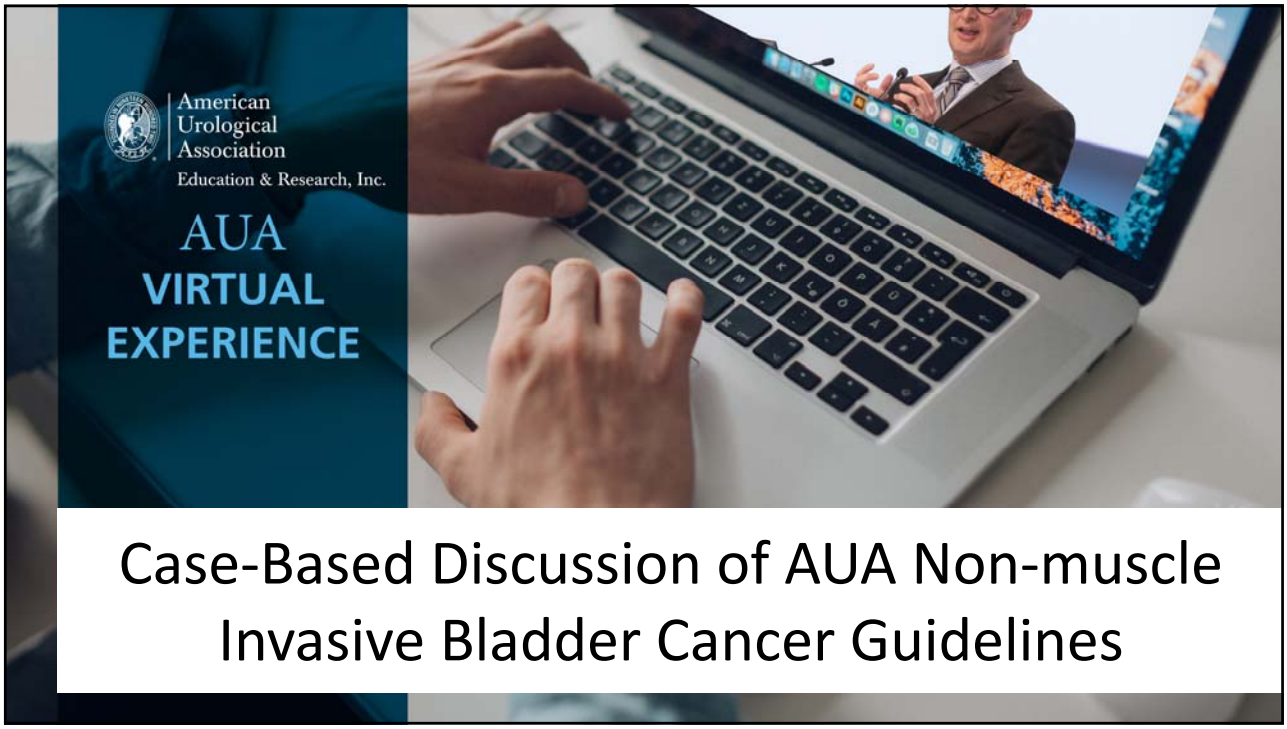

Case-Based Discussion of AUA Non-muscle Invasive Bladder Cancer Guidelines

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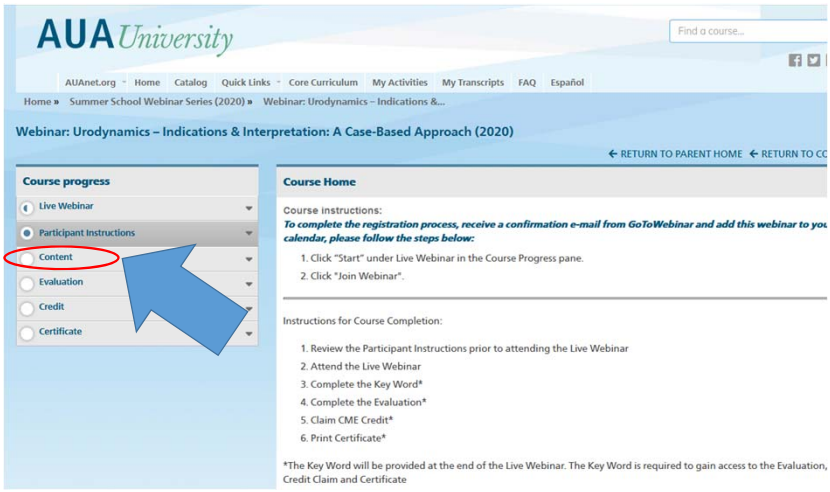

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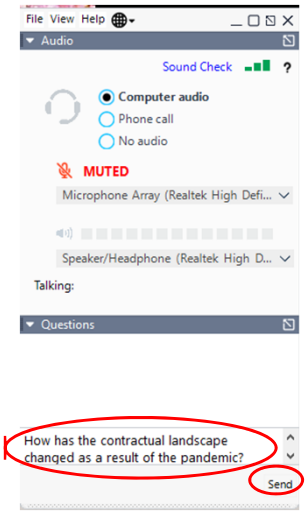

Submit Questions for
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DISCLOSURES

Please visit AUA University to view disclosures for all course faculty.

Learning Objectives

At the end of this activity, participants will be able to:

1. Describe the evaluation and appropriate surveillance of patients with bladder cancer.
2. Determine the clinical risk of patients and apply appropriate therapeutic interventions.
3. Formulate multidisciplinary options for patients with invasive cancer.
4. Apply evidence-based and guidelines-based actions to complex clinical scenarios.

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COURSE LEARNING OBJECTIVES

Following this course, participants will gain a greater understanding of the appropriate diagnosis and treatment of non-muscle invasive bladder cancer (NMIBC) and gain a greater understanding of the current literature base supporting best practices in the care of such patients.

COURSE OUTLINE

Purpose
Guideline Methodology
Background
- Epidemiology, Etiology, Presentation & Diagnosis, Staging & Grading, Prognosis, Risk Stratification

Guideline Statements
Future Directions
Treatment Algorithms
Case Studies

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PURPOSE

The survival rate for the majority of patients with NMIBC is favorable; however, the rates of recurrence and progression to muscle-invasive bladder cancer (MIBC) are major determinants of long-term outcome. The recurrence and progression probability rates depend on several clinical and pathologic factors.

Therefore, the ability to predict risk of recurrence and progression and treat the disease appropriately is important. This guideline provides a risk-stratified clinical framework for the management of NMIBC.

STAGING & GRADING

Staging of primary tumors (T) in bladder cancer	
TX	Primary tumor cannot be assessed
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma in situ (CIS)
T1	Tumor invades lamina propria
T2	Tumor invades muscularis propria
T2a	Tumor invades superficial muscularis propria (inner half)
T2b	Tumor invades deep muscularis propria (outer half)
T3	Tumor invades perivesical tissue/fat
T3a	Tumor invades perivesical tissue/fat microscopically
T3b	Tumor invades perivesical tissue fat macroscopically (extravesical mass)
T4	Tumor invades prostate, uterus, vagina, pelvic wall, or abdominal wall
T4a	Tumor invades adjacent organs (uterus, ovaries, prostate stoma)
T4b	Tumor invades pelvic wall and/or abdominal wall

Staging for bladder cancer is separated into clinical and pathologic stage, as outlined by the American Joint Committee on Cancer (AJCC), also known as the Tumor-Node-Metastases (TNM) classification. Clinical stage reflects the histologic findings at TURBT; the clinician's physical exam, including bimanual exam under anesthesia; and findings on radiologic imaging.

Edge 2010

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STAGING & GRADING

Tumor grade is an important prognostic factor for determining risk of recurrence and progression in bladder cancer.
The WHO/ISUP 2004 grading system is now the most widely accepted and utilized system in the United States.

