Non Muscle Invasive Bladder Cancer

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Objectives

Bladder Anatomy

Risk Factors for Bladder Cancer

Workup for Bladder Cancer

Staging

Management of LGTa

Management of HG disease

- BCG and intravesical chemotherapy

New intravesical treatments on the horizon

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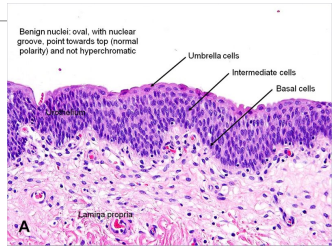
Bladder Anatomy

Urothelium

- Basal cells
- intermediate cells
- umbrella cells (closest to lumen).

Impermeable and inert due to umbrella cells characteristics

- glycosaminoglycan
- tight junctions
- uroplakin proteins
  - support bladder distension and maintain a blood-urine barrier.
  - Uroplakins are also the site where Uropathrogenic Escherichia coli attach via their type 1 fimbriae. Hence this boundary may be disrupted under pathological conditions, including chronic inflammation



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Bladder Anatomy

Deep to the urothelium is the lamina propria
- Fibroelastic tissue that allows for bladder distension

Deep to the lamina propria is the muscularis
- 3 layers of smooth muscle

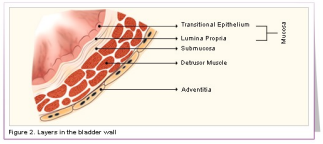

Figure 2. Layers in the bladder wall

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Non-Muscle Invasive Bladder Cancer (NMIBC)

Fourth most common cancer in men

Fifth most common cancer overall

M:F 4:1

75% of all new bladder cancer is NMIBC

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Risk Factors for Bladder Cancer

Smoking (RR=4), 50% of BC can be attributed to smoking

Cyclophosphamide/isofosphamide

Pelvic Radiation

Schistosoma or Chronic Foley → squamous cell carcinoma risk

Occupational Exposure

Cyclic Hydrocarbons (industrial chemicals, asphalt) = truck drivers, oilmen, coal miners, metal workers

Aromatic Amines (dyes) = Hairdresser, painter, textile worker, chemical plant

N-Nitrosamine = smoking, rubber plant, plastic/latex

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Signs/Symptoms

Gross Hematuria
- 13-30% of those with GH will have bladder cancer

Microscopic Hematuria
- 0.5% - 10% can have bladder cancer

Irritative Voiding symptoms + hematuria doubles risk of a type of NMIBC called carcinoma in situ (CIS)
- 5 → 10%

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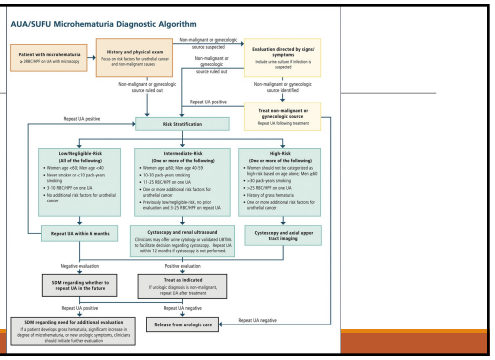

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Table 4: AUA/SUFU Microhematuria Risk Stratification System 2025

Risk of malignancy*	Low/Negligible 0-0.4%[9, 22, 24]	Intermediate 0.2-3.1%[9, 22, 24]	High 1.3-6.3%[22, 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

*Risk of malignancy is based on the definition from the 2020 AUA/SUFU Guideline in which women being age < 50 year was a criterion for low-risk, women being age 50-59 years was a criterion for intermediate-risk, and women being age > 60 was a criterion for high-risk. Based on interval studies showing significantly lower risk of urothelial malignancy in women, women being age < 60 years is a criterion for low-risk, women being age > 60 years is a criterion for intermediate-risk, and women cannot be categorized as high-risk based on age alone in the 2025 guideline iteration.

*HPF: High-Power Field

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Work Up

Cystoscopic evaluation

Upper tract imaging

Cytology – low sensitivity but high specificity

Urine-based tumor markers – not currently recommended due to poor specificity and high cost

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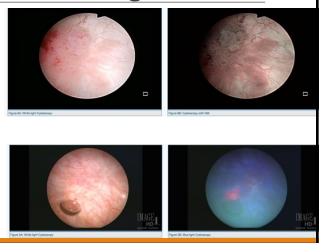
Narrow Band Imaging and BlueLight

NBI – splits visible light into green and blue filters.

