Bladder Cancer (NMIBC)

AUA Annual Review Course
June 2025

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Disclosures

- Photocure
- CxBladder
- Urogen

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Resources

AUA GUIDELINES

Microhematuria: AUA/SUFU Guideline (2025)

TREATMENT OF NON-METASTATIC MUSCLE-INVASIVE BLADDER CANCER: AUA/ASCO/ASTRO/SUO GUIDELINE (2017; Amended 2020, 2024)

DIAGNOSIS AND TREATMENT OF NON-MUSCLE INVASIVE BLADDER CANCER: AUA/SUO GUIDELINE

(Published 2016; Amended 2020, 2024)

AUA University

Bladder Neoplasms: Muscle Invasive Bladder Cancer

Bladder Neoplasms: Non-Muscle Invasive Bladder Cancer

Upper Tract Neoplasms

Urethral Neoplasms

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Outline

- Anatomy
- Epidemiology
  - Risk factors
- Presentation and diagnosis
- Staging and grading
- Risk stratification
- Treatment and Surveillance

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ANATOMY

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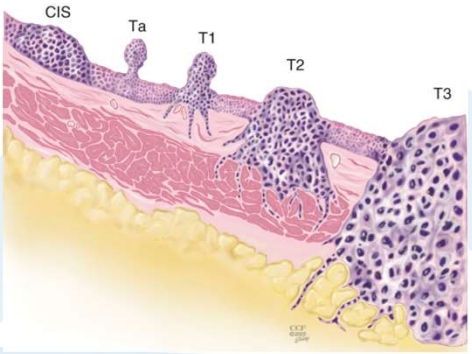
Anatomy

- Urothelium
  - *Basal* → *intermediate* → umbrella cells
  - Impermeable, inert
- Muscularis
  - 3 layers of smooth muscle
- Serosa
  - Bladder dome



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CAMPBELL-WALSH-WEIN UROLOGY, 12th EDITION

Anatomy

- Vascular:
  - Internal iliac → Superior, inferior vesical arteries
  - Superior, inferior vesical veins →internal iliac
- Lymphatic
  - Level 1: internal iliac, obturator, ***external iliac***
  - Level 2: common iliac, presacral
  - Level 3: paracaval, para-aortic, interaortocaval

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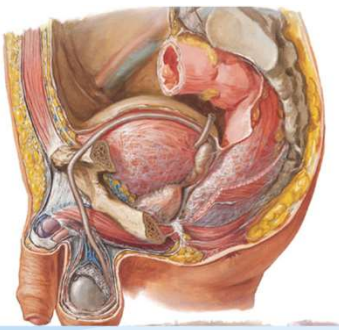
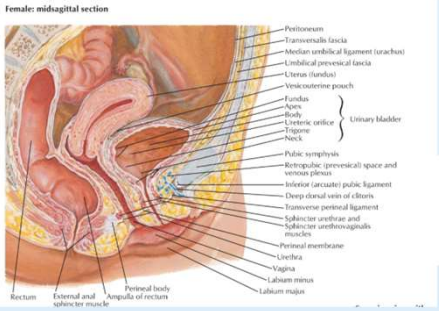
Anatomy

- Surrounding organs
  - M: Seminal vesicles, ureters, rectum, vas
  - F: Uterus, vagina, rectum





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EPIDEMIOLOGY

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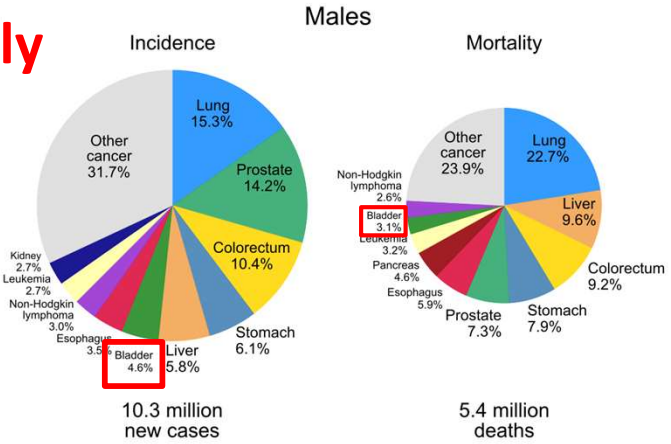
EPIDEMIOLOGY
Globally



Cancer site	Incidence Rank	New cases	% of all sites	Mortality Rank	Deaths	% of all sites
Bladder	9	613,791	3.1	13	220,349	2.3

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CA Cancer J Clin. 2024;74:229–263.

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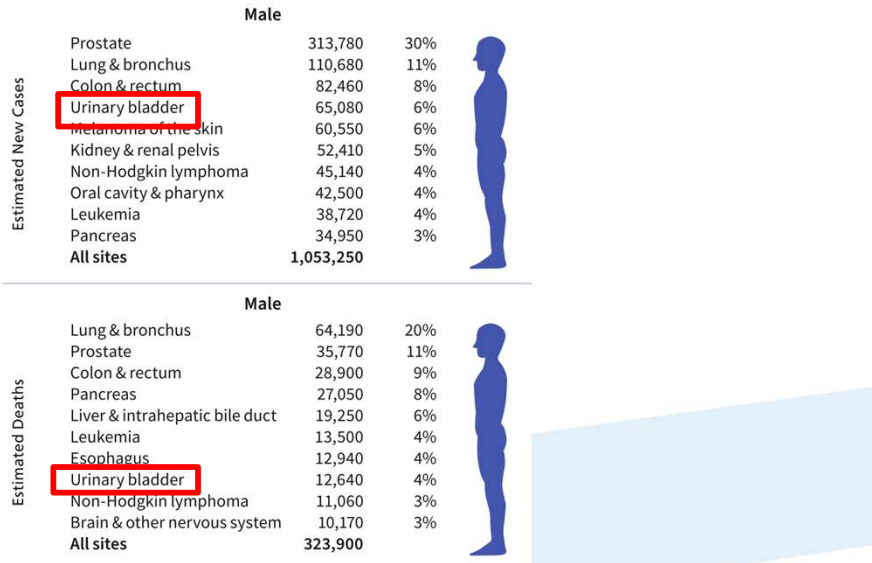
EPIDEMIOLOGY In US



Urinary bladder

Estimated new cases			Estimated deaths		
Both sexes	Male	Female	Both sexes	Male	Female
84,870	65,080	19,790	17,420	12,640	4780

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CA Cancer J Clin. 2025;75:10–45.

