain the diagnostic cystoscopy nor the pathology from 4/2013.

What category of risk does this tumor fall into?

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Case # 2: 55 year old male with microscopic hematuria

Pathology results from the July 2013 cystoscopy & TURBT

1. Urinary bladder, biopsy, mid trigone
   - Benign urinary mucosa showing chronic inflammation
2. Urinary bladder, biopsy, left wall
   - Papillary transitional cell carcinoma, grade ¾
   - No definitive lamina propria invasion is identified
   - No muscularis propria present in this specimen
3. Urinary bladder, biopsy, left base (same result as #2)
4. Urinary bladder, biopsy, anterior neck (same result as #2)
5. Urinary bladder, biopsy, base of anterior neck
   - Papillary transitional cell carcinoma, grade ¾
   - Focal areas suspicious for lamina propria invasion
   - No muscularis propria present in this specimen

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Case # 2: 55 year old male with NMIBC

Recurrence vs. Progression

The urologist called the 7/2013 episode his 1st "recurrent" tumor and treated him with BCG.

What is the definition of recurrence vs. progression?

Recurrence: tumor of same grade, type, either at same site or other
Progression: More advanced tumor, higher grade/depth

Bladder cancer has the highest recurrence rate of any malignancy. Unlike some cancers, recurrence does not translate into mortality for many.

Did this man have recurrence or progression or ?

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Case # 2: 55 year old male with NMIBC

What followed……..

The urologist called the 7/2013 episode his 1st "recurrent" tumor and treated him with BCG

1/2014 cysto "negative", doing well

5/2014 cysto: tumor implant on dome of the middle lobe of the prostate, tumor implant on the middle trigone, tumor extruding from the left ureteral orifice, tumor around the left ureteral orifice, area of velvety redness on left bladder wall (the tumors were fulgurated; "one was resected as an example")

- Left wall : noninvasive papillary transitional cell carcinoma, grade II/IV
- Right lateral wall: noninvasive papillary transitional cell carcinoma, grade II/IV
- Left ureter, orifice tumor – In situ high grade transitional cell carcinoma (flat lesion), grade III of III; no evidence of invasion into submucosal tissue or muscularis, but suggest clinical correlation

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Bladder Cancer

Discussion Questions

Are there tools to predict recurrence and progression of bladder cancer?

Table 6.1: Weighting used to calculate disease recurrence and progression scores

Factor	Recurrence	Progression
Number of tumours		
Single	0	0
2-7	3	3
≥ 8	6	3
Tumour diameter		
< 3 cm	0	0
≥ 3	3	3
Prior recurrence rate		
Primary	0	0
≤ 1 recurrence/year	2	2
> 1 recurrence/year	4	2
Category		
Ta	0	0
T1	1	4
Concurrent CIS		
No	0	0
Yes	1	6
Grade		
G1	0	0
G2	1	0
G3	2	5
Total Score	**0-17**	**0-23**

Table 6.2: Probability of recurrence and disease progression according to total score

Recurrence score	Probability of recurrence at 1 year		Probability of recurrence at 5 years	
	%	(95% CI)	%	(95% CI)
0	15	(10-19)	31	(24-37)
1-4	24	(21-26)	46	(42-49)
5-9	38	(35-41)	62	(58-65)
10-17	61	(55-67)	78	(73-84)

Progression score	Probability of progression at 1 year		Probability of progression at 5 years	
	%	(95% CI)	%	(95% CI)
0	0.2	(0-0.7)	0.8	(0-1.7)
2-6	1	(0.4-1.6)	6	(5-8)
7-13	5	(4-7)	17	(14-20)
14-23	17	(10-24)	45	(35-55)

NB: Electronic calculators for Tables 6.1 and 6.2, which have been updated for the iPhone, iPad and Android phones and tablets, are available at http://www.eortc.be/tools/bladdercalculator/.

