

Bladder Cancer Disease State Overview

For Use by Medical Science Liaisons (MSLs) and Value & Evidence Scientific Engagement (V&ESE) Field Personnel

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Medical Affairs

Bladder Cancer Disease State Education



**Bladder Cancer
Overview**



**NMIBC: Disease
& Risk**



**NMIBC
Treatment
Landscape**



MIBC



mUC

MIBC, muscle-invasive bladder cancer; mUC, metastatic urothelial carcinoma; NMIBC, non-muscle-invasive bladder cancer.

Bladder cancer: Key statistics¹



Bladder cancer is the 6th most common cancer in the US: incidence, mortality, and who it affects

84,530

estimated new cases in the US
in 2026

17,870

estimated deaths in 2026
(2.9% of all US cancer deaths)

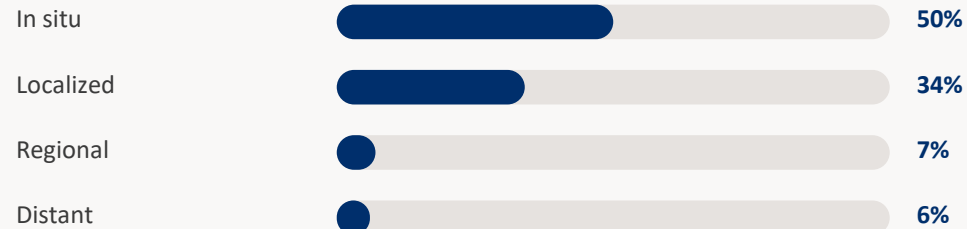
79.1%*

of patients survive 5 years

6th

most common cancer in the US;
10th leading cause of cancer death

Stage at diagnosis[†]



5-year relative survival by stage‡



73 yrs

median age at diagnosis

~94%

of patients are ≥55 years old at diagnosis

20.3 → 16.4

incidence per 100,000 declining
(1992–2023), while deaths hold flat
at 4.5 → 3.9 (1992–2024)

US, United States; yrs, years. Trend rates refer to observed rates; the 2020 incidence rate is displayed but not used in the fit of the trend line.

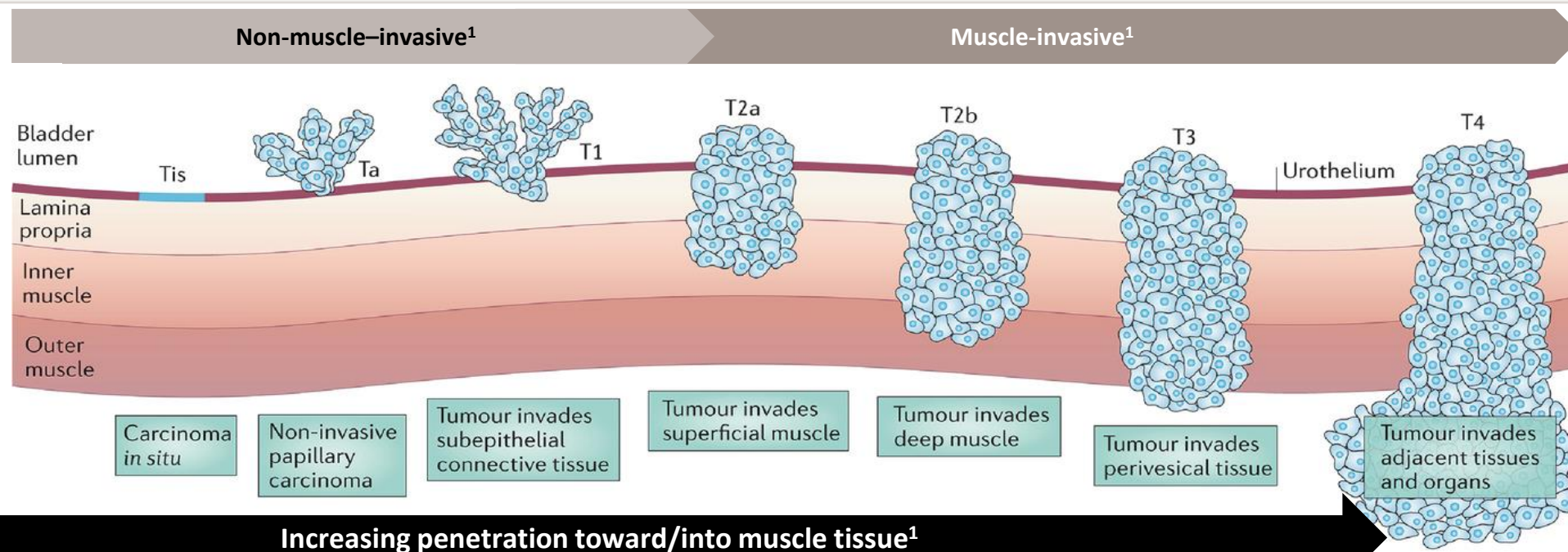
*Deaths come from US Mortality, 2016–2022. †3% of new cases are unstaged. ‡Based on data from SEER 21 (Excluding IL) 2016–2022 among patients initially diagnosed with each corresponding stage.

1. National Cancer Institute SEER. Cancer stat facts: bladder cancer. Accessed September 28, 2026. <https://seer.cancer.gov/statfacts/html/urinb.html>



Definition and bladder cancer stages

Bladder cancer commonly develops in the urothelium and may further progress to invade the bladder muscle where it may ultimately lead to metastatic disease¹



NMIBC

- Papillary tumors: non-invasive projections from the bladder surface²
- CIS: flat tumor found in the inner layer of bladder cells²

MIBC

- Tumors that have invaded bladder muscle with a higher probability of spreading to lymph nodes/other organs³

Metastatic bladder cancer

- Includes tumors that have spread to distant organs, such as the liver, lungs, or lymph nodes⁴

BC, bladder cancer; CIS, carcinoma *in situ*; MIBC, muscle-invasive bladder cancer; NMIBC, non-muscle-invasive bladder cancer.