2004 World Health Organization/ International Society of Urologic Pathologists: Classification of Non-muscle Invasive Urothelial Neoplasia
Hyperplasia (flat and papillary)
Reactive atypia
Atypia of unknown significance
Urothelial dysplasia
Urothelial CIS
Urothelial papilloma
Papillary urothelial neoplasm of low malignant potential
Non-muscle invasive low-grade papillary urothelial carcinoma
Non-muscle invasive high-grade papillary urothelial carcinoma

Eble 2004

RISK STRATIFICATION

EORTC

- Based on combined data from seven NMIBC trials
- Probability of recurrence/progression at 1&5 years
- Utilizes 1973 WHO Grading System
- Updated to include BCG patients
- Recurrence
- Prior recurrence rate, number of tumors, tumor size
- Progression
  - T-stage, presence of CIS, grade
- C-Index
  - Recurrence: 0.66; Progression: 0.75

CUETO

- Developed by the Spanish Urological Club for Oncological Treatment
- C-Index
  - Recurrence: 0.64; Progression: 0.7

Both tools are limited by lack of applicability to current patient populations because few patients from the development cohort received BCG maintenance, underwent re-staging TURBT, or received single-dose post-operative MMC.

Sylvester 2006; Fernandez-Gomez 2009; Cambier 2016; Ohman 2000; Fernandez-Gomez 2011; Altieri 2012, Rosevear 2011; Hernandez 2011; Vedder 2014; Xylinas 2013

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AUA RISK STRATIFICATION SYSTEM

Low Risk	Intermediate Risk	High Risk
LG[a] solitary Ta ≤ 3cm	Recurrence within 1 year, LG Ta	HG T1
PUNLMP[b]	Solitary LG Ta > 3cm	Any recurrent, HG Ta
	LG Ta, multifocal	HG Ta, >3cm (or multifocal)
	HG[c] Ta, ≤ 3cm	Any CIS[d]
	LG T1	Any BCG failure in HG patient
		Any variant histology
		Any LVI[e]
		Any HG prostatic urethral involvement

[a]LG = low grade; [b]PUNLMP = papillary urothelial neoplasm of low malignant potential; [c]HG = high grade; [d]CIS=carcinoma *in situ*; [e]LVI = lymphovascular invasion

GUIDELINE STATEMENTS: DIAGNOSIS

1. **At the time of resection of suspected bladder cancer, a clinician should perform a thorough cystoscopic examination of a patient's entire urethra and bladder that evaluates and documents tumor size, location, configuration, number, and mucosal abnormalities. (Clinical Principle)**

2. **At initial diagnosis of a patient with bladder cancer, a clinician should perform complete visual resection of the bladder tumor(s), when technically feasible. (Clinical Principle)**

   Incomplete TURBT is likely a significant contributing factor to early bladder cancer recurrences, as **tumors are seen at first surveillance cystoscopy in up to 45% of patients**

Brausi 2002

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GUIDELINE: DIAGNOSIS

3. **A clinician should perform upper urinary tract imaging as a component of the initial evaluation of a patient with bladder cancer. (Clinical Principle)**

4. **In a patient with a history of NMIBC with normal cystoscopy and positive cytology, a clinician should consider prostatic urethral biopsies and upper tract imaging, as well as enhanced cystoscopic techniques (blue light cystoscopy, when available), ureteroscopy, or random bladder biopsies. (Expert Opinion)**

GUIDELINE: RISK STRATIFICATION

5. At the time of each occurrence/recurrence, a clinician should assign a clinical stage and classify a patient accordingly as "low-," "intermediate-," or "high-risk." (Moderate Recommendation; Evidence Strength: Grade C)

EORTC/CUETO Model → Tumor size, tumor focality, grade, stage

AUA/SUO Additions → Lymphovascular invasion, prostatic urethral involvement, variant histology, unresponsive to BCG

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GUIDELINE: VARIANT HISTOLOGIES

6. An experienced genitourinary pathologist should review the pathology of a patient with any doubt in regard to variant or suspected variant histology (e.g., micropapillary, nested, plasmacytoid, neuroendocrine, sarcomatoid, etc), extensive squamous or glandular differentiation, or the presence/absence of lymphovascular invasion. (Moderate Recommendation; Evidence Strength: Grade C)

7. If a bladder sparing approach is being considered in a patient with variant histology, then a clinician should perform a restaging TURBT within four to six weeks of the initial TURBT. (Expert Opinion)

8. Due to the high rate of upstaging associated with variant histology, a clinician should consider offering initial radical cystectomy. (Expert Opinion)

GUIDELINE: URINE MARKERS

9. In surveillance of NMIBC, a clinician should not use urinary biomarkers in place of cystoscopic evaluation. (Strong Recommendation; Evidence Strength: Grade B)

Direct comparisons between markers are difficult, and given the uncertainty in sensitivity, these tests cannot be use to replace cystoscopy.

NMP22®	Protein-based; identifies nuclear matrix protein involved in the mitotic apparatus
BTA®	Protein-based; identifies a basement membrane antigen related to complement factor H
UroVysion® FISH	Cell-based; identifies altered copy numbers of specific chromosomes using fluorescent probes
ImmunoCyt™	Cell-based; identifies three cell surface glycoproteins
Cxbladder™	Cell-based; identifies the presence of five mRNA fragments

Tomasini 2013; O'Sullivan 2012

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GUIDELINE: URINE MARKERS

Marker	Sensitivity	Specificity	Pos. likelihood ratio (95% CI)	Neg. likelihood ratio (95% CI)
NMP22® quantitative			3.05 (2.28-4.10)	0.40 (0.32-0.50)
Overall	69%	77%		
Diagnosis	67%	84%		
Surveillance	61%	71%		
NMP22® qualitative			4.89 (3.23-7.40)	0.48 (0.33-0.71)
Overall	58%	88%		
Diagnosis	47%	93%		
Surveillance	70%	83%		
BTA® quantitative			2.52 (1.86-3.41)	0.47 (0.37-0.61)
Overall	65%	74%		
Diagnosis	76%	53%		
Surveillance	58%	79%		
BTA® qualitative			2.80 (2.31-3.39)	0.47 (0.30-0.55)
Overall	64%	77%		
Diagnosis	76%	71%		
Surveillance	60%	76%		
UroVysion® FISH			5.02 (2.93-8.60)	0.42 (0.30-0.59)
Overall	63%	87%		
Diagnosis	73%	95%		
Surveillance	55%	80%		
ImmunoCyt™			3.49 (2.82-4.32)	0.29 (0.20-0.41)
Overall	78%	78%		
Diagnosis	85%	83%		
Surveillance	75%	76%		
Cxbladder™	82%	85%	5.53 (4.28-7.15)	0.21 (0.13-0.36)

UPDATES COMING

Performance Characteristics of Commonly Used and FDA Approved Urinary Markers

Chou 2015

GUIDELINE: URINE MARKERS

10. In a patient with a history of low-risk cancer and a normal cystoscopy, a clinician should not routinely use a urinary biomarker or cytology during surveillance. (Expert Opinion)

11. In a patient with NMIBC, a clinician may use biomarkers to assess response to intravesical BCG (UroVysion® FISH) and adjudicate equivocal cytology (UroVysion® FISH and ImmunoCyt™). (Expert Opinion)

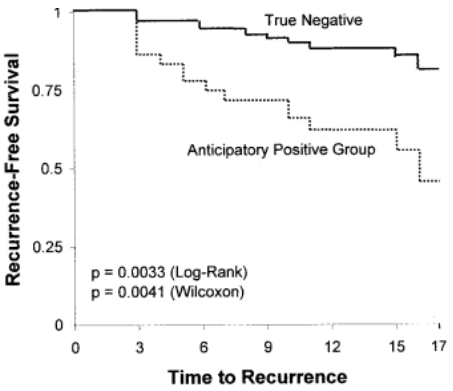

FIG. 3. Time to recurrence is significantly less (p = 0.014) for anticipatory positive cases (negative cystoscopy, positive FISH) versus negative cystoscopy, negative FISH cases.