EORTC Risk Tables

Babjuk M, Böhle A, et al. Guidelines on Non-muscle -invasive Bladder Cancer (Ta, T1 and Cis), European Association of Urology 2015, pg. 15

Bladder Cancer

Discussion Questions

What is the epidemiology & the most common presentation of bladder cancer?

What are the important prognostic factors for bladder cancer?

What is the treatment & appropriate follow up of bladder cancer?

What is the mortality of bladder cancer?

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Bladder Cancer Treatment

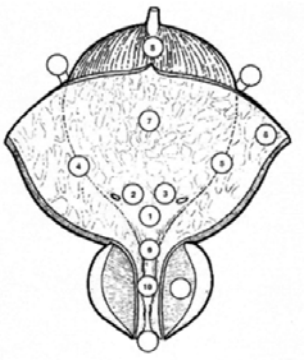
TURBT: initial step, is diagnostic, therapeutic and used in risk stratification

Configuration (flat, sessile, papillary), location (trigone, base, dome, lateral walls), size (cm), and number of tumors should be noted

Muscularis propria should be included except for superficial low-grade appearing tumors

Directed biopsies of abnormal appearing urothelium or prostatic urethra may be done

Before and following tumor resection, examination under anesthesia is performed



1 = Trigone
2 = Right ureteral orifice
3 = Left ureteral orifice
4 = Right wall
5 = Left wall
6 = Anterior wall
7 = Posterior wall
8 = Dome
9 = Neck
10 = Posterior urethra

Babjuk M, Böhle A, et al. Guidelines on Non-muscle -invasive Bladder Cancer (Ta, T1 and Cis), European Association of Urology 2015, pg. 11

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Non-Muscle Invasive Bladder Cancer

Management

Initial management depends on

- Stage & grade of urothelial tumor
- Presence or absence of CIS
- Health of the individual

Treatment will involve TURBT and *may* involve:

- Re-resection of tumor depending on T-stage, grade, and *adequacy of initial specimen*
- Intra-vesical chemotherapy
  - Single dose (e.g. Mitomycin-C) after TURBT
  - Induction therapy
  - Maintenance therapy
- Intra-vesical immunotherapy with BCG
  - Induction therapy
  - Maintenance therapy
- Cystectomy

Followed by regular cystoscopic & cytologic surveillance for recurrent disease; +/- periodic upper tract imaging

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Non-Muscle Invasive Bladder Cancer: Treatment

Table 7.3: Treatment recommendations in Ta, T1 tumours and CIS according to risk stratification

Risk category	Definition	Treatment recommendation
Low-risk tumours	Primary, solitary, Ta, LG/G1,< 3 cm, no CIS	One immediate instillation of chemotherapy.
Intermediate-risk tumours	All cases between categories of low and high risk	One immediate instillation of chemotherapy followed by further instillations, either chemotherapy for a maximum of 1 year or 1-year full-dose BCG.
High-risk tumours	Any of the following: • T1 tumours; • HG/G3 tumours; • CIS; • Multiple and recurrent and large (> 3 cm) Ta G1G2 tumours (all these conditions must be present).	Intravesical full-dose BCG instillations for 1-3 years or cystectomy (in highest-risk tumours).
Subgroup of highest-risk tumours	T1G3 associated with concurrent bladder CIS, multiple and/or large T1G3 and/or recurrent T1G3, T1G3 with CIS in prostatic urethra, unusual histology of urothelial carcinoma, LVI (see Sections 4.6 and 6.2).	Radical cystectomy should be considered in those who refuse RC, intravesical full-dose BCG instillations for 1-3 years.
	BCG failures	Radical cystectomy is recommended.

BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; GR = grade of recommendation; HG = high-grade; LG = low-grade; LVI = lymphovascular invasion.