1. Knowles M, et al. *Nat Rev Cancer*. 2014;15:25–41. 2. American Cancer Society. Accessed September 28, 2026. <https://www.cancer.org/cancer/bladder-cancer/about/what-is-bladder-cancer.html> 3. Patel V, et al. *CA Cancer J Clin*. 2020;70(5):404–423.

4. American Cancer Society. "Bladder Cancer Stages." Accessed September 28, 2026. <https://www.cancer.org/cancer/bladder-cancer/detection-diagnosis-staging/staging.html>.

Bladder cancer risk factors



Lifestyle, environmental, and genetic factors are all associated with bladder cancer development¹



Increasing age¹



Tobacco use (especially cigarettes)²



Genetic mutations³⁻⁵



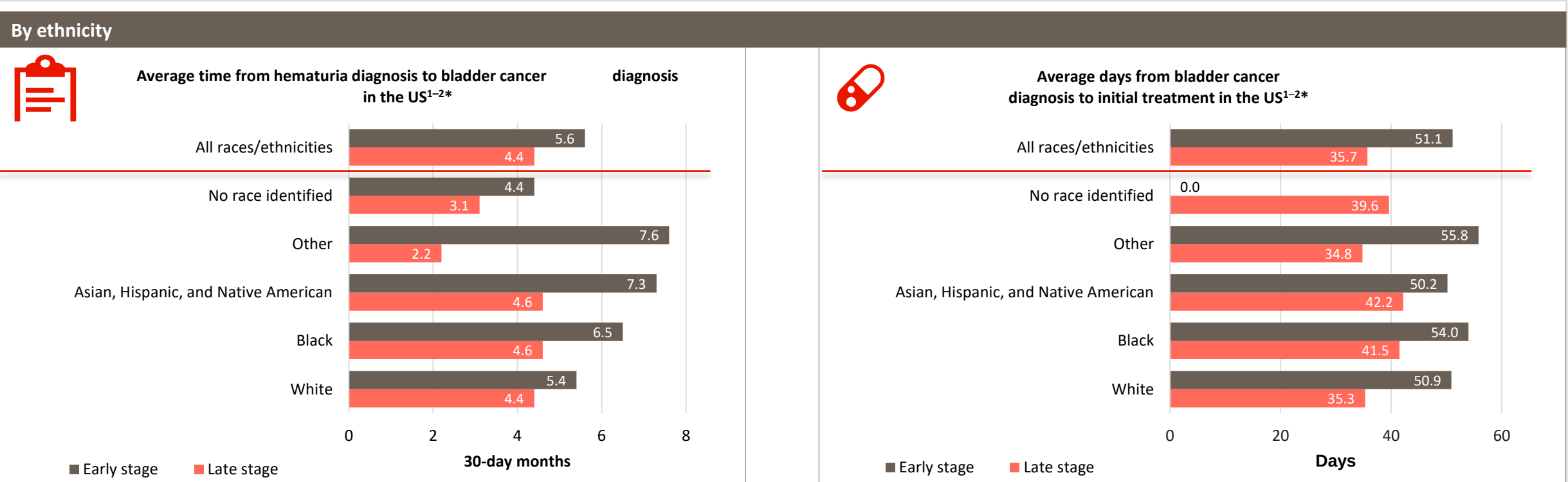
Occupational exposure¹



Prior chemotherapy or pelvic radiation therapy⁶⁻⁸

1. National Cancer Institute. Accessed September 28, 2026. <https://www.cancer.gov/types/bladder/hp/bladder-treatment-pdq> 2. Burger M, et al. *Eur Urol*. 2013;63(2):234–241. Cited by the National Cancer Institute. 3. Marees T, et al. *J Natl Cancer Inst*. 2008;100(24):1771–1779. Cited by the National Cancer Institute. 4. Gallagher DJ, et al. *Hematol Oncol Clin North Am*. 2010;24(5):861–883. Cited by the National Cancer Institute. 5. Lindor NM, et al. *J Natl Cancer Inst Monogr*. 2008;(38):1–93. Cited by the National Cancer Institute. 6. Nieder AM, et al. *J Urol*. 2008;180(5):2005–2009; discussion 2009–10. Cited by the National Cancer Institute. 7. Abern MR, et al. *Urol Oncol*. 2013;31(8):1628–1634. Cited by the National Cancer Institute. 8. Monach PA, et al. *Arthritis Rheum*. 2010;62(1):9–21. Cited by the National Cancer Institute.

Bladder cancer healthcare equity



Longer average time to diagnosis and treatment may be observed for Asian, Hispanic, Native American, and Black patients vs white patients¹⁻²

By gender

- Females are **less likely to receive bladder cancer treatment** overall and less likely to receive treatment within 12 weeks of diagnosis³
- Female sex is also associated with increased odds of **advanced disease** and **worse OS**³

*Medicare claims analysis of data between 2016–2019 involving n=4,356 patients diagnosed with bladder cancer in 2018.

OS, overall survival; US, United states.