Sarosdy 2002

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GUIDELINE: TURBT/REPEAT RESECTION

12. In a patient with non-muscle invasive disease who underwent an incomplete initial resection (not all visible tumor treated), a clinician should perform repeat transurethral resection or endoscopic treatment of all remaining tumor if technically feasible. (Strong Recommendation; Evidence Strength: Grade B)

13. In a patient with high-risk, high-grade Ta tumors, a clinician should consider performing repeat transurethral resection of the primary tumor site within six weeks of the initial TURBT. (Moderate Recommendation; Evidence Strength: Grade C)

14. In a patient with T1 disease, a clinician should perform repeat transurethral resection of the primary tumor site to include muscularis propria within six weeks of the initial TURBT. (Strong Recommendation; Evidence Strength: Grade B)

GUIDELINE: INTRAVESICAL THERAPY

15. In a patient with suspected or known low- or intermediate-risk bladder cancer, a clinician should consider administration of a single postoperative instillation of intravesical chemotherapy (e.g., mitomycin C or epirubicin) within 24 hours of TURBT. In a patient with a suspected perforation or extensive resection, a clinician should not use postoperative chemotherapy. (Moderate Recommendation; Evidence Strength: Grade B)

Sylvester 2004

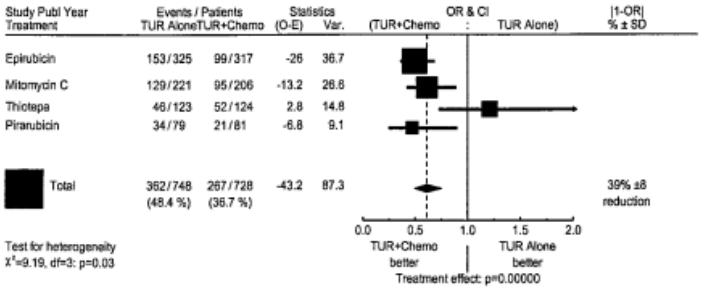

FIG. 2. Forest plot of recurrence by treatment

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GUIDELINE: INTRAVESICAL THERAPY

16. In a low-risk patient, a clinician should not administer induction intravesical therapy. (Moderate Recommendation; Strength of Evidence Grade C)

17. In an intermediate-risk patient a clinician should consider administration of a six week course of induction intravesical chemotherapy or immunotherapy. (Moderate Recommendation; Evidence Strength: Grade B)

18. In a high-risk patient with newly diagnosed CIS, high-grade T1, or high-risk Ta urothelial carcinoma, a clinician should administer a six-week induction course of BCG. (Strong Recommendation; Evidence Strength: Grade B)

GUIDELINE: INTRAVESICAL THERAPY

There is insufficient evidence to recommend one particular strain of BCG

- Several small studies suggest that different strains may have different efficacies

There is insufficient evidence to prescribe a particular strength of BCG

- EORTC 30962 recommends full dose for three years for high-risk patients
- For lower-risk patients, no difference in recurrence free survival between full or 1/3 dose at 1 or 3 years

There is insufficient evidence to recommend using BCG in combination with other intravesical agents

- Several ongoing trials are currently examining synergistic combinations

Rentsch 2014; Oddens 2013; Houghton 2013

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GUIDELINE: INTRAVESICAL THERAPY

19. In an intermediate-risk patient who completely responds to an induction course of intravesical chemotherapy, a clinician may utilize maintenance therapy. (Conditional Recommendation; Evidence Strength: Grade C)

20. In an intermediate-risk patient who completely responds to induction BCG, a clinician should consider maintenance BCG for one year, as tolerated. (Moderate Recommendation; Evidence Strength: Grade C)

21. In a high-risk patient who completely responds to induction BCG, a clinician should continue maintenance BCG for three years, as tolerated. (Moderate Recommendation; Evidence Strength: Grade B)

GUIDELINE: BCG RELAPSE & SALVAGE REGIMENS

22. In an intermediate- or high-risk patient with persistent or recurrent disease or positive cytology following intravesical therapy, a clinician should consider performing prostatic urethral biopsy and an upper tract evaluation prior to administration of additional intravesical therapy. (Conditional Recommendation; Evidence Strength: Grade C)

23. In an intermediate- or high-risk patient with persistent or recurrent Ta or CIS disease after a single course of induction intravesical BCG, a clinician should offer a second course of BCG. (Moderate Recommendation; Strength of Evidence C)

24. In a patient fit for surgery with high-grade T1 disease after a single course of induction intravesical BCG, a clinician should offer radical cystectomy. (Moderate Recommendation; Evidence Strength: Grade C)

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GUIDELINE: BCG RELAPSE & SALVAGE REGIMENS

25. A clinician should not prescribe additional BCG to a patient who is intolerant of BCG or has documented recurrence on TURBT of high-grade, non-muscle-invasive disease and/or CIS within six months of two induction courses of BCG or induction BCG plus maintenance. (Moderate Recommendation; Evidence Strength: Grade C)

26. In a patient with persistent or recurrent intermediate- or high-risk NMIBC who is unwilling or unfit for cystectomy following two courses of BCG, a clinician may recommend clinical trial enrollment. A clinician may offer this patient intravesical chemotherapy when clinical trials are unavailable. (Expert Opinion)

GUIDELINE: BCG RELAPSE & SALVAGE REGIMENS

Open Enrollment Study	Sponsor/ *PI*	Years of Activity	Design	Inclusion	Intervention
Radiofrequency-Induced Thermochemotherapy Effect-EUROPE [RITE-EUROPE] (NCT02471495)	Medical Enterprises Europe, *Gerson Leudecke*	April 2016 – Jan. 2019	Phase III	- BCG-refractory* CIS with or without concurrent NMIBC - Life expectancy ≥ 13 months	- 8 weekly treatments of MMC (40mg/50mL) with Synergo® System - Maintenance every 6 weeks x12 months
Intravesical Cabazitaxel, Gemcitabine, and Cisplatin (CGC) in the Treatment of Urothelial Carcinoma (NCT0220772)	Columbia, *James McKiernan*	Dec. 2014 – Jan. 2017	Phase I	- Persistent NMIBC at first post-BCG induction exam or relapse at 6-month follow-up - ECOG ≤ 1	- All drugs administered intravesically as 6 weekly instillations (Gem dose constant 2000mg) - 5 treatment groups: - Gem/Cab (2.5mg) - Gem/Cab (5mg) - Gem/Cab(5mg)/Cis (66mg) - Gem/Cab (5mg)/Cis (80mg) - Gem /Cab (5mg/Cis 100mg)
Intravesical nab-Rapamycin in NMIBC (NCT02009332)	Columbia, *James McKiernan*	April 2014 – Dec. 2017	Phase I/II	- BCG-refractory* NMIBC - ECOG ≤ 2	- Phase I: Dose escalation from 100mg/wk to 400mg/wk over 6 weeks - Phase II: Max. dose from phase I given as 6 weekly instillations
Intravenous Pembrolizumab in High Risk NMIBC (NCT02625961)	Merck	Feb. 2016 – May 2020	Phase II	- BCG-refractory* NMIBC - ECOG ≤ 2	- Pembrolizumab 200mg IV every 3 weeks for 2 years
BCG + PANVAC v. BCG Alone for NMIBC (NCT02015104)	NCI, *Piyush Agarwal*	Dec. 2013 – Jan. 2019	Phase II	- Persistent or relapsing HG NMIBC following ≥ 1 BCG induction course - ECOG ≤ 1	- Randomly assigned to 2 arms - All patients receive 6 weekly instillations of BCG 50mg (Tice) - One group will be assigned to receive PANVAC as 5 injections over 15 weeks

GUIDELINE: BCG RELAPSE & SALVAGE REGIMENS

Ongoing Study (Enrollment Completed)	Sponsor/ *PI*	Years of Activity	Design	Inclusion	Intervention
Oral Everolimus and Intravesical Gemcitabine for BCG-refractory CIS (NCT01259063)	MSKCC, *Guido Dalbagni*	Dec. 2010 – Dec. 2016	Phase I/II	- Persistent CIS (only) following at least 1 induction course of BCG - KPS ≥ 70%	- Phase I/II: 2 cycles of Gem 2000mg twice a week for 3 weeks with 1 week rest between cycles - Phase I: Everolimus PO 5mg qod or qd or 10mg qd - Phase II: Everolimus dose TBD by phase I - Everolimus continued for 12 months in responders
Oral Dovitinib in BCG Refractory Urothelial Carcinoma With FGFR3 Mutations or Over-expression (NCT01732107)	Hoosier Cancer Research Network, *Noah Hahn*	March 2013 – Dec. 2015	Phase II	- Persistent or relapsing NMIBC after ≥ 2 BCG induction courses - Presence of FGFR3 mutation or overexpression - ECOG ≤ 2	- Dovitinib PO 500mg 5 days on, 2 days off for 6 months
Intravesical Administration of rAd-IFN (NCT01162785)	MD Anderson, *Colin Dinney*	April 2011 – Jan. 2017	Phase Ib	- BCG-refractory* NMIBC - KPS ≥ 70% - Life expectancy ≥ 3 months	- 2 doses intravesical rAd-IFN given initially then additional 2 doses + Syn3 for any CRs at 12 weeks
Intravenous Il-2 fusion protein (ALT-801) in Patients with BCG Failure NMIBC (NCT01625260)	Altor Bioscience, *Hing Wong*	April 2012 – Sept. 2016	Phase Ib/II	- Persistent or relapsing NMIBC following ≥ 1 BCG induction course - ECOG ≤ 2	- IV administration of ALT-801 and Gem as 2 treatment course and 1 maintenance course
Intravesical DTA-H19/PEI for Intermediate Risk NMIBC (NCT00595088)	Univ. Arizona, *Donald Lamm*	Jan. 2008 – Jan. 2013	Phase IIb	- Persistent or relapsing intermediate risk NMIBC (HG/LG Ta or LG T1) after ≥ 1 induction course with BCG or other intravesical chemotherapy - ≥2 but ≤ 7 tumors on cystoscopy with sufficient material to leave marker lesion - H19 expression in tumor - KPS ≥ 60%	- 6 weekly intravesical instillations of study drug (BC-819/PEI)

What About BCG Shortage?