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Risk Factors (Exposures)

Occupational risk: 5 – 10% of all urothelial cancer

- Dyes, paint, petroleum, rubber, textile, printing industries, chimney sweep

Cigarette smoking: 2 – 3x risk; 30 – 40 % of all urothelial cancer

- Risk decreases by 40% after quitting 1-4 years then by 60% after 25 years
- Smoking increases risk for local recurrence in NMIBC

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Islami et al. 2015
Cumberbatch 2015

Smoking Cessation

- Most important risk factor for development of bladder cancer
  - Duration, intensity
- Impact on prognosis
  - Recurrence, progression, mortality
- But… we are seeing them *after* the diagnosis. Does it matter then?
- Controversial but **yes** it does
  - Highlight importance of smoking prevention *early*

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Cancers 2022;14:4022
J Urol 2022;207:1200

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Risk Factors (*more* Exposures)

Drugs: phenacetin, cyclophosphamide, ifosfomide

Pelvic radiation: cervical, uterine, prostate, rectal

Chronic cystitis: chronic indwelling foley (SCC), bilharziasis recurrent infection

Misc: arsenic, bracken fern, Balkan nephropathy, Aristolochia sps (Chinese herb; grows in Balkans)

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Islami et al. 2015
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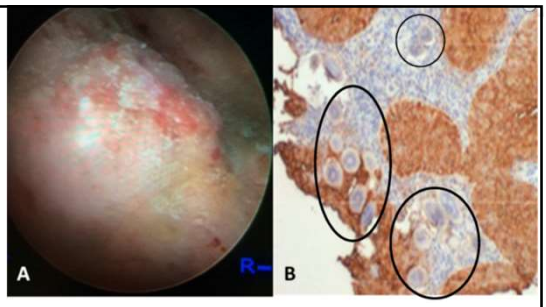
Risk Factors



- Bihlarzial/Schistosomal Cystitis
  - S. haematobium, S. mansoni
  - Account for 1-5% will develop bladder cancer (SCC>adeno)
- Liver (mature) →mesenteric and pelvic veins (produce ova) → chronic granulomatous inflammation
- Bladder finding = hyperplasia, calcification, ulcers/fibrosis, keratizing squamous metaplasia

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J Clin Med 2021;10:205

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Risk Factors (Genetics)

- Several inherited tumor syndromes
  - Lynch (UTUC > bladder)
    - MSH2, MLH1, MSH6, PMS2
    - Cancers: colon, endometrial, gastric, ovarian
  - Li-Fraumeni, Costello, Muir-Torre, Cowden
- Genes associated with increased bladder cancer risk
  - Polymorphisms in detoxification process (NAT1, **NAT2**, GST) contribute to higher susceptibility to environmental carcinogens

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Molecular Pathways

- Non-invasive pathway (low grade)
  - Oncogene mutations: FGFR3, PIK3CA
  - Loss of heterozygosity: chromosome 9q
- Invasive pathway (high grade)
  - Tumor suppressor gene mutations: TP53, RB1

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PRESENTATION AND DIAGNOSIS

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MICROSCOPIC HEMATURIA

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Asymptomatic Microscopic Hematuria

- 25 statements
  - Diagnosis and definition → ≥ 3 RBCs per hpf; NOT dipstick
  - Initial evaluation → Thorough eval considering medical renal disease, gyn, and non-malignant causes; antiplatelets and anticoagulation
  - Risk stratification → Low, intermediate, high
  - Risk-based evaluation → According to risk
  - Urinary markers → Not routine; consider if LUTS
  - Follow up → Negative work up? Consider repeat ua in 12 mos;
    - if negative, discontinue further evaluation for AMH
    - If persistent +, engage in SDM
    If develops GH, increase in degree, or new GU SX, initiate further WU

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J Urol 2025 27 Feb

Risk Factors Included in AUA Microhematuria Risk Stratification System	Additional Urothelial Cancer Risk Factors[6, 14,55-59]
Age	Irritative lower urinary tract symptoms
Male sex	Prior pelvic radiation therapy
Smoking use	Prior cyclophosphamide/ifosfamide chemotherapy
Degree of microhematuria	Family history of urothelial cancer or Lynch Syndrome
Persistence of microhematuria	Occupational exposures to benzene chemicals or aromatic amines (e.g., rubber, petrochemicals, dyes)
History of gross hematuria	Chronic indwelling foreign body in the urinary tract
* The Panel recognizes that this list is not exhaustive.	

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J Urol 2025 27 Feb

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Risk of malignancy*	Low/Negligible 0-0.4%[21, 22, 24]	Intermediate 0.2-3.1%[21, 22, 24]	High 1.3-6.3%[21, 22, 24]
Number of criteria patient must meet	All	One or more	One or more
Degree of hematuria on a single urinalysis	3-10 RBC/HPF+	11-25 RBC/HPF+	>25 RBC/HPF+
Alternative criteria for degree of hematuria		Previously low/negligible-risk patient with no prior evaluation and 3-25 RBC/HPF* on repeat urinalysis	History of gross hematuria
Age for women	<60 years	≥60 years	*Women should not be categorized as high-risk solely based on age*
Age for men	<40 years	40-59 years	≥60 years
Smoking history	Never smoker or <10 pack years	10-30 pack years	>30 pack years
Presence of additional risk factors for urothelial cancer (see Table 3)	None	Any	One or more plus any high-risk feature