1. Association of Community Care Centers. 2022;37(3):65–70. https://www.accc-cancer.org/docs/documents/oncology-issues/articles/2022/v37-n3/understanding-and-mitigating-disparities-in-bladder-cancer-care.pdf?sfvrsn=8db75549_8 2. Boehmer L, et al. Association of Community Care Centers. 2021;Abstract #e18815. https://www.accc-cancer.org/docs/documents/presentations/2022_asco-am-poster_abstract-e18815_v05-18-20.pdf?sfvrsn=5ec24588_0_3 3. Weiner AB, et al. *Urol Oncol*. 2018;36(5):237-e9–237-e17.

FGFR alterations in bladder cancer: Prevalence



FGFR alterations provide a promising therapeutic target in urothelial carcinoma, including NMIBC^{1–4}

FGFR alterations are prevalent in NMIBC^{1–4}



FGFRs are transmembrane kinase proteins that **regulate key cellular processes** and play essential roles in organ development, angiogenesis, metabolism, and tissue homeostasis^{5–8}



FGFR alterations occur in approximately **5–10% of cancers**, and are common in urothelial carcinomas^{1–4}



FGFR alterations are thought to promote tumor cell growth and proliferation, making FGFR inhibition a **promising therapeutic target** across multiple tumor types^{1,3}



FGFR3 alterations are observed in **>70% of NMIBC**, and approximately 10–20% of MIBC⁴

FGFR, fibroblast growth factor receptor; FGFR3, fibroblast growth factor receptor 3; MIBC, muscle-invasive bladder cancer; NMIBC, non-muscle-invasive bladder cancer.

1. Helsten T, et al. *Clin Cancer Res*. 2016;22(1):259–267. 2. Krook MA, et al. *Br J Cancer*. 2021;124(5):880–892. 3. Di Martino E, et al. *Future Oncol*. 2016;12(19):2243–2263. 4. Liu X, et al. *Genet Mol Res*. 2014;13(1):1109–1120.

5. Pacini L, et al. *Cells*. 2021;10(5):1154. 6. Ruan R, et al. *Mol Cancer*. 2023;22:60. 7. Shang S, et al. *Explor Target Antitumor Ther*. 2024;5(3):641–677. 8. Xie Y, et al. *Signal Transduct Target Ther*. 2020;5:181.

FGFR alterations in bladder cancer: Diagnostic testing



FGFR diagnostic testing

- The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) **recommend testing for driver mutations, including *FGFR3***, in certain cancers to identify potential targeted therapies¹
- Diagnostic approaches for FGFR alterations detection includes^{2,3}:
 - Tumor tissue: NGS, hybridization capture, and FISH
 - Tumor DNA/RNA: NGS, RT-PCR
 - Blood/cell-free DNA/RNA: NGS
 - Urine: DNA single nucleotide polymorphism analysis of urinary biomarkers
- In a retrospective study of 761 patients with advanced urothelial cancer, less than half (**45%**) of patients were tested for *FGFR* alterations⁴
- **utDNA** testing may provide a practical, non-invasive approach to risk stratification to help inform clinical management in patients with bladder cancer^{5,6}

FGFR, fibroblast growth factor receptor; *FGFR3*, fibroblast growth factor receptor 3; FISH, fluorescence *in situ* hybridization; NCCN, National Comprehensive Cancer Network® (NCCN®); NGS, next-generation sequencing; RT-PCR, reverse transcription polymerase chain reaction; utDNA, urinary tumor DNA.

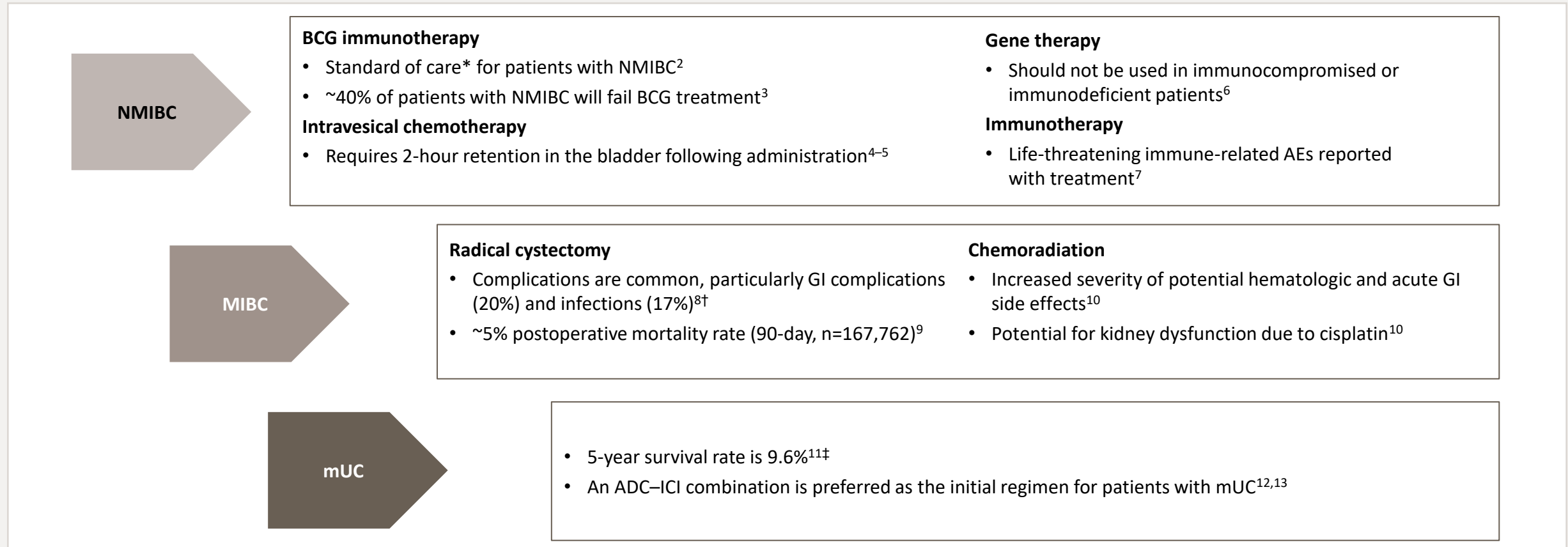
1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Bladder Cancer. V.3.2026. © National Comprehensive Cancer Network, Inc. 2026. All rights reserved. Accessed September 28, 2026. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 2. Krook MA, et al. *Br J Cancer*. 2021;124(5):880–892. 3. Neil JL, et al. *Bladder Cancer*. 2026;5;12(2):23523735261447112. 4. Nimgaonkar V, et al. *JAMA Oncol*. 2022;8(7):1070–1072.