AUA Statement: February, 2019

"The current shortage of BCG has become a great concern to our organizations. Despite Merck increasing production by ~ 100% since the last shortage, the increase in demand has exceeded production. Merck indicates that they will ship approximately 72% of the weekly distribution to each purchaser. Distribution is not direct but through wholesalers, so you should contact your wholesaler to ensure that you are getting your proper allotment. Merck has not indicated when this shortage will end though they are working hard to increase production."

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What About BCG Shortage? AUA STATEMENT

1. BCG should not be used for patients with low risk disease
2. Intravesical chemotherapy should be used as the first-line option for patients with intermediate-risk NMIBC. Patients with recurrent/multifocal low-grade Ta lesions who require intravesical therapy should receive intravesical chemotherapy such as mitomycin, gemcitabine, epirubicin, or docetaxel instead of BCG.
3. If BCG would be administered as second-line therapy for patients with intermediate-risk NMIBC, an alternative intravesical chemotherapy should be used rather than BCG in the setting of a BCG shortage

What About BCG Shortage? AUA STATEMENT

4. For patients with high-risk NMIBC, high-grade T1 and CIS patients receiving induction therapy should be prioritized for use of full-strength BCG. If not available, these patients and other high-risk patients should be given a reduced 1/2- 1/3 dose if feasible.

5. If supply exists for maintenance therapy for patients with NMIBC, every attempt should be made to use 1/3 dose BCG and limit dose to one year.

6. In the event of BCG supply shortage, maintenance therapy should not be given and BCG naïve patients with high risk disease prioritized for induction BCG

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What About BCG Shortage? AUA STATEMENT

- 7. If BCG is not available, a preferable alternative to BCG is mitomycin (induction and monthly maintenance up to one year). Other options such as gemcitabine, epirubicin, docetaxel, valrubicin, or sequential gemcitabine/docetaxel or gemcitabine/mitomycin may also be considered with an induction and possible maintenance regimen.
- 8. Patients with high-risk features (i.e., high-grade T1 with additional risk factors such as concomitant CIS, lymphovascular invasion, prostatic urethral involvement, or variant histology) who are not willing to take any potential oncologic risks with alternative intravesical agents should be offered initial radical cystectomy if they are surgical candidates.

What About BCG Shortage? AUA STATEMENT

- ADDITIONAL NOTES:
- If 1/2 to 1/3 dose BCG is used, every attempt should be made to treat multiple patients on the same day to avoid drug wastage.
- Every effort should be made to enroll patients in clinical trials to offer an appropriate alternative management strategy where this is feasible.

- A link to the official AUA Risk Stratification Table can be found here: www.auanet.org/NMIBCrisktable

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GUIDELINE: ENHANCED CYSTOSCOPY

30. In a patient with NMIBC, a clinician should offer blue light cystoscopy at the time of TURBT, if available, to increase detection and decrease recurrence. (Moderate Recommendation; Evidence Strength: Grade B)

31. In a patient with NMIBC, a clinician may consider use of NBI to increase detection and decrease recurrence. (Conditional Recommendation; Evidence Strength: Grade C)

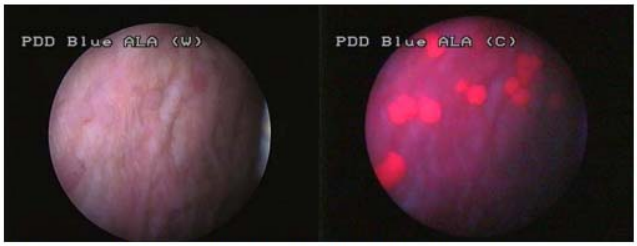

Figure 1. Cystoscopy of papillary bladder tumours under white (left) and blue (right) cystoscopy

Soloway 2012

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GUIDELINE: SURVEILLANCE & FOLLOW UP

32. After completion of the initial evaluation and treatment of a patient with NMIBC, a clinician should perform the first surveillance cystoscopy within three to four months. (Expert Opinion)

33. For a low-risk patient whose first surveillance cystoscopy is negative for tumor, a clinician should perform subsequent surveillance cystoscopy six to nine months later, and then annually thereafter; surveillance after five years in the absence of recurrence should be based on shared-decision making between the patient and clinician. (Moderate Recommendation; Evidence Strength: Grade C)

34. In an asymptomatic patient with a history of low-risk NMIBC, a clinician should not perform routine surveillance upper tract imaging. (Expert Opinion)

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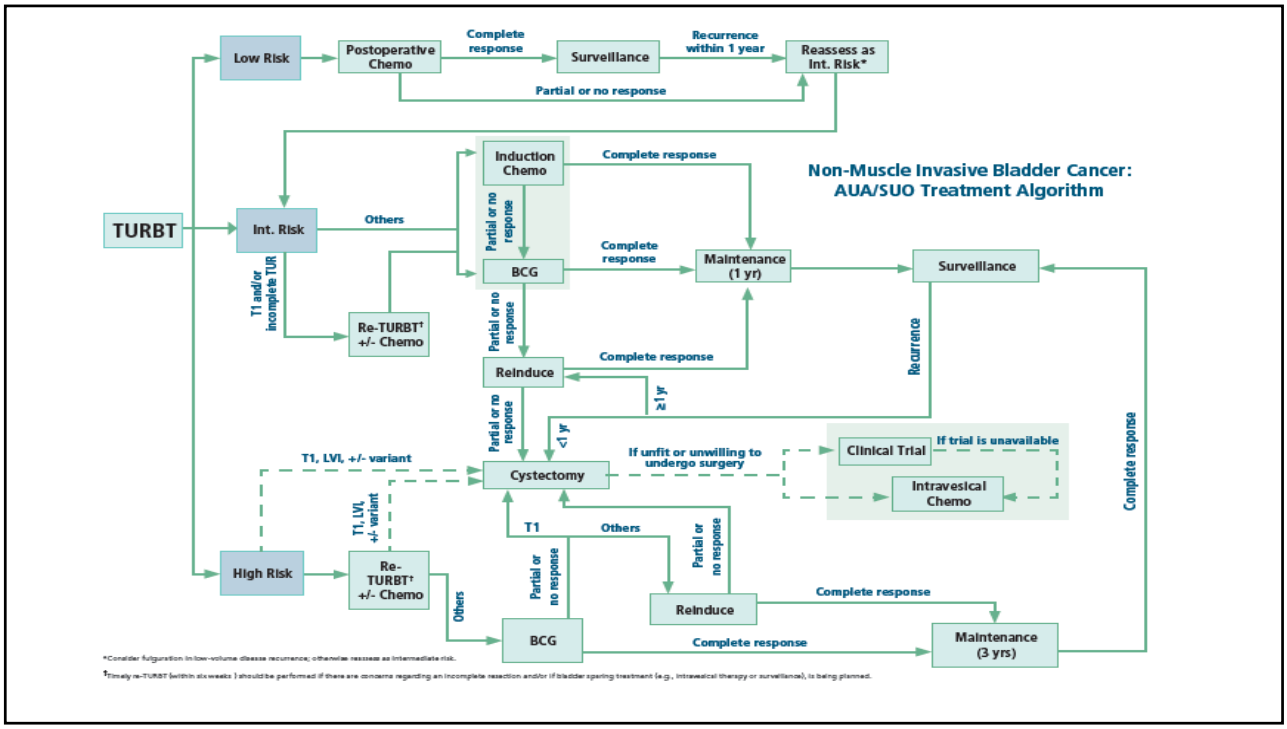
GUIDELINE: SURVEILLANCE & FOLLOW UP