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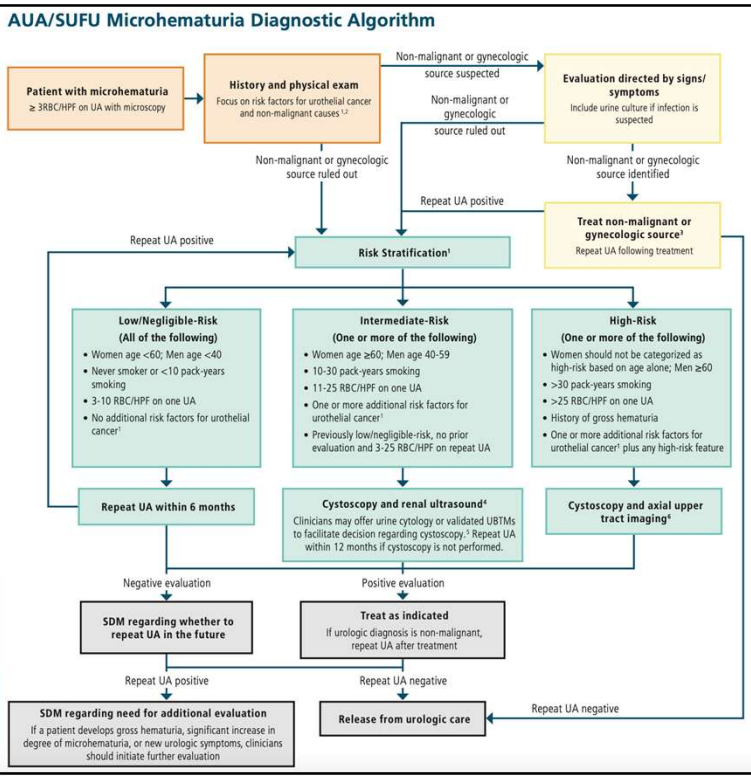
J Urol 2025 27 Feb



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Signs and Symptoms

- **Hematuria**
  - Microscopic (~3% → bladder ca)
  - Gross (10-13% → bladder ca)
- Irritative voiding symptoms
  - CIS
- Advanced disease
- Incidental

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Diagnosis

- Cystoscopy – office vs. anesthetic
  - Imaging and urine tests suggestive of cancer
- Urine cytology
- Transurethral biopsy or resection
- Bimanual examination

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TURBT

- Monopolar vs. Bipolar electrocautery
- Cold cup biopsy
- Quality metrics
  - Complete resection
  - Muscle in specimen
- Complete bladder inspection

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)

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)

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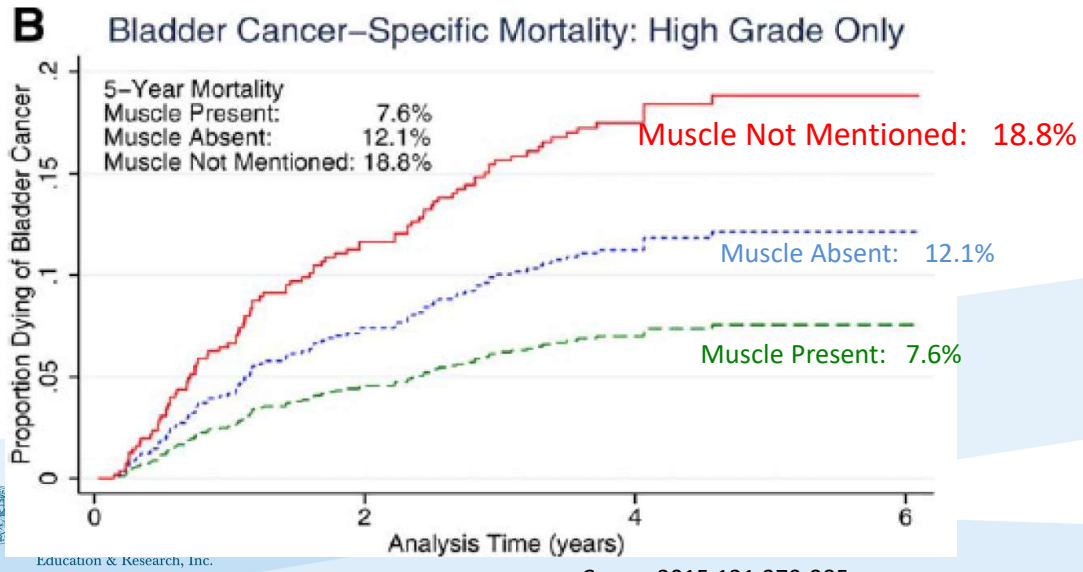
Muscle in the Specimen:
Makes a Difference, Especially in High Grade Cancer



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Cancer 2015;121:379-385

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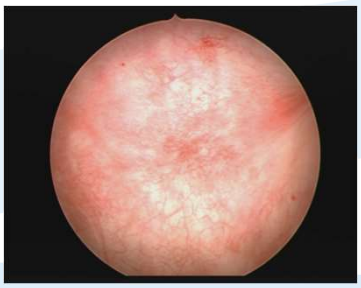
White Light Cystoscopy (WLC)

- Endoscopy with WLC resection is mainstay of diagnosis, staging, and management
- Flat tumors, CIS can appear normal



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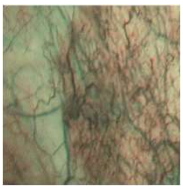
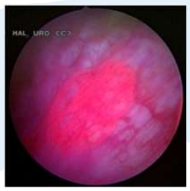
Enhanced Cystoscopy



Narrow Band Imaging (Olympus – 2008)

- Filters white light
- Hemoglobin

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



Blue Light Cystoscopy (Photocure – 2010)

- Intracellular accumulation photoactive porphyrins
- Fluoresce tumor tissue "hot pink"

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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)

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"2nd Look" TURBT (ie. re-resect)

- ***Why?*** HgTa ~ 50% residual, 15% upstage
  HgT1 ~ 50% residual, 30% upstage
- ***When?*** Within 2 – 6 weeks of initial

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)

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)

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)