- Vascular structures better seen
- improves in 3-month and 1-year recurrence

Bluelight Cystoscopy with Cysview

- Instill Hexaminolevinulate (HAL) 1 hr before cystoscopy
- Malignant cells uptake preferentially = intracellular accumulation of photoactive porphyrins = malignant cells preferentially fluoresce pink under blue light.
- fewer recurrences at 12 months, HR 0.75
- Improved detection of CIS compared to white light
- Can detect as much as 20% of recurrences on cystoscopy for NMIBC that would not have been seen otherwise
- Does reduce recurrence rates at 3 years
- May not improve progression-free or overall survival



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Work Up

Transurethral Resection of Bladder Tumor (TURBT)

- Both forms of staging and treating
- inclusion of muscle in the specimen and instillation of intravesical chemotherapy have been associated with disease recurrence and progression.
  - intravesical chemotherapy within 24 hours of TURBT to reduce recurrence by up to 35%

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Histologies of Urothelial Cancer

Papillary Urothelial Neoplasm of Low Malignant Potential (PUNLMP)

Low Grade
- Frondular papillary tumors
- Rarely T1

Low Grade

High Grade
- sessile or papillary (cauliflower or brain-like) lesions

High Grade

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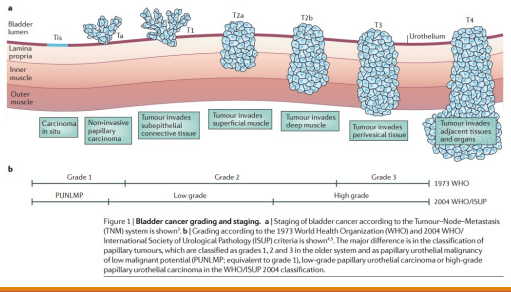

Figure 1 | **Bladder cancer grading and staging.** **a** | Staging of bladder cancer according to the Tumour–Node–Metastasis (TNM) system is shown[4]. **b** | Grading according to the 1973 World Health Organization (WHO) and 2004 WHO/International Society of Urological Pathology (ISUP) criteria is shown[14,15]. The major difference is in the classification of papillary tumours, which are classified as grades 1, 2 and 3 in the older system and as papillary urothelial malignancy of low malignant potential (PUNLMP; equivalent to grade 1), low-grade papillary urothelial carcinoma or high-grade papillary urothelial carcinoma in the WHO/ISUP 2004 classification.

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Recurrence and Progression

Low Grade
- Recurrence is the Rule 15-70% recur in 1 year
- Progression is rare – <5% progress to muscle invasive disease

High Grade
- Recurrence and Progression common
  - Ta: 13-40% can progress to T1 and 6-25% to T2
  - T1 : 80% recur and 50% progress to muscle invasion in 3 years
  - Tis : 82% recur, 40-80% progress to muscle invasion without treatment

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AUA Risk Stratification

Low Risk	Intermediate Risk	High Risk
LGTa, solitary, <3cm	HGTa, solitary, <3cm	HGT1
PUNLMP	LGTa, recurrent, <1yr	Any recurrent HGTa
	LGTa, solitary >3cm	HGTa, multifocal or >3cm
	LGTa, multifocal	Any CIS
	LGT1	Any BCG failure
		Any LVI
		Any variant histology
		Any HG prostatic urethra involvment.

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LGTa management

Cystoscopy surveillance
- 3 months, 12 months, annually for 5 years

Strong management recommendation for fulguration (including in the office) of recurrent low risk LGTa disease (<3cm) due to the very low rates of progression
- decreased overall burden of therapy
- lower costs.
- larger low-grade tumors (>3 cm) may require intervention with transurethral resection under anesthesia as these may reclassify patients to a different risk group.

The surveillance cycle restarts every time a new tumor is identified

If a tumor is identified on surveillance cystoscopy and thought to be high grade, the patient will require another TURBT to reassess

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Adjuvant Bacille Calmette-Guerin (BCG)

Standard of care for patients with High Risk NMIBC

For intermediate risk patients, BCG and chemotherapy are similar in efficacy

BCG should be considered first line therapy for CIS since the response rate is double that of chemotherapy

Contraindications: gross hematuria, traumatic catheterization, active TB, symptomatic UTI, febrile illness, 7-14 days of urologic surgery.

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Adjuvant Bacille Calmette-Guerin (BCG)

Induction BCG: 1x instillation weekly x 6 weeks
- No drinking for 4 hours before, hold for 2 hours, urinate

Maintenance Therapy 1x weekly x 3 weeks
- **3,6,12,18,24,30,36 months after initiation of BCG**
- Duration: 1 year for intermediate risk, 2-3 years for high risk (presuming full-dosing)

Is still effective in immunosuppressed patients and not contraindicated.
- Chronic steroids, treated HIV, etc.

May be less effective in those taking warfarin and statins.

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HGTa and HGT1 surveillance

First surveillance cystoscopy at 3 months
- recurrence at this time is recognized as an important prognosticator for both recurrence and progression

Cystoscopy every 3-6 months
- High risk patients are usually assessed cystoscopically at 3 month intervals for the first two years, and then at 6 month intervals for the next 2-3 years, and then annually thereafter.