5. Guerrero-Ramos F, et al. ESMO 2024. Poster 1973P. 6. Catto JW, et al. EAU 2026. Oral presentation.



Bladder cancer treatments, complications and quality of life considerations by stage

Quality of life steadily worsens as patients progress through each stage of disease and the accompanying treatments¹



*Post TURBT.² †Systematic review and meta-analysis of 44 RCTs; pooled rates are based on patients from studies reporting data for each respective complication. ‡Among patients initially diagnosed with metastatic bladder cancer.

ADC, antibody-drug conjugate; AE, adverse event; BCG, Bacillus Calmette-Guérin; GI, gastrointestinal; ICI, immune checkpoint inhibitor; MIBC, muscle-invasive bladder cancer; mUC, metastatic urothelial carcinoma; NMIBC, non-muscle-invasive bladder cancer; RCT, randomized controlled trial; TURBT, transurethral resection of bladder tumor.

1. Smith A, et al. *Bladder Cancer*. 2022;8(1):55–70. 2. Kates M, et al. *Clin Cancer Res*. 2020;26(4):882–891. 3. Chakra MA, et al. *Front Biosci*. 2026;31(5):47606. 4. Au JL, et al. *J Natl Cancer Inst*. 2001;93(8):597–604. 5. Gontero P, Freja B. *Ann Oncol*. 2006;17:v123–v128. Cited by Di Lorenzo G, et al. *Cancer*. 2010;1893–1900. 6. Nadeem A, et al. *Front Urol*. 2023;3:1206398. 7. Balar AV, et al. *Lancet Oncol*. 2021;22(7):919–930. 8. Katsimperi S, et al. *Eur Urol Focus*. 2023;9(6):920–929. 9. Korkes F, et al. *Urol Int*. 2023;107(1):96–104. 10. McHaffie D, et al. *Urol Oncol*. 2016;34(6):271–278. 11. National Cancer Institute SEER. Accessed September 28, 2026. <https://seer.cancer.gov/statfacts/html/urinb.html> 12. Powles T, et al. *NEJM*. 2024;390(10):875–888. 13. Zhang T, et al. *Oncol*. 2024;29(12):1003–1013.

NMIBC definition and manifestations



NMIBC arises in the epithelium or mucosa and can progress to the subepithelial connective tissue or lamina propria¹

NMIBC



At diagnosis, ~75% of bladder cancers are **non-muscle invasive**²



Hematuria is the most common presenting bladder cancer symptom; patients may also experience frequent and/or painful urination, urgency, and difficulty urinating³

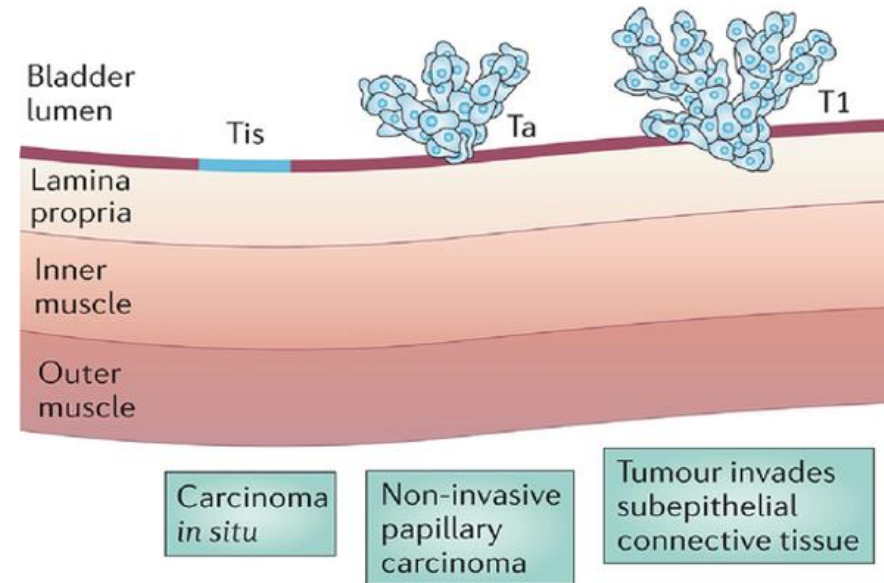


Tumors are **stratified** by risk status based on the risk of **recurrence** and **progression**^{4,5}



Approximately **39%** of patients experience recurrence within 5 years, while the predicted 5-year risk of progression to MIBC ranges from **<1 to >40%**, depending on risk group^{6,7}

NMIBC manifestations⁸



- Papillary tumors: non-invasive projections from the bladder surface⁹
- CIS: flat tumor found in the inner layer of bladder cells⁹