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Guideline body	Recommendation on suitable reTUR candidates	Level of evidence given	Major differences
EAU (European Association of Urology)	1. Incomplete initial TUR 2. No muscle in specimen with the exception of LG-Ta/Gl and primary CIS 3. T1 tumors.	All Grade A (Strong)	*Used as the reference standard*
AUA (American Urological Association)	1. Incomplete initial TUR 2. HG-Ta tumours 3. T1 tumours	1. Grade B (strong) 2. Grade C (moderate) 3. Grade B (strong)	No comment is made that HG-Ta tumours do not need reTUR if muscle is present in the initial TUR
NCCN (National Comprehensive Cancer Network)	1. Incomplete initial TUR 2. No muscle in initial TUR for HG disease 3. Large or multi-focal lesions 4. T1 tumours 5. Select HG-Ta especially if no muscle in initial TUR	All Strong	Include large or multi-focal lesions as a reason to re-resect. Doesn't specifically mention CIS
CUA (Canadian Urology Association)	1. Incomplete initial TUR 2. T1 tumour in absence of muscle 3. Any HG or T1 tumour with benign muscle	1. Grade A 2. Grade A 3. Grade C	Recommend reTUR in T1 or HG-Ta where muscle is present and not malignant.
NICE (Natioanl Institue for Clinical Excellence)	1. All high-risk non-muscle invasive bladder cancer	1. Low	Does not specify whether presence of muscle changes the approach.
ICUD (International Consultation on Bladder Cancer) 2012	1. T1 tumours (regardless of the presence of muscle)	1.Strong	Does not specify whether presence of muscle changes the approach. Does not discuss HG-Ta tumours.

Eur Urol 2018;73:925-933

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Urinary Biomarkers - Cytology

- Most common; adjunct to cystoscopy
- Non-invasive, **highly specific** (90%+) for high grade tumors
  - Low sensitivity – neg test does not rule out cancer

Limitations:

- Dependent on cytopathologist and has range of results
- False positives associated with ancillary testing and costs
- Need certain volume and cellularity
- Expensive (up to $100 per test)

Urinary Biomarkers

- Cell-based and protein-based markers
- Several FDA approved
  - NMP22, BTA, CxBladder, UroVysion FISH
- None are standard as of yet

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

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)

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)

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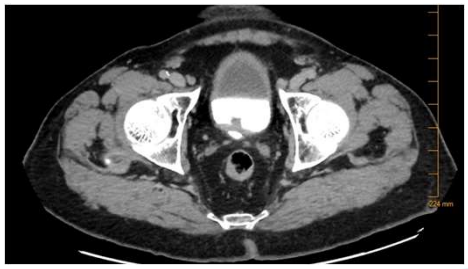
Imaging

- Often done for hematuria
- CT or MR Urogram
- Retrograde studies



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

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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STAGING AND GRADING

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Staging

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

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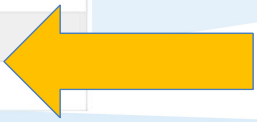
Grading

Table 5. 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



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Histology (Conventional)

- 90-95% Urothelial carcinoma (UC)
- ~ 5% Squamous cell carcinoma (SCC) EXCEPT ↑ risk for spinal cord pts, endemic bilharziasis
- 0.5-2% Adenocarcinoma
  - Urachus (allantois) or trigonal region
  - Prior bladder extrophy
  - History of long-term inflammation or infection
  - Non-urachal adenoCA must be distinguished from extension of colorectal primary

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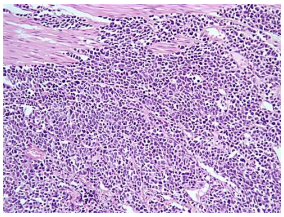

Small cell

Histology - Variants

- UC with mixed features such as squamous or glandular differentiation ~30%
  - Similar prognosis and treatment stage for stage
- Pure SCC or Adeno Ca
  - Often understaged; typically require cystectomy
- Small cell (neuroendocrine)
  - Stain with synaptophysin, neuron specific enolase or chromogranin
  - Treat with upfront chemo: platinum + etoposide (VP-16)

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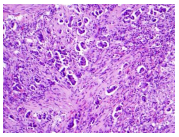

Micropapillary

Histology - Variants

- Plasmacytoid and Nested variants *(do **worse**)*
- Micropapillary- unusual variant of UC *(relatively chemoresistant)*
- Sarcomatoid - only epithelial –> Cystect

An experienced genitourinary pathologist should revie egards to variant or suspected variant histology (e.g., microp sarcomatoid), extensive squamous or glandular differe ate Recommendation; Evidence Strength: Grade C)

Remember a general rule of thumb is that variants are AGGRESSIVE and OFTEN UNDERSTAGED

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

RISK STRATIFICATION

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Risk Stratification

- Important to define
  - risk of progression/recurrence
  - need for and intensity of adjuvant therapy
  - frequency/duration of surveillance
- EORTC risk calculator, CUETO, AUA

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)

Recurrence and Progression

Table 5 – Weights used to calculate the recurrence and progression scores

Factor	Recurrence	Progression
Number of tumors		
Single	0	0
2 to 7	3	3
≥8	6	3
Tumor size		
<3 cm	0	0
≥3 cm	3	3
Prior recurrence rate		
Primary	0	0
≤1 rec/yr	2	2
>1 rec/yr	4	2
T category		
Ta	0	0
T1	1	4
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 – Probability of recurrence and progression according to total score

Recurrence score	Prob recurrence 1 year (95% CI)	Prob recurrence 5 years (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	**Prob progression 1 year (95% CI)**	**Prob progression 5 years (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%)

Sylvester RJ et al. Eur Urol 2006

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AUA Risk Stratification

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

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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

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[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