Babjuk M, Böhle A, et al. Guidelines on Non-muscle -invasive Bladder Cancer (Ta, T1 and Cis), European Association of Urology 2015, pg. 25

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Bladder Cancer Treatment

Re-Staging TURBT

Second TURBT is recommended for

- Incomplete initial TURBT
- No muscle in specimen from 1st TURBT with the exception of TaG1 tumors and primary CIS
- All T1 tumors
- All G3 tumors, except primary CIS

Persistent disease found at re-staging TURBT

- T1 tumors: 33 – 55%
- TaG3 tumors: 41.4%

Upstaging to muscle invasive disease

- Muscle-invasive disease found in cT1 tumors ranges from 4 – 25%
  - *If no muscle on initial resection of cT1, muscle invasive disease found in 45%*

Babjuk M, Böhle A, et al. Guidelines on Non-muscle -invasive Bladder Cancer (Ta, T1 and Cis), European Association of Urology 2015,

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Non-Muscle Invasive Bladder Cancer

Follow up depends on initial stage & grade

NCCN 2015 Guidelines:

- Low grade cTa: cystoscopy q 3 months, increasing interval as appropriate
- High grade cTa, low grade cT1, high grade cT1: cystoscopy and urine cytology q 3-6 months x 2 years, then increasing intervals as appropriate; consider imaging of upper tracts collecting system q 1- 2 years for high grade tumors; urinary urothelial tumor markers optional

European Association of Urology 2015 Guidelines:

- Cystoscopy at 3 months for all Ta, T1 tumors and CIS
- For low risk tumors with negative 3month cystoscopy, repeat cystoscopy at 9 months, then annual for 5 years
- High risk tumors: cystoscopy & urine cytology every 3 months x 2 years, then q 6 months to 5 years, then yearly for life
- Yearly upper tract imaging for high risk tumors

In what circumstances is fulguration of bladder tumors acceptable?

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Non-Muscle Invasive Bladder Cancer

Urine Cytology & Biomarkers

Urine cytology: exfoliated urothelial cells, collected via voided specimen or barbotage (bladder washing)

- Very dependent on pathologist's expertise
- Good at detecting CIS but can miss low grade papillary tumors
- Overall sensitivity ~30%, overall specificity ~ 95%

Biomarkers: NMP22, NMP22 BladderChek (POC), BTA Stat (POC), BTA TRAK, Immunocyt, UroVysion (FISH), Microsatellite analysis

- Sensitivity & specificity depends on the clinical context when used (screening, primary detection, follow up [high-risk or low/intermediate risk])
- None of these tests can replace cystoscopy

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Bladder Cancer

What is the mortality from bladder cancer?

NMIBC:

- Low risk disease: mortality rates are non-existent
- High risk disease approaches mortality rates of 30% at 10 years
- The risk in NMIBC is progression of disease

Muscle invasive bladder cancer (MIBC):

- Five year survival after radical cystectomy alone is 66% for pT2, 35% for pT3 and 27% for pT4
- Neoadjuvant cisplatin based combination chemotherapy may improve survival

Metastatic urothelial carcinoma:

- Five year survival ~5% (SEER)

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Case #3: 60 year old male for $1.5 million permanent life insurance

CT scan done for abdominal pain one year prior to applying for life insurance.

MDCT w/w/o contrast showed a 13 mm enhancing lesion, concerning for renal neoplasm in the posterior right upper renal pole. There was no evidence for vascular invasion, no other suspicious findings.

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The Incidental Renal Mass

SRMs – Small Renal Masses

Incidental SRMs

- May be cystic, solid, or a combination
- May represent a cyst, a tumor or a "pseudotumor"
- Most incidental SRMs are benign renal cysts

Definition of a solid renal mass: A mass with little or no fluid components; consists predominantly of enhancing soft tissue

- Enhancement of 20 HU – definitive enhancement
- 10 to 19 HU – equivocal for enhancement
- < 10 HU – no enhancement

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Bosniak Classification of Cystic Renal Masses by CT Scan