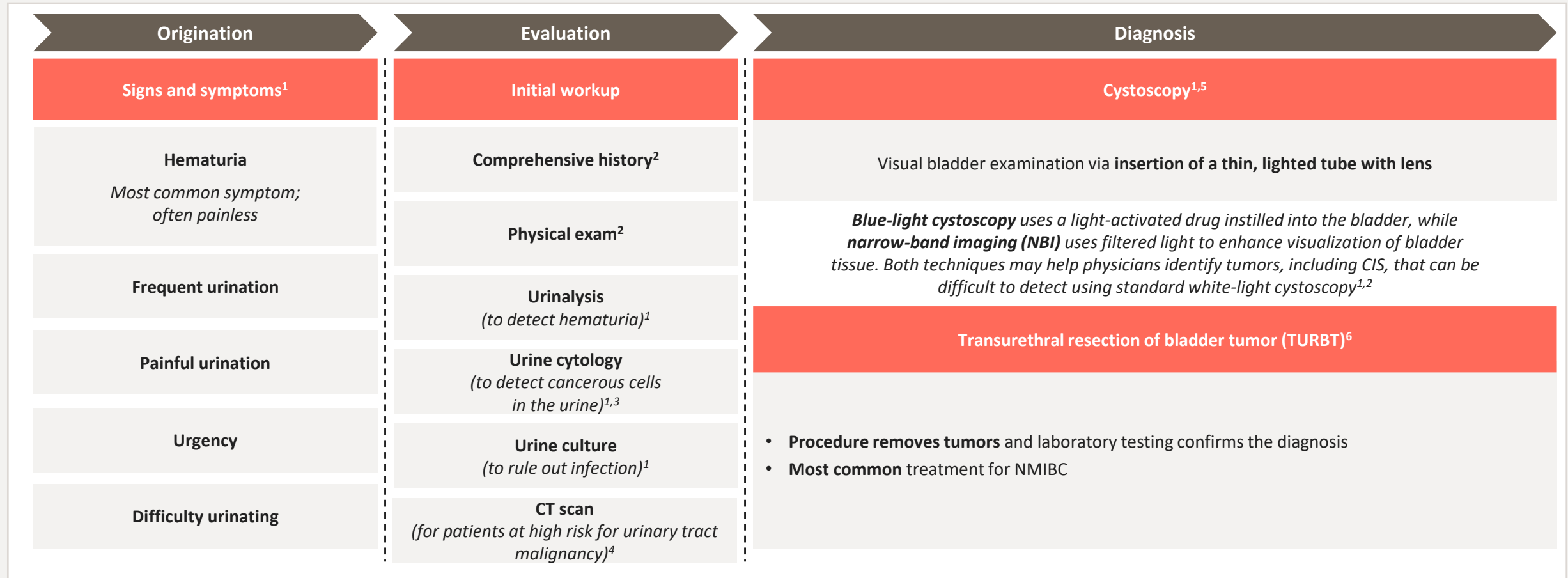
CIS, carcinoma *in situ*; MIBC, muscle-invasive bladder cancer; NMIBC, non-muscle-invasive bladder cancer.

1. Isharwal S, et al. *Indian J Urol.* 2015;31(4):289–296. 2. Manivasagam SS, et al. *Future Sci OA.* 2026;12(1):2622297. 3. American Cancer Society. Bladder cancer early detection, diagnosis, and staging. Accessed August 14, 2026. <https://www.cancer.org/cancer/bladder-cancer/detection-diagnosis-staging/signs-and-symptoms.html> 4. Lopez-Beltran A, et al. *BMJ.* 2024;384:e076743. 5. Guerrero-Ramos F, et al. *Bladder Cancer.* 2022;8(4):339–357. 6. Hof JP, et al. *Clin Genitourin Cancer.* 2026;24(1):102464. 7. Sylvester RJ, et al. *Eur Urol.* 2021;79(4):480–488. 8. Knowles M, et al. *Nat Rev Cancer.* 2014;15:25–41. (Image). 9. American Cancer Society. About bladder cancer. Accessed September 28, 2026. <https://www.cancer.org/cancer/bladder-cancer/about/what-is-bladder-cancer.html>

NMIBC origination, evaluation, and diagnosis



Hematuria or other voiding symptoms may lead to an initial clinical workup with cystoscopy and TURBT used to diagnose NMIBC¹



CT, computed tomography; NMIBC, non-muscle-invasive bladder cancer; TURBT, transurethral resection of bladder tumor.

1. American Cancer Society. Bladder cancer early detection, diagnosis, and staging. Accessed September 28, 2026. <https://www.cancer.org/cancer/bladder-cancer/detection-diagnosis-staging/signs-and-symptoms.html> 2. Lai LY, et al. *Cochrane Database Syst Rev*. 2022 Apr 8;4(4):CD014887.