35. In a patient with a history of low-grade Ta disease and a noted sub-centimeter papillary tumor(s), a clinician may consider in-office fulguration as an alternative to resection under anesthesia. (Expert Opinion)

36. For an intermediate-risk patient whose first surveillance cystoscopy is negative for tumor, a clinician should perform subsequent cystoscopy with cytology every 3-6 months for 2 years, then 6-12 months for years 3 and 4, and then annually thereafter. (Expert Opinion)

37. For a high-risk patient whose first surveillance cystoscopy is negative for tumor, a clinician should perform subsequent cystoscopy with cytology every three to four months for two years, then six months for years three and four, and then annually thereafter. (Expert Opinion)

38. For an intermediate- or high-risk patient, a clinician should consider performing surveillance upper tract imaging at one to two year intervals. (Expert Opinion)



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Case Presentations

Recurrent Low Grade Tumors

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Case

61 year old female w/ microhematuria

- Office cystoscopy: 2 tumors on posterior wall (1 cm and 0.5 cm)

- TURBT (no blue light): LG Ta papillary urothelial carcinoma
  - Postoperative dose of MMC 40mg in 40ml NS

QUESTIONS FOR PANEL:
WHAT AUA RISK GROUP?
ANY POST-OP THERAPY: ?

Case – Recurrent LG Ta

QUESTIONS:

WHAT AUA RISK GROUP?
INTERMEDIATE (multifocal LG)

POST-OP THERAPY:
COULD CONSIDER INTRAVESICAL CHEMOTHERAPY, WOULD NOT DO BCG DURING ESP DURING BCG SHORTAGE

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Case

Surveillance cysto done when?
- @ 2 mos
- @ 3mos
- @ 6mos

- Office cysto: 2 new tumors on right lateral wall
- CT Urogram negative
- TURBT: LG Ta papillary urothelial carcinoma

Case: Panel Questions

- Perioperative chemotherapy is given, so what agent do you use?
  - Mitomycin
  - Epirubicin
  - Gemcitabine

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Case: Panel Question

NEXT STEPS FOR THIS PATIENT: INDUCTION INTRAVESICAL THERAPY VS SURVEILLANCE?

Patient undergoes enhanced cystoscopy and biopsy

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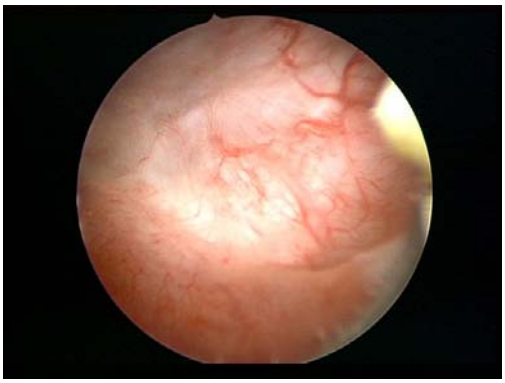
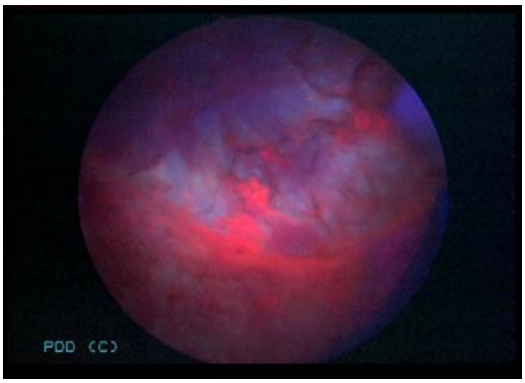
Case





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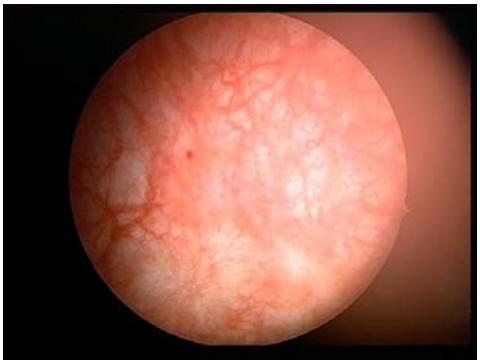
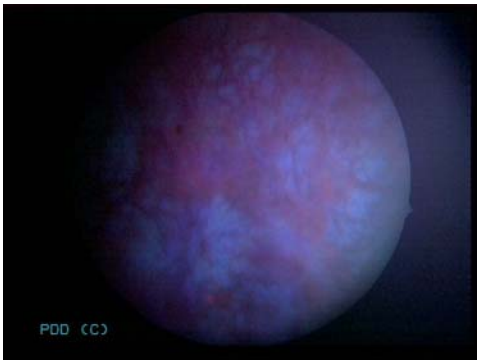
Case





Case

- Path reveals: High grade papillary and focal CIS
- Next step treatment is: 6 week induction BCG started (no maintenance)
- WHAT NEXT PANEL? Cysto in office, cytology in office, TURBT, Blue light?
- Surveillance cysto @ 3mos negative then @6mos: tumor at trigone and then TURBT (blue light): LG Ta papillary urothelial carcinoma and postoperative dose of Gemcitabine 2G in 100ml NS

QUESTIONS:

RE-INDUCTION INTRAVESICAL THERAPY?

BCG OR MMC OR SOMETHING ELSE?

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Case: T1 Bladder Cancer

Case Presentation- FJ

- **HPI**: 81 yo male first diagnosed with high grade, non-invasive bladder cancer 5 years ago
  - Solitary
  - 3 cm
  - Received a single dose of mitomycin
- Disease-free during this time
- TURBT reveals High grade T1 urothelial carcinoma, 2 cm with muscularis propria present

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Patient FJ:

- What next panel?
  - NEEDS RE-TURBT because of T1 disease as per recommendations, even with muscle present

Patient: FJ Panel Questions

- He undergoes a repeat TURBT: High grade T1 with multifocal CIS, and muscle is present on this TURBT

- What next?
  - Repeat TURBT—again??
  - BCG
  - Alternative BCG
  - Radical cystectomy
  - Tri-modal therapy

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Patient FJ: Question

- He receives BCG and he completes 5/6 instillations of full strength BCG
  - Did not tolerate well due to worsening irritative voiding symptoms
  - Also had low grade fevers for the last two instillations

  - With these symptoms do you?
    - Dose reduce
    - Skip treatments
    - Not give BCG anymore
  - Should he get maintenance?

Patient: FJ

- He does not receive maintenance and is tumor-free for one year but then develops an anterior small bladder wall lesion
- TURBT reveals a high, grade T1 bladder cancer that is difficult to resect although muscle present, not involved.
- What next? He's now 83 but active.

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Patient: FJ

- He undergoes radical cystectomy with ileal conduit
  - pT1 with CIS and negative margins, 0/22 LN
  - Multifocal CIS in prostatic ducts with focal positive margin
- What next for the panel—do you just follow?

Case: Positive Cytology Only

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Case

- 65 y/o M referred with history HgTa UC, positive urine cytology, negative WLC
- PMH: HTN, DM, Obesity, NMIBC
- PSH: lap chole
- Meds: HCTZ, metformin, NKDA
- SH: Non-smoker, married
- FH: Colon Ca, urolithiasis

Panel Questions

- Repeat cytology?
- Other biomarker?
- Operative management?
  - Random bladder biopsies
  - Urethral biopsies
  - Upper tract cytology/endoscopy

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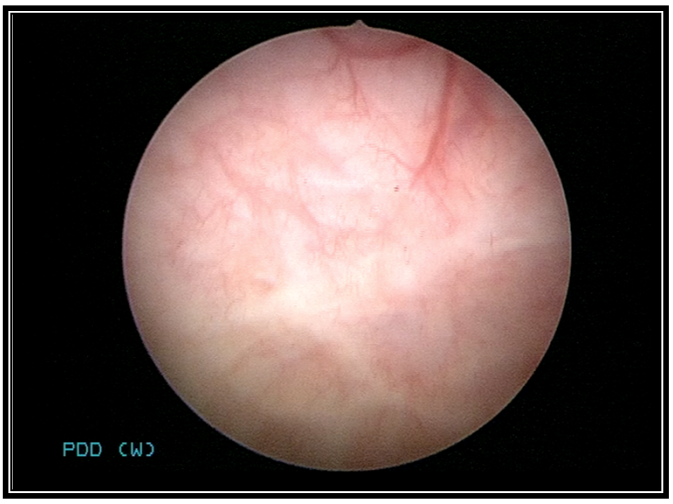
Chose to Do Blue Light



Provided by Dr. James McKiernan

Panel Questions

- What would you do if you do not have Blue Light Cystoscopy?
- What would you do if you continue to have positive cytology and CANNOT find tumor?