Bosniak Classification	Findings
Category I Simple benign cyst	Hairline thin wall Density < 20 Hounsfield units [similar to water] No septa, calcification , or solid components Does not enhance
Category II Cystic lesion	A few hairline septa "Perceived" enhancement may be present, but no measurable enhancement Uniformly high attenuation lesions < 3 cm , well-marginated and w/o enhancement
Category IIF Minimally complicated cysts [tend to be well-marginated]	Multiple hairline thin septa or minimal smooth thickening of the wall or septa "Perceived" enhancement of septa or wall may be present Thick & nodular calcification of wall or septa, but no measurable contrast enhancement
Category III Indeterminate cystic lesion	Thickened irregular or smooth walls or septa in which measureable enhancement is present
Category IV Mostly malignant	All category III criteria Enhancing soft-tissue components adjacent to, but independent of, the wall or septum

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Bosniak Classification

What is the appropriate type of follow up for a Bosniak IIF lesion & why?

- Imaging with and without contrast is necessary because morphologic characteristics and enhancement of the mass is needed
  - Development of septa, wall thickening or new areas of enhancement suggest malignancy
- CT or MRI at 6 & 12 months followed by yearly for 5 years
  - If a Bosniak IIF lesion has not changed morphologically in 5 years, it is likely benign

Why isn't growth of a lesion part of the Bosniak Classification?

- Simple cysts may grow & renal cell carcinomas may not

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The Incidental Renal Mass

SRMs – Small Renal Masses

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- Most incidental SRMs are benign renal cysts

Definition of a solid renal mass: A mass with little or no fluid components; consists predominantly of enhancing soft tissue

- Enhancement of 20 HU – definitive enhancement
- 10 to 19 HU – equivocal for enhancement
- < 10 HU – no enhancement

Most solid renal neoplasms in adults are renal cell carcinoma

What type of lesion does this applicant have?
What is the risk of malignancy?

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Solid Renal Mass Size & Presence of Malignancy

2,770 adults who underwent radical nephrectomy or nephron sparing surgery for sporadic unilateral non-metastatic solid renal tumors between 1970 – 2000

- 2935 tumors
- 376 (12.8%) benign
  - Mean tumor size 4.2 cm (median 3.3, range 0.2 – 25.0)
- 2559 (87.2%) malignant
  - Mean tumor size 6.3 cm (median 5.5, range 0.1 – 24.0)

Proportion of Benign vs. RCC Tumors According to Tumor Size		
Tumor Size (cm)	Number Benign (%)	Number RCC (%)
0.0 - < 1.0	37 (46.3)	43 (53.8)
1.0 - < 2.0	38 (22.4)	132 (77.7)
2.0 - < 3.0	75 (22.0)	266 (78.0)
3.0 - < 4.0	71 (19.9)	285 (80.1)
4.0 - < 5.0	37 (9.9)	336 (90.1)
5.0 - < 6.0	40 (13.0)	267 (87.0)
6.0 - < 7.0	11 (4.5)	232 (95.5)
7.0 or greater	67 (6.3)	998 (93.7)

Frank I, Blute M et al. Solid renal tumors: an analysis of pathological features related to tumor size. J Urol. 2003 Dec;170(6 Pt 1):2217-20.

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Renal Cell Carcinoma

Discussion Questions

What is the epidemiology & the most common presentation of RCC?

What are the important prognostic factors & mortality of RCC?

What is the treatment & appropriate follow up of RCC?

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Renal Cell Carcinoma

What is the epidemiology & the most common presentation of RCC?

Most common primary renal neoplasm (~85%)

- 62,000 new cases each year; 14,000 deaths each year

Male : Female 1.5 : 1

Occurs most often in the 6th to 8th decade of life

- Median age at diagnosis 64

Risk factors for development: HTN, obesity, tobacco; heritable conditions [like von Hippel Lindau]

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Renal Cell Carcinoma

What is the epidemiology & the most common presentation of RCC?

More than 50% of RCC are detected incidentally on imaging done for other reasons; shift of presentation to asymptomatic, early stage organ confined disease with a better prognosis.

- Less than 10% of RCC cases present with the classic triad of hematuria, flank or abdominal pain, palpable mass.
- Localized disease 62%; regional (spread to regional LN) 17%; Metastatic 17%; (remainder unstaged)

Increasing annual incidence of RCC by 3% to 4% has occurred since the 1970s; largest increase is in small tumors < 4 cm.