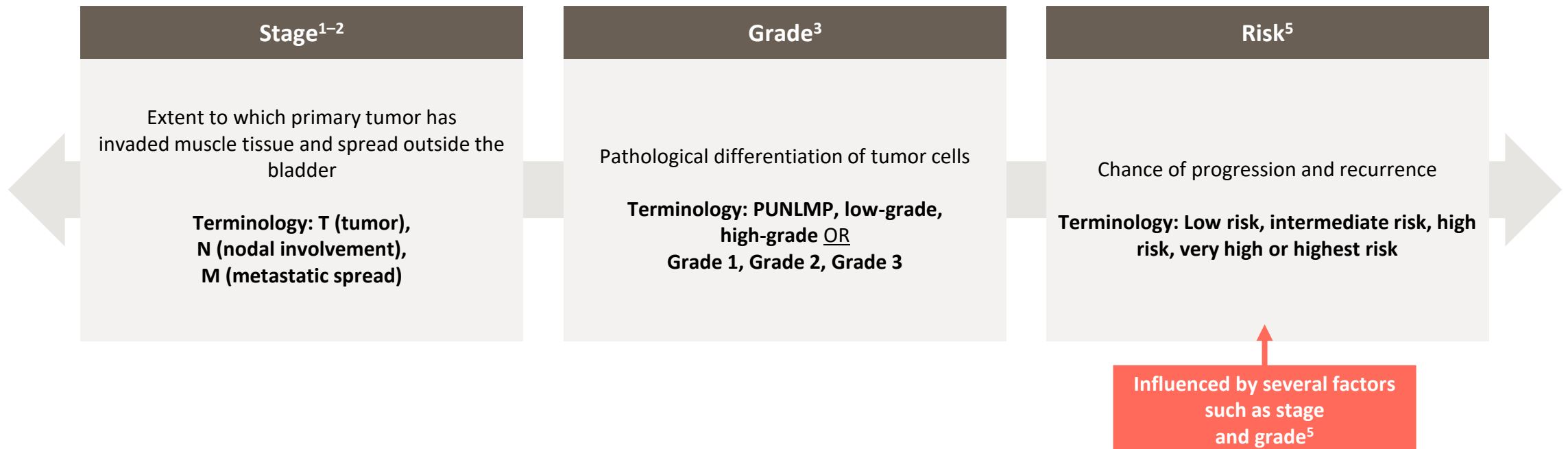
3. Woldu S, et al. *BJU Int*. 2017;119(3):371–380. 4. Maas M, et al. *World J Urol*. 2019;37:1741–1749. 5. Barocas DA, et al. *J Urol*. 2025;213(5):547–557. 6. Daneshmand S, et al. *Nat Rev Urol*. 2014;11(10):589–596.

7. American Cancer Society. Treating bladder cancer. Accessed September 28, 2026. <https://www.cancer.org/cancer/bladder-cancer/treating/surgery.html>

NMIBC characterization



The TNM stage system, WHO pathological grade classification, and risk status based on clinical guidelines are the main dimensions used to classify NMIBC^{1–5}



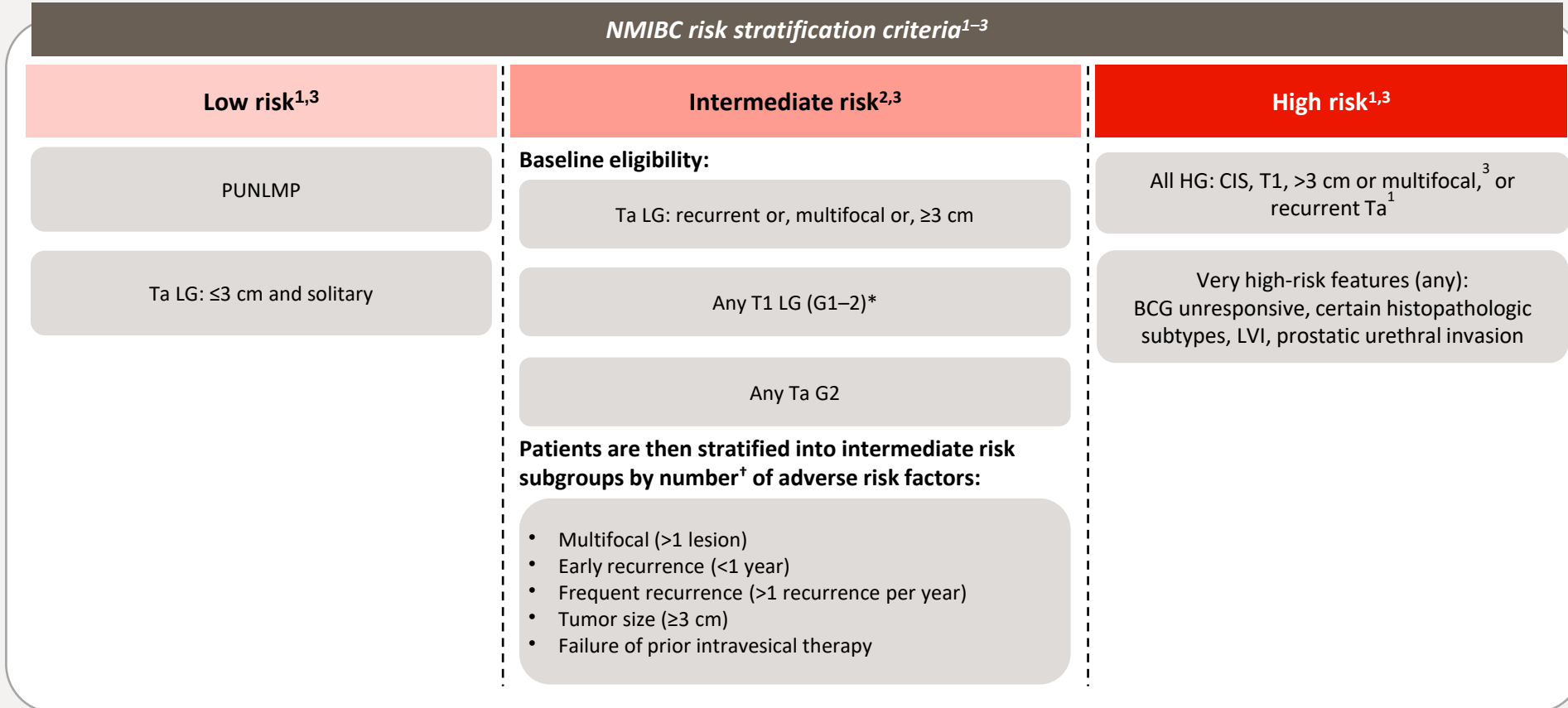
NMIBC, non-muscle-invasive bladder cancer; PUNLMP, papillary urothelial neoplasm of low malignant potential; TNM, tumor, node, metastasis; WHO, World Health Organization.