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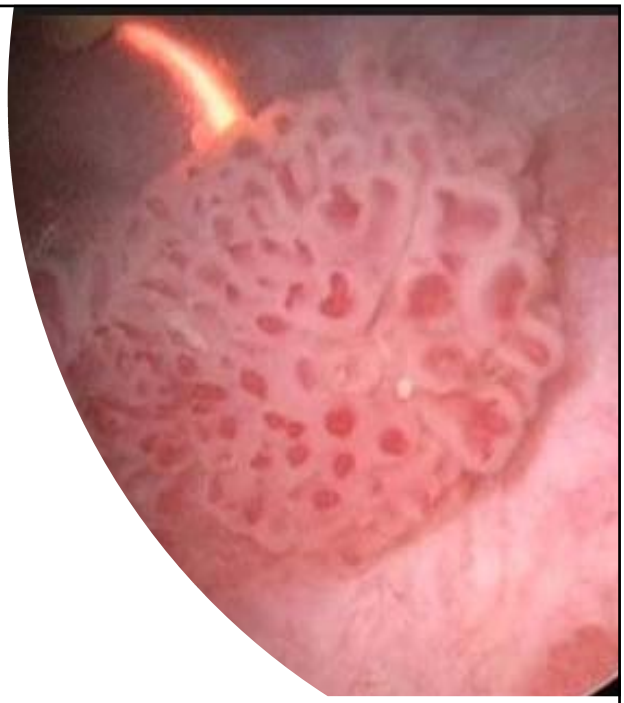
Case: BCG Discussion

Case

- A 62- year-old man is diagnosed with a 1 cm HG Ta bladder cancer



- He undergoes BCG induction and has a complete response. He does not get offered maintenance
- Eighteen months later he relapses with Cis and HG Ta disease.

Case: Panel Questions

- At this time is he considered BCG unresponsive?
- How should he proceed?

BCG UNRESPONSIVE DISEASE - FDA 2018

"Patients with CIS at trial entry can be studied in either a RCT or a single-arm trial. In BCG-unresponsive a single-arm clinical trial with complete response rate and duration of response as primary endpoint can provide evidence of effectiveness to support marketing application."

- Persistent or recurrent CIS +/- Ta/T1 within 12 months of completion of "adequate" BCG
- Recurrent HG Ta/T1 within 6 months of completion of "adequate" BCG
- T1 HG at first evaluation following induction BCG course

In this context, adequate BCG therapy defined as at least one of the following:

- At least 5/6 doses of an initial induction course plus at least 2/3 doses of maintenance
- At least 5/6 doses of an initial induction course plus at least 2/6t doses of a second induction

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Case:

- He elects repeat BCG induction and three months later he has a negative cytology and normal biopsy.
- This time he opts for BCG maintenance and he undergoes his first three week booster treatment.
- His next cystoscopy reveals a lesion and a positive cytology. He undergoes TURBT and this shows cancer.

Case: Panel Question

- What are his options and what would you do?
  - More BCG
  - Intravesical chemotherapy—if so what regimen
  - Clinical trial—what is most promising?
  - Wait for new agents—if so, which ones?
  - Radical cystectomy

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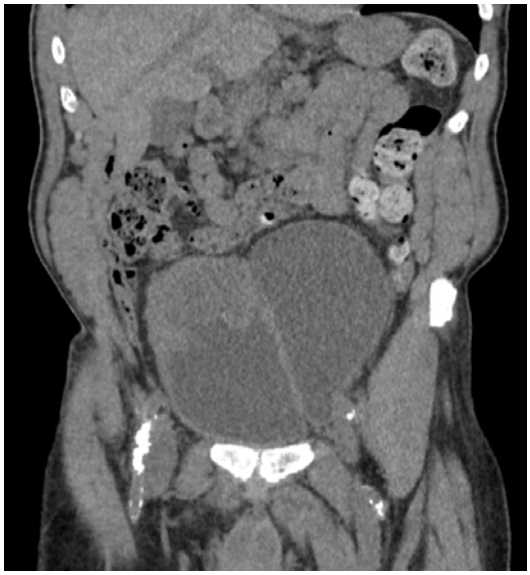
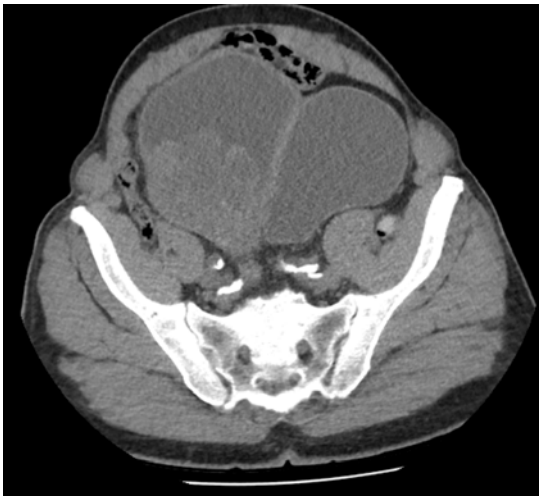
Case: Unable to Resect All Tumor

Case SC

59 yo man referred to you for evaluation of a bladder tumor.

- Diagnosed with large bladder dome tumor after presenting with hematuria
- Urologist attempted TURBT but unable to reach tumor due to location at dome and patient's long urethra and large bladder





Potential options

1. Extra-long resectoscope
2. Perineal urethrostomy
3. Percutaneous endoscopic resection
4. Flexible cystoscope with laser
5. Partial cystectomy
6. Radical cystectomy

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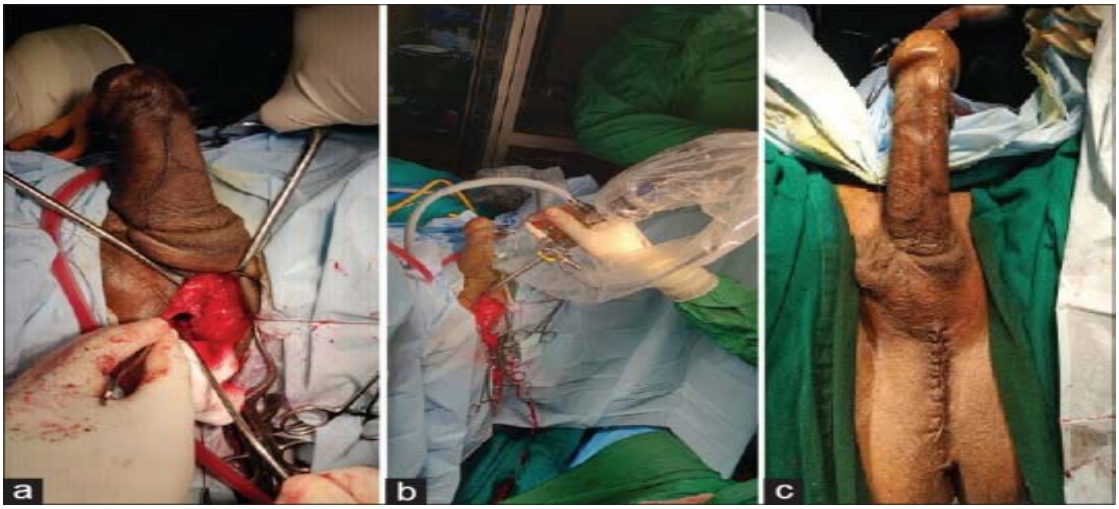