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TREATMENT AND SURVEILLANCE

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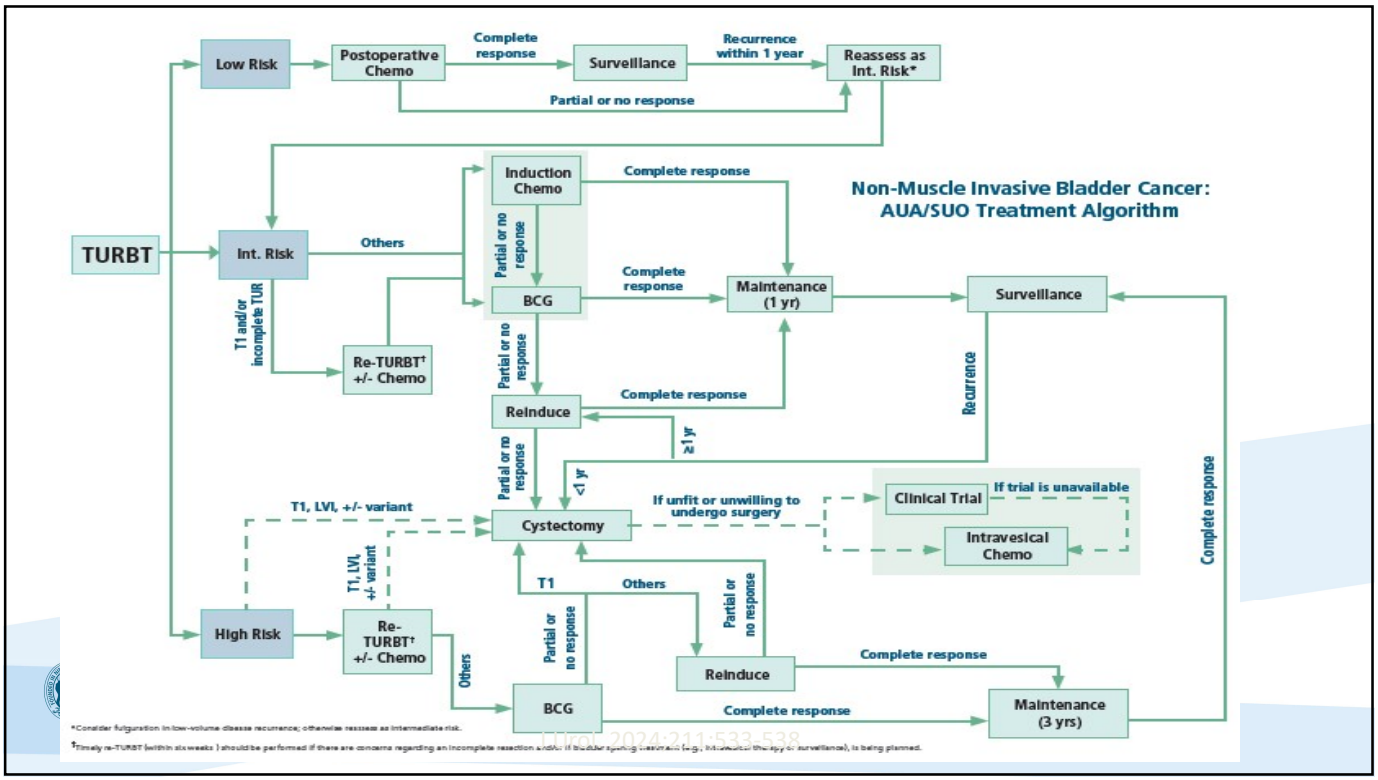

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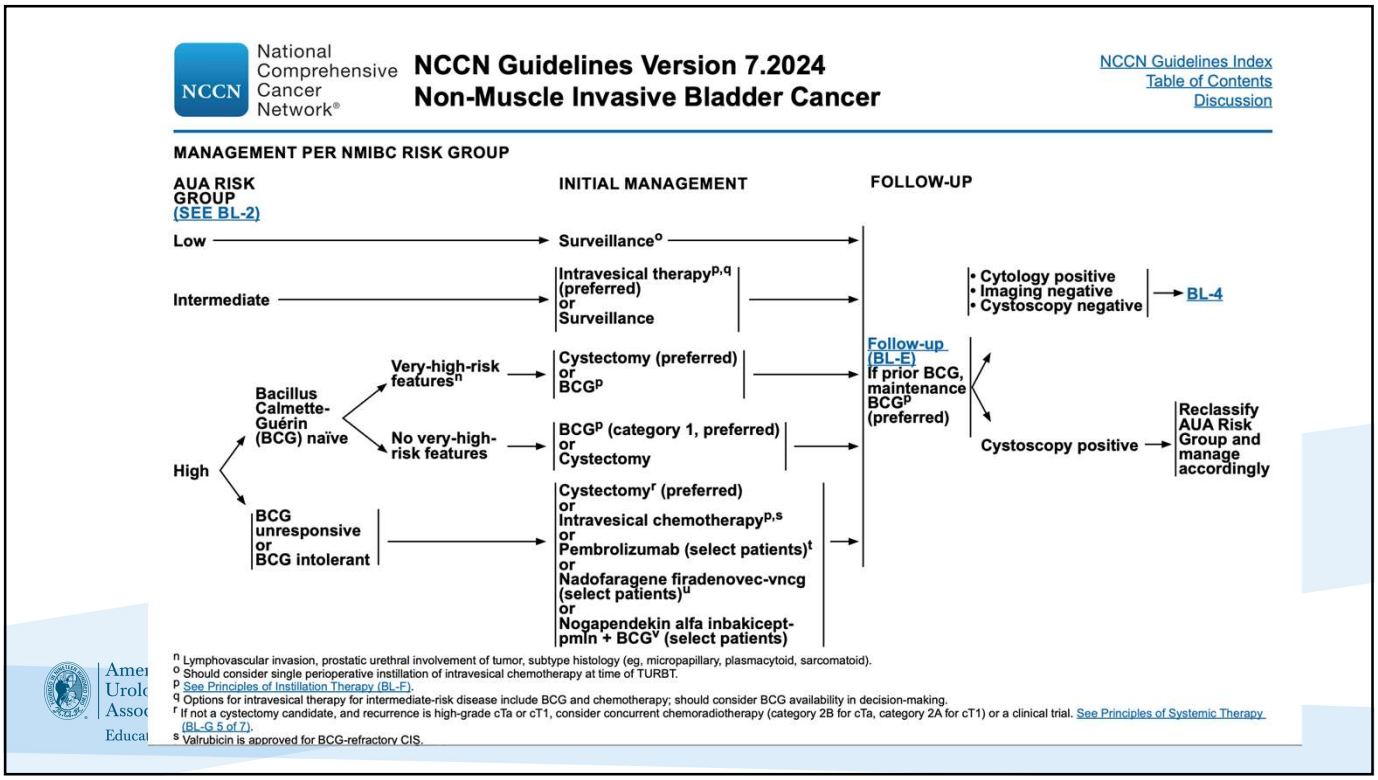