1. National Cancer Institute. Bladder cancer stages. Accessed September 28, 2026. <https://www.cancer.gov/types/bladder/stages> 2. National Cancer Institute. Cancer staging. Accessed September 28, 2026. <https://www.cancer.gov/about-cancer/diagnosis-staging/staging> 3. Knowles M, et al. *Nat Rev Cancer*. 2014;15:25–41. 4. Brausi M, et al. *J Urol*. 2011;186(6):2158–2167. 5. Matulewicz RS, et al. *Rev Urol*. 2020;22(2):43–51.

National Comprehensive Cancer Network® (NCCN®) uses AUA/IBCG risk stratification criteria for NMIBC



View NCCN treatment recommendations



*IBCG recommend that T1 LG/G1-G2 tumors be excluded from clinical trials of patients with intermediate-risk NMIBC due to the high possibility of misclassification and variation among pathologists.² [†]Lower risk: 0; Intermediate risk: 1-2; High risk: ≥3.^{2,3}

AUA, American Urological Association; BCG, Bacillus Calmette-Guérin; CIS, carcinoma *in situ*; HG, high grade (Grade 2, all Grade 3); IBCG, International Bladder Cancer Group; LG, low grade (Grade 1, some Grade 2); LVI, lymphovascular invasion; NCCN, National Comprehensive Cancer Network® (NCCN®); NMIBC, non-muscle-invasive bladder cancer; PUNLMP, papillary urothelial neoplasm of low malignant potential.

1. Clark PE, Holzbeierlein J, Chang SS, et al. 2026 Updates to the Diagnosis and Treatment of Non-muscle Invasive Bladder Cancer: AUA/SUO Guideline. J Urol. Published online September 28, 2026. doi: 10.1097/JU.0000000000005280. 2. Tan WS, et al. Eur Urol Oncol. 2022;5(5):505-516.

3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Bladder Cancer V3. 2026. © National Comprehensive Cancer Network, Inc. 2026. All rights reserved. Accessed September 28, 2026. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.



The unmet need in intermediate-risk NMIBC

Recurrence remains high despite available intravesical therapy



Intermediate risk is a **highly heterogeneous group substratified by five factors:**¹

Multifocality, tumor size ≥ 3 cm, recurrence within 1 year, >1 recurrence/year, prior intravesical failure

59%

of patients with intermediate-risk NMIBC experienced a recurrence over a median 63 months of follow-up in a Swedish population-based study (n=7,396)^{2,3}

37%

of intermediate-risk patients received intravesical therapy in a systematic review of NMIBC guideline compliance (N=10,575)^{2,4}

Treatment is under-delivered and not always completed²

- Of patients with NMIBC who receive BCG, induction therapy is completed by 80–90%, but maintenance therapy completion ranges from 10–76%
- 8–20% discontinue BCG in trials, driven by toxicity and its impact on daily and social activities
- Ongoing BCG shortages continue to delay or prevent initiation and maintenance therapy

High recurrence rates and limitations of current treatments in intermediate-risk NMIBC highlight the need for novel, effective therapies²

BCG, Bacillus Calmette-Guérin; NMIBC, non-muscle-invasive bladder cancer.

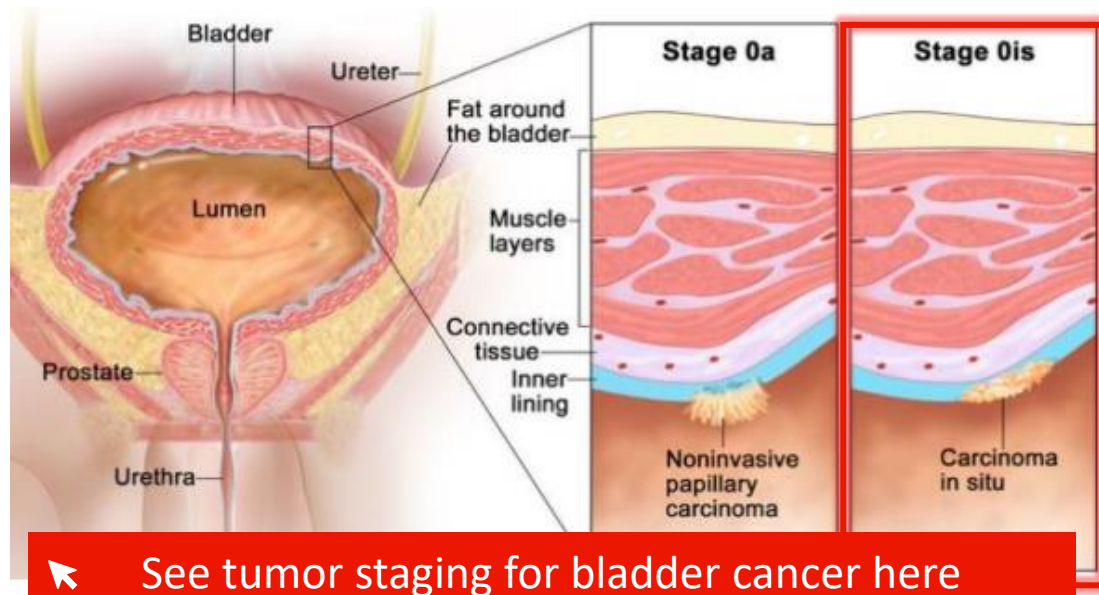
1. Li R, et al. *Eur Urol Oncol.* 2025;8:1685–1695. 2. Grabe-Heyne K, et al. *Front Oncol.* 2023;13:1170124. 3. Wang EYH, et al. *Scand J Urol.* 2022;56:221–226. 4. Mori K, et al. *Urol Oncol.* 2020;38:774–782.