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HGTa and HGT1 surveillance

Up to 5% of patients with bladder tumors develop upper tract urothelial carcinomas
- Highter with higher risk disease, tumors near the UO, tumor multifocality, frequent recurrences or predisposing factors such as Lynch syndrome
- High-risk patients should get upper tract imaging every 1 to 2 years.
  - CTU or MRU

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Adjuvant Bacille Calmette-Guerin (BCG)

BCG induction lowers the risk of disease recurrence by 40–59%

Up to 50% of high risk NMIBC patients will ultimately experience recurrence of bladder cancer following BCG treatment.

15-25% of patients with CIS will have residual disease at 6months after induction BCG (BCG Refractory)

The standard of care for patients with recurrence after BCG is radical cystectomy

- Salvage intravesical therapy with chemotherapy agents, gene therapy, or novel immunotherapies, systemic immunotherapy, and clinical trials are alternative options based on disease characteristics albeit at a higher risk of recurrence and progression.

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BCG Failure

Definitions:

- BCG Refractory
  - Persistence of disease despite therapy at 6 months OR stage progression of disease at 3 months
  - Highest rates of progression to MIBC and metastasis in these groups
- BCG Relapsing
  - New disease after being disease free for 3 months (starts at 6 months for CIS)
  - Early relapse is <12 months; Late relapse is >24 months
- BCG Intolerance
  - Inability to receive adequate BCG 2/2 toxicity/SE
- BCG Unresponsive
  - BCG refractory or BCG relapsing within 6 months
  - No benefit to additional BCG treatment, discuss RC

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Further Therapy after BCG Failure

If persistent Ta or CIS after induction BCG, can offer second round of induction BCG

If T1 disease after BCG → Radical Cystectomy

2nd line chemotherapies have <10% efficacy at 12 months in BCG-refractory CIS

- The 2-year recurrence and progression rates for those who fail first-line intravesical therapy are typically around 60-80% and 10-20%, respectively.

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Gemcitabine/Docetaxel intravesical chemotherapy

Administration:
- gemcitabine 1g in 50 mL water (pH adjusted) x 1 hour
- drain bladder
- docetaxel 37.5 mg in 50 mL saline x 1-2 hours.

Induction x6 weeks with monthly maintenance thereafter for two years has 1-year RFS 65-70% and 2-year RFS of 50-60%.

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Gem/Doce Intolerance strategies

1300mg NaHCO3 to alkalinize the urine the night before and the morning of treatment

Pretreated with anticholinergic or B3agonist medications

Pretreated with NSAIDs

Instillation of lidocaine (40cc or 2% mixed with 4cc of 8.4% standard sodium bicarbonate solution) for 10-15min prior to chemotherapy instillation

Low volume in catheter balloon

Half the drug dosing, do the protocol twice (4 instillations instead of 2)

Gravity reflux closed drainage system

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ANKTIVA = Nogapendekin alfa inbakicept NAI

The FDA recently approved the combination of BCG with ANKTIVA for the treatment of BCG unresponsive CIS +/- papillary disease

IL-15 superagonist that promotes CD8+ T cell and natural killer (NK) cell activation.

For BCG unresponsive CIS, overall CR was 71% with 51% CR at 45 months

For BCG unresponsive HGTa/HGT1, DFS is 58% at 12 months and 54% at 24 months

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Nadofaragene firadenovec

Replication-incompetent type 5 adenovirus

Stimulates anticancer cytokine IFN α_{2b}

Administered with Syn3 = a polyamide surfactant that inproves infection of urothelium

53% CR at 3 months and 24% CR at 12 months and 13% CR at 5 years in BCG-unresponsive CIS

44% CR at 12 months and 33% CR at 5 years in BCG-unresponsive HGTa/HGT1

5% progress to MIBC at 1 year

3 x 10^{10} viral particles per mL, 75 mL, 1 hour dwell time, q3 months x 5 doses

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Pembrolizomab (Keytruda)

FDA-approved systemic option for patients with BCG-unresponsive NMIBC:

For BCG-unresponsive CIS, CR was 41% and lasted on average 16 months

- Of those who achieved CR, 51% eventually had a recurrence

For BCG-unresponsitve HGTa/HGT1, DFS of 44% at 12 months and 35% at 36 months

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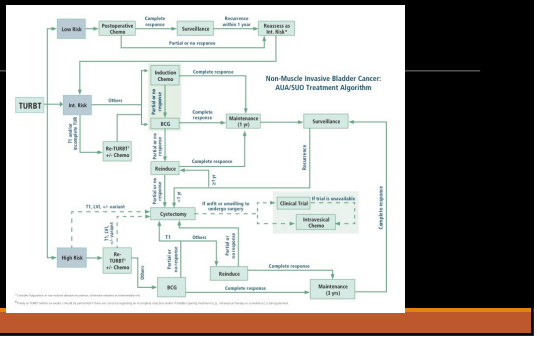

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