Intravesical Therapy

Perioperative chemotherapy

- Within 24 hrs of TURBT *(suspected low, intermediate risk)*
  - Most commonly mitomycin-c, gemcitabine
- Reduces recurrence rate
- Do not use if suspected bladder perforation or in case of incomplete resection

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., gemcitabine, mitomycin C) within 24 hours of TURBT. In a patient with a suspected perforation or extensive resection, a clinician should not use postoperative intravesical chemotherapy. (Moderate Recommendation; Evidence Strength: Grade B)

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JAMA | Original Investigation

Effect of Intravesical Instillation of Gemcitabine vs Saline Immediately Following Resection of Suspected Low-Grade Non–Muscle-Invasive Bladder Cancer on Tumor Recurrence

SWOG S0337 Randomized Clinical Trial

Table 2. Primary and Secondary Analysis Comparisons by Treatment Group

Outcomes and Populations	Gemcitabine Group		Saline Group			
	No. With Outcome/ Total No.[a]	4-y Recurrence Rate, % (95% CI)[b]	No. With Outcome/ Total No.[a]	4-y Recurrence Rate, % (95% CI)[b]	Hazard Ratio (95% CI)[c]	*P* Value by 1-Sided Log-Rank Test
Primary Outcome and Primary Population						
Recurrence among all randomized, eligible patients (intention-to-treat population)	67/201	35 (29-42)	91/205	47 (41-54)	0.66 (0.48-0.90)	<.001[d]
Secondary Populations						
Recurrence among all patients who received instillation and had low-grade non-muscle-invasive disease	34/102	34 (26-44)	59/113	54 (45-65)	0.53 (0.35-0.81)	.001[d]
Recurrence among all patients who received instillation and had high-grade non-muscle-invasive disease	17/44	40 (27-58)	19/42	45 (32-63)	0.84 (0.45-1.60)	.38[d]
Secondary Outcomes						
Muscle invasion in intention-to-treat population	5/201		10/205		0.51 (0.17-1.49)	.11
Death due to any cause in intention-to-treat population	17/201		25/205		0.68 (0.37-1.27)	.12

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Messing, JAMA 2018

Intravesical Therapy

Adjuvant

- Adjuvant chemotherapy or BCG
- Induction +/- maintenance
- To limit recurrence and progression in patients with *intermediate* and *high-risk* disease

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Intravesical Therapy

Adjuvant chemotherapy

MMC	Gemcitabine	Doxorubicin	Docetaxel	Valrubicin
Alkylating agent	Nucleoside analog	Anthracycline	Taxane	Anthracycline
40mg/20ml	2g/100ml	50mg/50ml	75mg/100ml	800mg/75ml
LUTS, hematuria, pain, rash, **severe chemical cystitis**, **severe skin reaction**, myelosuppr.	LUTS, pain, hematuria, rash, itch, chemical cystitis, myelosuppr., **pulmonary fibrosis**	LUTS, hematuria, **cardiotoxicity**, myelosuppr.	LUTS, hematuria, myelosuppr., **hand-foot syndrome**, change in nail color	LUTS, hematuria, **cardiotoxicity**, myelosuppr.

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Adapted from AUA Core Curriculum

Intravesical Therapy

Adjuvant Immunotherapy - BCG

- Avoid
  - active infection, gross hematuria, urethral trauma
- ***Not*** for low risk NMIBC
- Retain drug for 2 hours for peak efficacy
- Standard induction weekly x 6 weeks
- Maintenance weekly x 3 weeks, 1 – 3 years, SWOG 6+3 protocol

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Intravesical Therapy

Adjuvant Immunotherapy - BCG

- Standard of care in HR-NMIBC
  - 19% improvement in 5-yr RFS
  - 6% improvement in 5-yr PFS
- Reduced efficacy in immunosuppressed
  - *but* can be safely given

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Lamm, J Urol. 2000
Herr, BJUI. 2013

Intravesical Therapy

Adjuvant Immunotherapy - BCG

Common Side Effects

- Inflammatory cystitis
  - Common (mild)
- Flu-like symptoms (10%)
- Fever (5%)
- Granulomatous prostatitis (1%)

Significant Side Effects

- BCG cystitis
  - severe; 2-5%
- BCG sepsis
  - serious; 0.5%

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BCG Shortage *(Take Home Points)*

- BCG should **not** be used for **low-risk disease**.
- **Intravesical chemotherapy** should be used as the **first-line** option for patients with **intermediate-risk** NMIBC.
- If BCG would be administered as **second-line** therapy for intermediate-risk NMIBC, an **alternative intravesical chemotherapy** should be used in the setting of BCG shortage.

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AUA Statement, 2020

BCG Shortage *(Take Home Points)*

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

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AUA Statement, 2020

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BCG Shortage *(Take Home Points)*

- For **maintenance therapy**, limit BCG therapy to **one year**.
- In the event of BCG supply shortage, maintenance therapy should not be given and BCG naïve patients with high-risk disease should be **prioritized for induction BCG.**
- If BCG is not available, use **alternatives** to BCG
  - **gemcitabine, epirubicin, docetaxel, valrubicin, mitomycin, or sequential gemcitabine/docetaxel or gemcitabine/mitomycin**

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AUA Statement, 2020

BCG Shortage *(Take Home Points)*

- Additional risk factors (concomitant CIS, LVI, 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.