Pandya 2019

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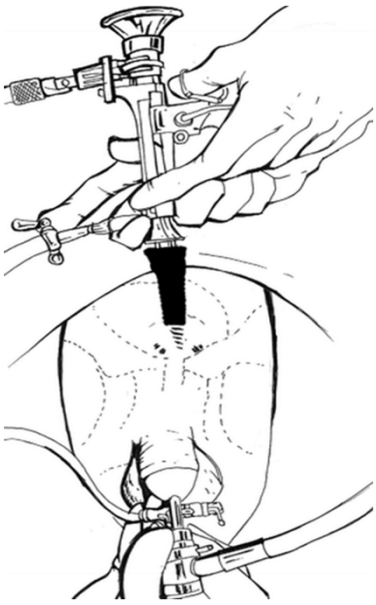

Kibar 2007

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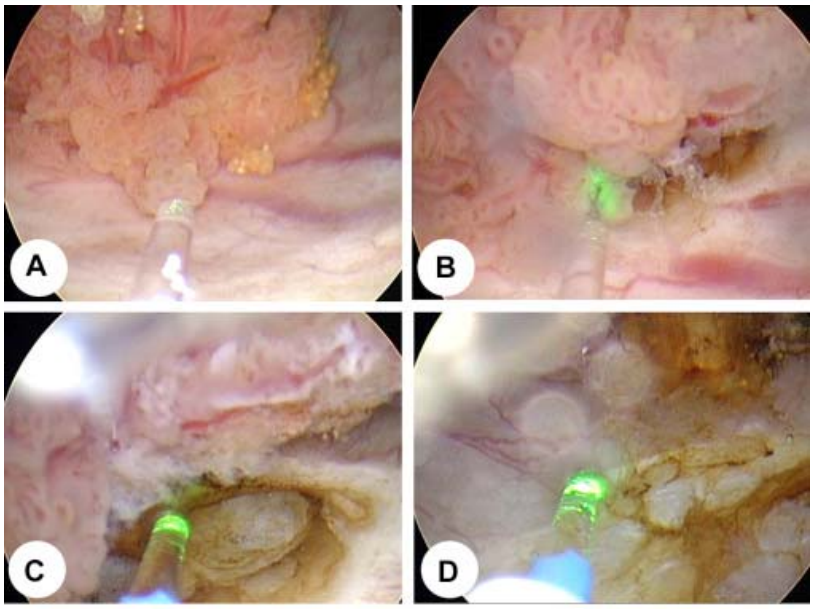

Case: Panel Questions

- Pathology is high grade Ta tumor but with variant histology- micropapillary changes
- How do you treat this patient now?

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Case: Ureteral Orifice Tumor

Case

- 74 y/o M referred with gross hematuria
- PMH: BPH, COPD, seizures
- PSH: None
- Meds: ASA 81, finasteride, tegretol, albuterol, carbamazepine; NKDA
- SH: remote tobacco (45 pack years)
- FH: non-contributory

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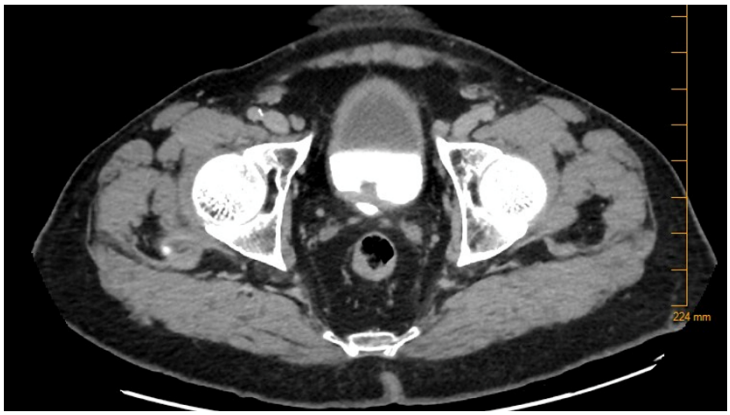
Case

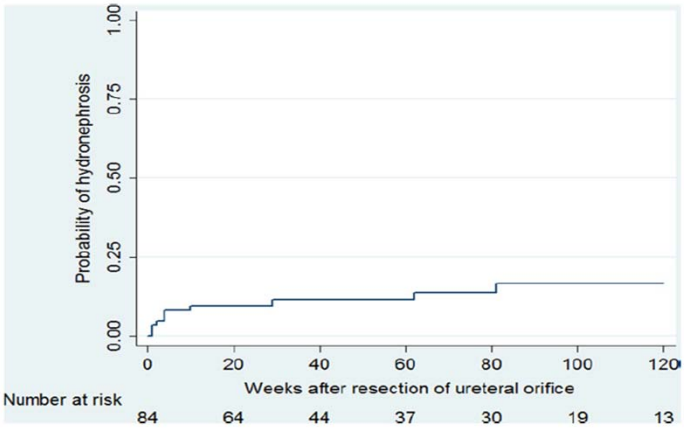
- PE: Unremarkable
- CT: Bilateral simple cysts; 10 mm nodular filling defect at the right base of the urinary bladder; large prostate, no hydronephrosis



Case: Panel Question
What Technique Do You Use?

- BEFORE YOU ANSWER, SOME DATA

Risk of upper tract obstruction and tumor recurrence?



Kaplan-Meier estimate of new onset hydronephrosis after trans-urethral resection of ureteral orifice involved by tumor.

THE JOURNAL OF UROLOGY®

13% developed hydronephrosis

Predictive factors for ureteral stenosis and recurrent UTUC?

Independent factors for stenosis:

Tumor greater than 1.5 cm

T1 tumor stage

Backward stepwise univariate and multivariate Cox regression models of ureteral stenosis and recurrent UTUC

	Ureteral Stenosis				Recurrent UTUC			
	Crude HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value	Crude HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
Age	0.957 (0.916–1.001)	0.055	–	–			–	–
Sex:								
Female (referent)	1		–	–	1		–	–
Male	0.741 (0.198–3.519)	0.741	–		0.523 (0.163–1.682)	0.001		
Previous recurrence:			–	–			–	–
No (referent)	1				1			
Yes	5.586 (1.444–11.609)	0.013			4.768 (2.350–8.707)	0.001		
Primary tumor:								
No (referent)	1		1		1		1	
Yes	0.179 (0.046–0.693)	0.013	0.106 (0.015–0.751)	0.025	0.114 (0.031–0.425)	0.001	0.039 (0.003–0.375)	0.003
Size (cm):							–	–
Less than 1.5 (referent)	1		1		1			
1.5 or Greater	5.122 (2.332–8.187)	0.001	4.521 (1.879–7.234)	0.023	4.280 (1.300–9.097)	0.017		
Complete TURBT:			–	–			–	–
No (referent)	1				1			
Yes	0.198 (0.05–0.788)	0.022			0.299 (0.079–1.135)	0.076		
Ureteral stent:			–	–			–	–
No (referent)	1				1			
Yes	1.667 (0.429–6.469)	0.460			0.628 (0.217–1.812)	0.389		
Bladder tumor stage:			–	–				
Ta (referent)	1				1		1	
T1	4.608 (1.379–9.398)	0.014			5.862 (3.485–7.381)	0.001	7.255 (4.251–10.280)	0.001
Bladder tumor 2004 grade:			–	–			–	–
Low (referent)	1				1			
High	1.435 (0.540–3.816)	0.469			10.027 (2.175–26.228)	0.003		
Associated bladder CIS:			–	–			–	–
No (referent)	1				1			
Yes	1.756 (0.490–6.288)	0.387			6.000 (1.996–11.034)	0.001		
IMPDU stage:							–	–
Ta, Tis (referent)	1		1		1			
T1	6.870 (1.997–11.641)	0.002	8.525 (1.257–15.252)	0.005	4.922 (1.664–7.732)	0.004		
IMPDU 2004 grade:			–	–			–	–
Low (referent)	1				1			
High	1.191 (0.373–3.809)	0.469			10.000 (2.159–26.250)	0.003		
Associated IMPDU CIS:			–	–				
No (referent)	1				1		1	
Yes	5.670 (1.646–10.528)	0.006			7.501 (5.825–9.250)	0.001	6.850 (4.202–8.253)	0.006
Treatment:	–	–	–	–			–	–
Mitomycin (referent)					1			
BCG					2.464 (0.525–11.596)	0.300		

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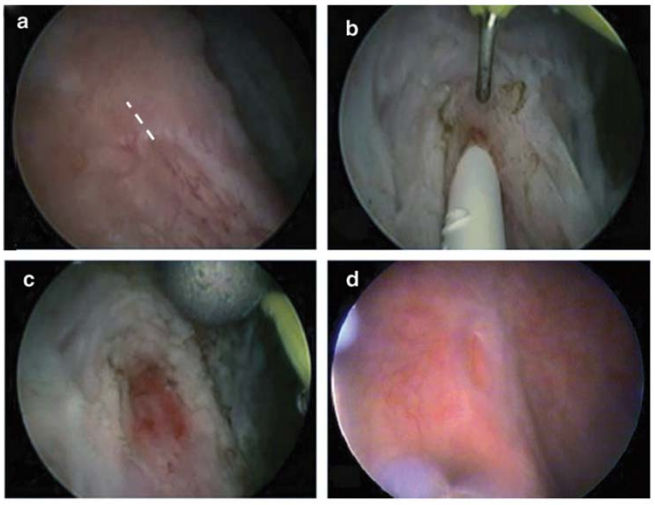
Incise the intramural ureter?