- Mean size at presentation is 3.6 cm

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Case #3: 60 year old male for $1.5 million permanent life insurance

Surgical pathology: what stage is this?

DIAGNOSIS:

1. Kidney, right partial nephrectomy (A-H):
Papillary renal cell carcinoma with clear cell features; by immunohistochemistry, the tumor cells are positive for CK-7, CA-9 and Pax-2 and negative for P504S, supporting the diagnosis. See synoptic report.
2. Right perinephric fat over tumor (I):
Fibroadipose tissue, unremarkable.

Kidney: Nephrectomy, Partial or Radical Synopsis
Staging according to American Joint Committee on Cancer Staging Manual -- 7th Edition, 2009

MACROSCOPIC

Procedure: Partial nephrectomy.

Specimen Laterality: Right.

Tumor Focality: Unifocal.

Tumor Size: Greatest dimension: 1.6 cm. Additional dimensions: 1.5 cm x 1.2 cm.

Macroscopic Extent of Tumor:
Tumor limited to kidney.

MICROSCOPIC

Histologic Type: Papillary renal cell carcinoma, clear cell type.

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TNM staging system for kidney cancer

Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1	Tumor 7 cm or less in greatest dimension, limited to the kidney		
T1a	Tumor 4 cm or less in greatest dimension, limited to the kidney		
T1b	Tumor more than 4 cm but not more than 7 cm in greatest dimension, and limited to the kidney		
T2	Tumor more than 7 cm in greatest dimension, limited to the kidney		
T2a	Tumor more than 7 cm but less than or equal to 10 cm in greatest dimension, limited to the kidney		
T2b	Tumor more than 10 cm, limited to the kidney		
T3	Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota's fascia		
T3a	Tumor grossly extends into the renal vein or its segmental (muscle containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond Gerota's fascia		
T3b	Tumor grossly extends into the vena cava below the diaphragm		
T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava		
T4	Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in regional lymph node(s)		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic stage/prognostic groups			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1 or T2	N1	M0
	T3	N0 or N1	M0
Stage IV	T4	Any N	M0
	Any T	Any N	M1

Note: cTNM is the clinical classification, pTNM is the pathologic classification.

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Atkins, MB. Clinical manifestations, evaluation, and staging of renal cell carcinoma. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2015.
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Renal Cell Carcinoma

Discussion Questions

What is the epidemiology & the most common presentation of RCC?

What are the important prognostic factors & mortality of RCC?

What is the treatment & appropriate follow up of RCC?

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Renal Cell Carcinoma

What are the important prognostic factors & mortality of RCC?

Prognostic Factors:

- Stage
- Fuhrman Grade I to IV: Higher grade associated with larger tumor size and advanced stage
  - Correlates to tumor size, stage and metastasis in *clear cell* RCC
  - Questioned role in papillary & chromophobe RCC
    - Papillary: Type I and Type II
    - Chromophobe: High vs. Low grade
- Microscopic coagulative necrosis
- Microvascular invasion
- Sarcomatoid features
- Invasion of the collecting system

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Prognostic Indicator: Histologic Subtypes of RCC

RCC is a very heterogeneous malignancy

Table 1
WHO 2004 classification: RCC type versus proportion of cases and generalizations on outcome to date

RCC Subtype	Proportion (%)	Outcome vs Clear Cell RCC
Clear cell RCC	80	—
Papillary RCC	10	Favorable
Chromophobe RCC	5	Favorable
Collecting duct	1	Unfavorable
RCC, unclassified	4–6	Unfavorable
Multilocular clear cell RCC	Exact proportion undetermined but rare tumors likely to account for <2% of tumors overall	Low malignant potential
Renal medullary carcinoma		Highly aggressive
Xp11 translocation carcinoma		Undetermined
Carcinoma associated with neuroblastoma		Similar to clear cell RCC
Mucinous tubular and spindle cell carcinoma		Favorable with exception

Deng FM, Melamed J. Histologic Variants of Renal Cell Carcinoma: Does Tumor Type Influence Outcome? Urol Clin N Am 39(2012) 129

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What is the mortality of RCC?