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AUA Statement, 2020

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Disease Recurrence after BCG

(terminology)

- **Refractory**
  - persistent disease after 6 mos or progression at 3 mos
- **Relapsing**
  - recur after BCG; early (<12 mos), Intermediate (12-24 mos), late (>24 mos)
- **Intolerant**
  - inability to receive adequate BCG
- **Unresponsive**
  - Recurs after two induction courses or one induction course plus one maintenance cycle

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Disease Recurrence after BCG

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; Evidence Strength: Grade C)

~50% of patients will respond to second induction course of BCG after single course

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Disease Recurrence after BCG

In a patient with persistent or recurrent high-grade NMIBC within 12 months of completion of adequate BCG therapy (two induction courses or one induction course plus one maintenance cycle) who is unwilling or unfit for cystectomy, a clinician may recommend clinical trial enrollment, an alternative intravesical therapy (i.e., nadofaragene [firadenovec-vncg]) or alternative intravesical chemotherapies (gemcitabine/docetaxel). A clinician may also offer systemic immunotherapy with pembrolizumab to a patient with CIS within 12 months of completion of adequate BCG therapy. (*Conditional Recommendation; Evidence Strength: Grade C*)

Nadofaragene firadenovec

Systemic Pembrolizumab

Gemcitabine/docetaxel

Valrubicin
- CR 18%, 10% at 1 YR

Clinical trial

Radical cystectomy

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Newer Intravesical Agents

Nadoferagene Firadenovec

- FDA approved 12/2022
  - High-risk, BCG unresponsive, with CIS +/- papillary
- Recombinant, non-replicating adenovirus
- q3 months x 5 doses
- 53% CR at 3 mos, 45% of CR have durable response at 12 mos

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Boorjian, Lancet Oncol 2021

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Newer Intravesical Agents

Nadoferagene Firadenovec

- 70% drug-related side effects

	Grade 1–2	Grade 3	Grade 4–5
Patients with study drug-related adverse events*	103 (66%)	6 (4%)	0
Types of events			
Discharge around the catheter during instillation	39 (25%)	0	0
Fatigue	31 (20%)	0	0
Bladder spasm	24 (15%)	1 (1%)	0
Micturition urgency	22 (14%)	2 (1%)	0
Chills	18 (12%)	0	0
Dysuria	17 (11%)	0	0
Pyrexia	16 (10%)	0	0
Syncope	0	1 (1%)	0
Hypertension	2 (1%)	1 (1%)	0
Urinary incontinence	4 (3%)	1 (1%)	0

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Boorjian, Lancet Oncol 2021

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Newer Intravesical Agents

Nogapendakin alfa inbakicept-pmin (N-803)

- FDA approved 2024 BCG unresponsive NMIBC
  - QUILT-3.032 (N803+BCG)
  - IL-15 super-agonist
  - CR in 71% of 82 patients with CIS +/- papillary disease, mDOR 26.6 months
  - Well tolerated - most TAEs Grade 1-2

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Chamie 2022

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Systemic Therapy Alternatives

Pembrolizumab

- FDA approved for BCG unresponsive NMIBC
  - KEYNOTE-057; 200mg IV q 3 wk x 2 yrs
  - CIS patients (w or w/o papillary tumors)
    - 41% initial CR, 21% durable response
  - PD-1 inhibitor

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Balar, Lancet Oncol 2021

Systemic Therapy Alternatives

Pembrolizumab

Side-effects

Category	Grade 1,2	Grade 3,4
Any	53%	13%
Immune TAE*	18%	3%

* Immune TAEs: hypothyroidism, hyperthyroidism, pneumonitis, adrenal insufficiency, colitis, hepatitis, hypophysitis, nephritis, type 1 diabetes

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Balar, Lancet Oncol 2021

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Surveillance of NMIBC

- Risk-adjusted
- After initial evaluation/treatment, first surveillance at 3-4 mos
  - **Low-risk**: at 6-9 mos, then annually
  - **Intermediate-risk**: 3-6 mos (2 yrs), 6-12 mos (2 yrs), then annually
  - **High-risk**: every 3-4 mos (2 yrs), 6 mos (2 yrs), then annually

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Radical Cystectomy *(for NMIBC)*

- High-risk with persistent HGT1 on repeat TURBT or T1 with CIS, LVI, variant histology
  - high rate of upstaging with variant histology
- High-risk with persistent/recurrent within one year of adequate BCG
- ***Fit for surgery*** ***(there are objective measures)***

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TURBT can be a morbid operation!

- Readmission rates 3.7% and 30-day complication rate Grade 3 or higher is 5%
- Surveillance cystoscopy and TURBT are expensive and contribute to financial toxicity
- Anesthesia can cause cognitive decline in older patients

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Clinicoecon Outcomes Res. 2020;12:693-709.
Scand J Urol. 2020;54:281-289

Active Surveillance for Bladder Cancer

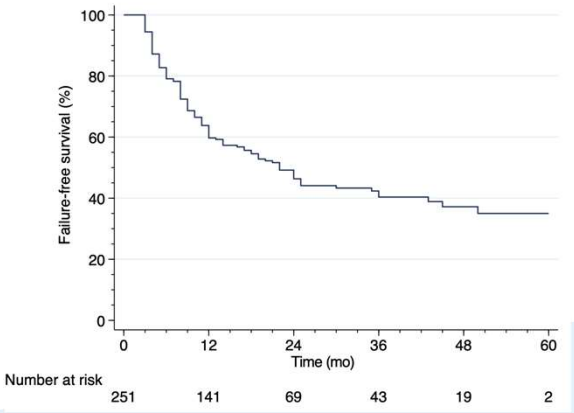

Table 2 – Multivariable Cox proportional hazards regression analysis of factors associated with AS failure for patients with low-grade non–muscle-invasive bladder cancer recurrence

Factor	HR (95% CI)	*p* value
Age at AS entry	1.02 (0.99–1.04)	0.139
Gender		
Male	1 (reference)	
Female	1.63 (0.92–2.88)	0.093
Smoking status		
Not an active smoker	1 (reference)	
Active smoker	0.99 (0.63–1.55)	0.960
Number of previous TUR procedures		
1 TUR	1 (reference)	
≥2 TURs	1.59 (1.01–2.51)	**0.047**
Time from last TUR to AS	0.99 (0.99–1.00)	0.572
Number of lesions at AS entry		
1 lesion	1 (reference)	
≥2 lesions	1.63 (1.05–2.54)	**0.029**
Lesion size at AS entry		
≤5 mm	1 (reference)	
>5 mm	1.12 (0.73–1.76)	0.591

AS = active surveillance; CI = confidence interval; HR = hazard ratio; TUR = transurethral resection.