CRETA ET AL.

Should we stent?

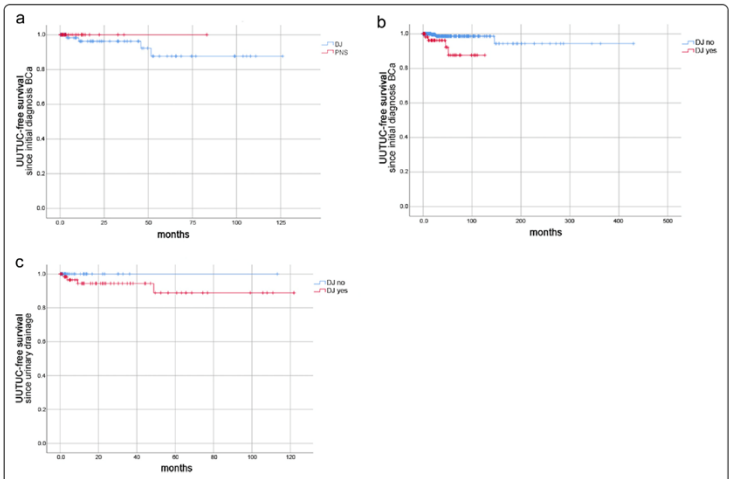


Fig. 3 UUTUC-free survival data according to urinary drainage of the upper urinary tract. **a** UUTUC-free survival since initial diagnosis BCa for patients with DJ stents compared to those with nephrostomy tubes ($n = 103$ patients; four events; $p = 0.415$) (**b**) UUTUC-free survival since initial diagnosis BCa for patients with DJ stents compared to those without DJ stents ($n = 617$; eight events; $p = 0.001$) (**c**) UUTUC-free survival rates since urinary drainage of the upper urinary tract for patients with DJ stents compared to those without DJ stents ($n = 113$; four events; $p = 0.26$)

? Risk of upper tract disease

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Case: Panel Question
What Technique Do You Use?

- Impact on development of obstruction?
- Impact on development of upper tract disease?
- Stent vs. PCN vs observation?
- Other?

Case: Prostatic Urethral Involvement

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Case presentation CR

68 year old male presented with gross hematuria.

- CT urogram notable for bladder nodule, no upper tract or extravesical disease
- TURBT with blue light cystoscopy: 3cm papillary tumor at bladder neck with extension into proximal prostatic urethra, completely resected. Bimanual exam negative for masses or nodules.
  - HG Ta urothelial carcinoma in bladder (muscle present and uninvolved)
  - HG urothelial carcinoma involving prostatic urothelium (CIS)

Prostatic urethral cancer

20-40% prostatic urothelial cancer at radical cystectomy (Patel 2009, Bruins 2013)

<10% of unselected NMIBC patients with prostatic urethral involvement (Mungan 2005, Palou 2012)

Risk factors for prostatic urethral involvement (Mungan 2005, Patel 2009):

- Bladder neck/trigone tumor
- Bladder CIS
- High grade tumor
- Higher tumor stage
- Tumor multifocality

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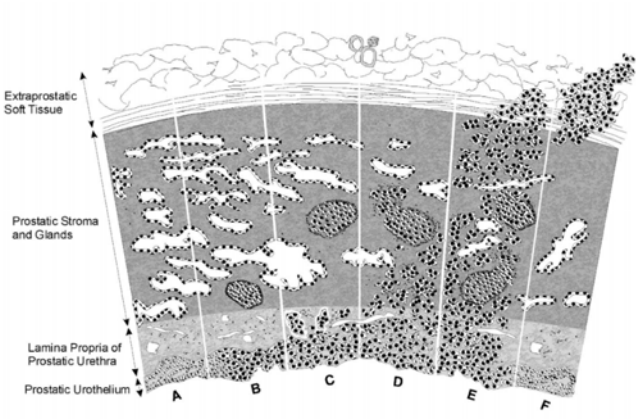
Depth of invasion

T stage	Primary tumor
Ta	Non-invasive papillary
Tis	Carcinoma in situ involving prostatic urethra or periurethral or prostatic ducts without stromal invasion
T1	Tumor invades urethral subepithelial connective tissue immediately underlying urothelium
T2	Tumor invades the prostatic stroma surrounding ducts either by direct extension from the urothelial surface or by invasion from prostatic ducts
T3	Tumor invades the periprostatic fat
T4	Tumor invades other adjacent organs (bladder wall, rectal wall)

Shen 2006

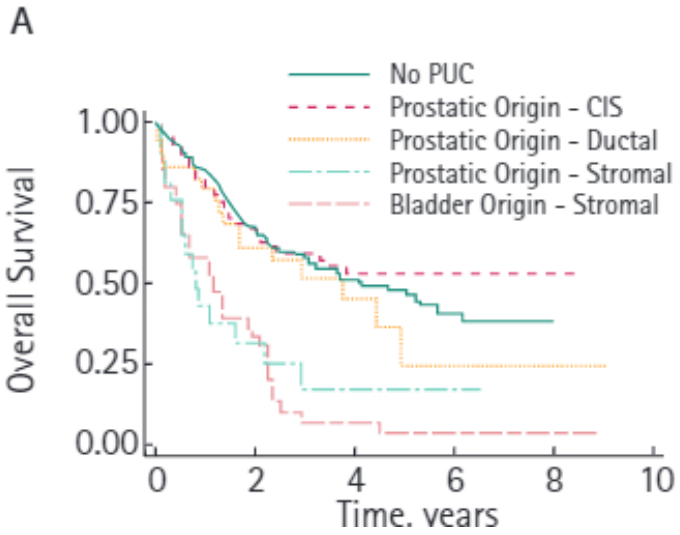


Depth of Invasion

CIS = favorable prognosis

Ductal invasion = intermediate prognosis

Stromal invasion = poor prognosis



Esrig 1996, Cheville 1998, Barocas 2009

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What is best initial management for prostatic urethral CIS? Panel

A. TRUS biopsy
B. TURP followed by intravesical BCG
C. Intravesical gemcitabine
D. Radical cystectomy
E. Intravesical BCG

What is best initial management for prostatic urethral CIS?

A. TRUS biopsy

B. TURP followed by intravesical BCG

C. Intravesical gemcitabine

D. Radical cystectomy

E. Intravesical BCG

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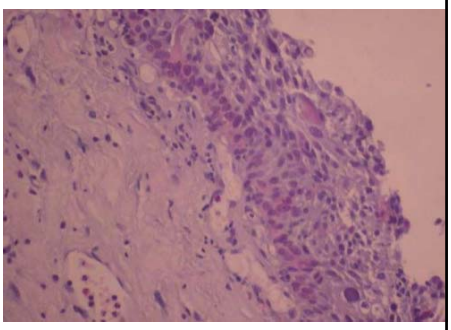
Prostatic urethral CIS management

RC historically recommended for any prostatic urethral involvement (pT4)

Conservative management **may now be preferred** for CIS and involvement of acini and ducts:

- Aggressive TURP (Gofrit 2009)
- Intravesical therapy (BCG)



- Complete response rates: 50-80%
  - Bladder recurrences >>> prostatic recurrences
  - Progression rates up to 40% (high risk patients!)

Canda 2004, Gofrit 2009