Mortality:

- Stage I : Five year survival > 90%
- Stage II: Five year survival 75 - 95%
- Stage I or II RCC with invasion into collecting system:
  - Ten year survival 43%, 41 % respectively
- Stage III: Five year survival 59% - 70%
  - Invasion into collecting system, five year survival 30%
- Stage IV: Five year survival ~ 11%

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Renal Cell Carcinoma

Discussion Questions

What is the epidemiology & the most common presentation of RCC?

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Treatment of Localized Renal Cell Carcinoma

Localized = Stage I, II, III; Advanced or mRCC = Stage IV

Definitive surgery:

- Radical nephrectomy [RN], open or laparoscopic
  - ORN vs. LRN with similar oncologic outcomes at 5 year CSS [91% vs. 93%], recurrence free survival at 5 years [91% vs. 93%] and incidence of renal insufficiency [4%]
- Partial nephrectomy or nephron sparing surgery, open or laparoscopic
  - May be appropriate for tumors < 7 cm
- RN vs. PN for disease limited to the kidney [T1 or T2]
  - Similar 10 year progression rates 3% RN vs. 4.5% PN

Clinically negative nodes by imaging

- Low likelihood of nodal involvement

Ablative procedures such as RFA, cryoablation or active surveillance of small tumors [< 4 cm]

- Primarily for those with limited life span or significant co-morbidities

Chemotherapy has no role in localized RCC

- Adjuvant therapy with immunotherapy – no survival benefit
- Molecularly targeted therapy – still under investigation

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Treatment of Localized Renal Cell Carcinoma

Localized = Stage I, II, III; Advanced or mRCC = Stage IV

Recurrence or metastasis develops in 10-28% of those who have had surgery for localized dz

- Even after 5 years, the recurrence rate is 15-19%

RCC is unique amongst solid tumors: removal of the primary tumor is an essential component of the treatment of mRCC

- The primary tumor is believed to have an immunosuppressive effect

Five year survival for those with *distant* mRCC is ~10%

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Renal Cell Carcinoma

Surveillance After Definitive Surgical Treatment for Localized Disease

Greatest risk of recurrence is within years 3 to 5.

- T1: recurrence rate is < 10%
- T2: recurrence rate is 16 – 26%
- T3: risk of metastatic disease 33 – 43% at 5 years

However…..late recurrence & metastasis occur:

- 1454 patients, nephrectomy for localized RCC between 1970 and 2000 who were disease free for 5 years, the rates of recurrence and metastatic disease in the ensuing 10 years :
  - Renal recurrence ~5%
  - Metastatic disease ~15%

Sites of metastatic disease

- Lung, bone, liver, renal fossa, brain
- Clear cell tumors – lung; chromophobe tumors -- liver

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Renal Cell Carcinoma

Surveillance After Definitive Surgical Treatment for Localized Disease

Multiple protocols, none universally agreed upon

Some based on primary tumor (T stage), some based upon histologic type, some integrated protocols

- AUA 2013 Guidelines for clinically localized renal neoplasms are based upon “Low risk” (pT1, N0, Nx) vs. “Moderate to High Risk” (pT2-4N0 Nx or any stage N+)
- NCCN Guidelines based upon stage
  - TNM I & II: H&P, Labs, CXR at 6 & 12 months, then annually through 7th year; abdominal CT at 6 months
  - TMN III: H&P, Labs, CXR q 4 months through year 2, then q 6 months through 4th year, then q year through 6th year; abdominal CT at 4 & 12 months, at 2 & 3 years, then annually from 4th through 6 year
- UISS (UCLA Integrated Staging System) Guidelines based upon stage, histologic grade & ECOG performance status

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The End

Thank You!

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