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Contieri R et al. Eur Urol Oncol. 2021

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CASE

- 72-year-old female referred for asymptomatic, micros
  - 15 RBC/HPF
  - Non-smoker
  - No family history of urothelial carcinoma, Lynch Syndrome
- Office cystoscopy
  - 3 small tumors: right lateral wall 0.5 cm, posterior wall 0.5 cm, 1.0 cm
- TURBT - LG Ta, muscle present

Intermediate 0.2-3.1%[21, 22, 24]	High 1.3-6.3%[21, 22, 24]
One or more	One or more
11-25 RBC/HPF*	>25 RBC/HPF*
Previously low/negligible -risk patient with no prior evaluation and 3-25 RBC/HPF* on repeat urinalysis	History of gross hematuria
≥60 years	*Women should not be categorized as high-risk solely based on age*
40-59 years	≥60 years
10-30 pack years	>30 pack years
Any	One or more plus any high-risk feature

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J Urol 2025 27 Feb
J Urol 2020;204:778

TABLE 4: AUA Risk Stratification for NMIBC		
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

Prognostic Factors
- Grade
- Stage
- Size
- Multiplicity

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J Urol. 2024;211:533-538

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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., gemcitabine, mitomycin C) within 24 hours of TURBT. In a patient with a suspected perforation or extensive resection, a clinician should not use postoperative intravesical chemotherapy. (*Moderate Recommendation; Evidence Strength: Grade B*)

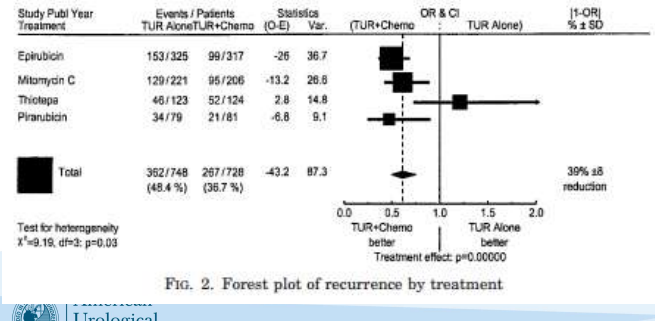
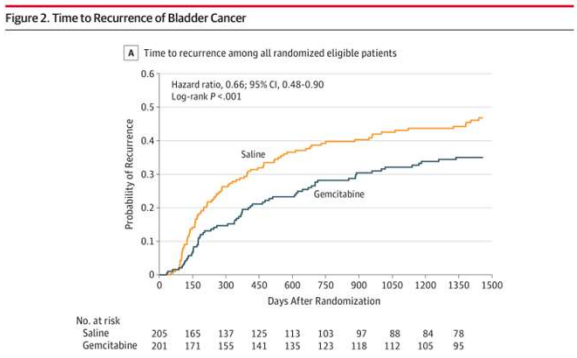


FIG. 2. Forest plot of recurrence by treatment



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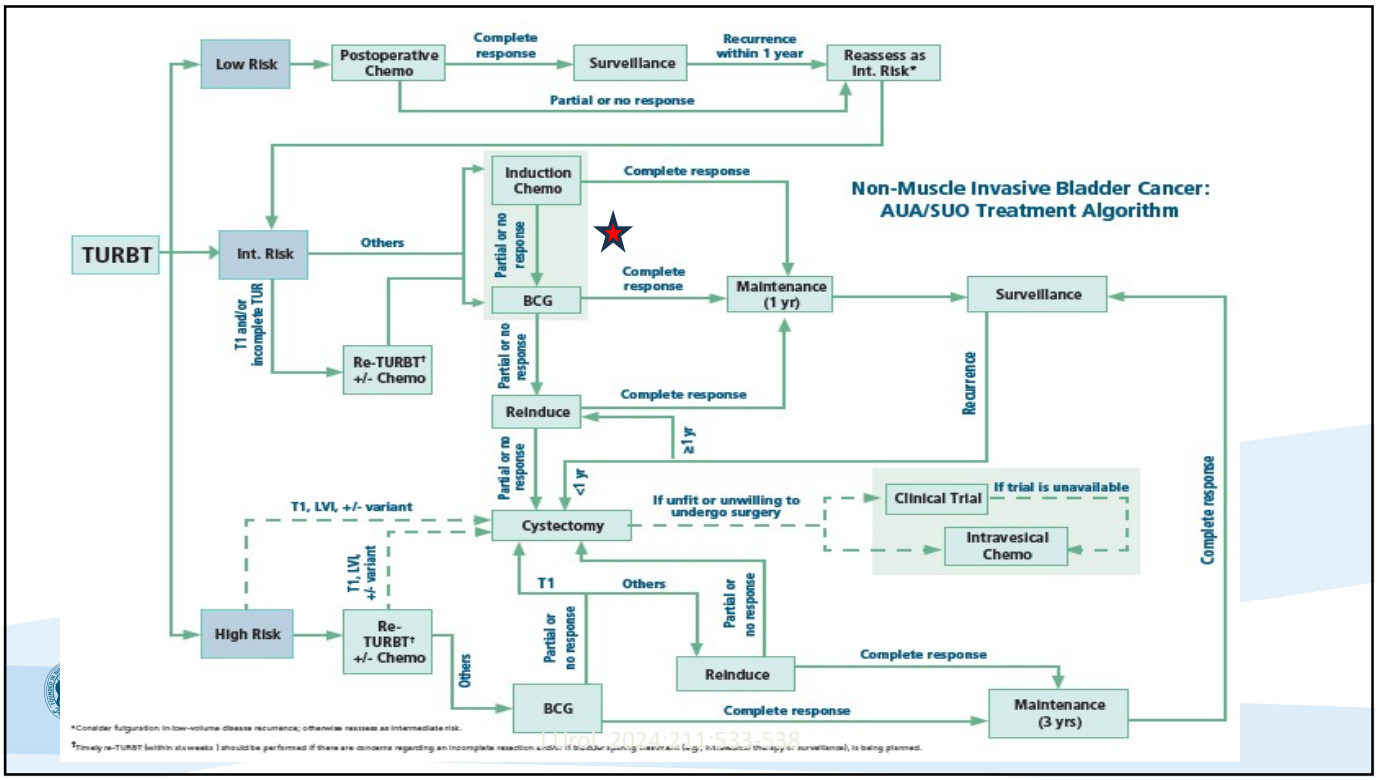
Sylvester 2004, Messing 2018

J Urol. 2024;211:533-538



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Thank You and Good Luck!

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