NMIBC with CIS: Disease characteristics and clinical significance

CIS is a flat, high-grade and aggressive, non-muscle invasive cancer that develops in the inner lining of the bladder.¹
Approximately 10% of individuals with NMIBC are reported to have CIS²

CIS manifestation of NMIBC³



Clinical implications of CIS



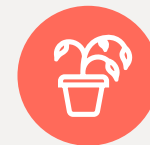
Worse clinical outcomes

- In patients with high-risk NMIBC the presence of CIS was associated with poorer clinical outcomes (N=1,178)⁴:
 - RFS** was worse: HR 1.39 (95% CI: 1.05–1.85)
 - PFS** was worse: HR 1.95 (95% CI: 1.36–2.82)
 - OS** was worse: HR 2.28 (95% CI: 1.60–3.25)



Increased risk of progression

- In patients with pTa/pT1 NMIBC, progression to MIBC or mUC was more frequent in patients with concomitant CIS (N=2,923)⁵:
 - Multifocal CIS** is associated with **increased risk of progression**: HR 1.60 (95% CI: 1.09–2.33; p=0.02)



Lower survival/ risk of death

- Patients with CIS have among the highest cancer-specific mortality rates across NMIBC subtypes (N=98,238)⁶:
 - In a population-based cohort long-term cancer-specific mortality was 15.6% for CIS vs 9.2% for Ta HG and 3.8% for Ta LG disease

CI, confidence interval; CIS, carcinoma *in situ*; HG, high-grade; HR, hazard ratio; LG, low-grade; MIBC, muscle-invasive bladder cancer; mUC, metastatic urothelial carcinoma; NMIBC, non-muscle-invasive bladder cancer; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival.

1. Sanguedolce F, et al. *Diagnostics (Basel)*. 2025;15(17):2163. 2. Lopez-Beltran A, et al. *BMJ*. 2024;384:e076743. 3. National Cancer Institute. Bladder cancer treatment (PDQ®) – Health Professional Version. Accessed August 14, 2026. <https://www.cancer.gov/types/bladder/stages>.

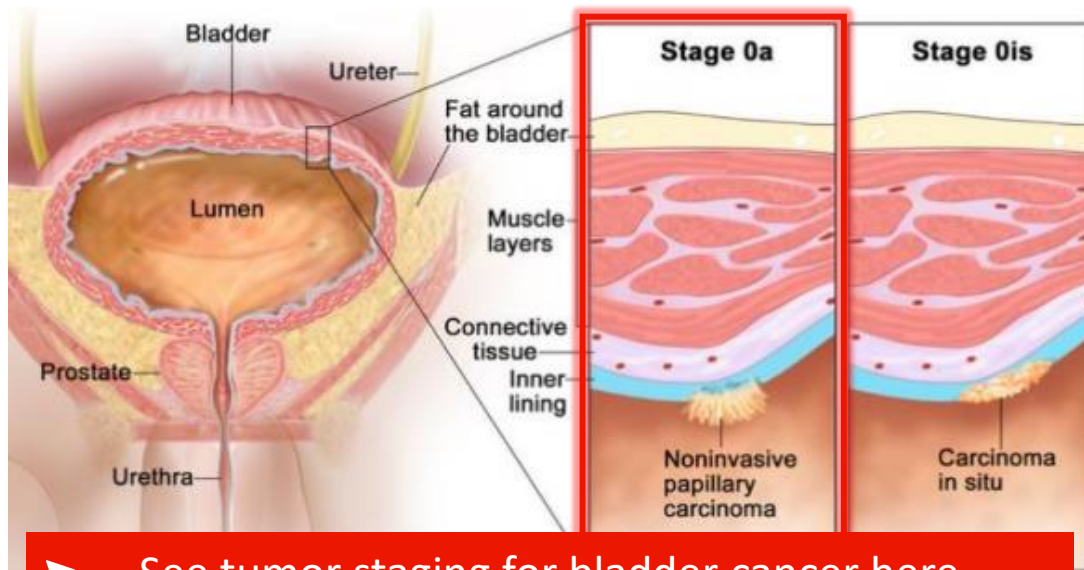
4. Del Giudice F, et al. *Cancer*. 2026;18(3):500. 5. Kwong JCC, et al. *BJU Int*. 2025;136(2):236–244. 6. Ślusarczyk A, et al. *Ann Surg Oncol*. 2023;30(12):7892–7902.

Papillary NMIBC: Disease characteristics and clinical significance



Papillary NMIBC refers to non-muscle invasive tumors that grow as **finger-like projections** in the bladder lumen and can range from low- to high-grade disease¹

Papillary NMIBC²



See tumor staging for bladder cancer here

Clinical implications of papillary NMIBC



Recurrence is common

- In a **real-world analysis** of patients with BCG-experienced/unresponsive papillary-only high-risk NMIBC (N=1,690), **63.9% of recurrences occurred within 12 months of BCG discontinuation**³



Progression risk varies

- The **risk of progression** is strongly influenced by stage/grade as opposed to papillary morphology alone⁴



CIS can occur concomitantly with papillary tumors and are associated with increased progression risk⁵

Accurate diagnosis and detection require a combination of cystoscopic evaluation, tissue sampling, cytology and imaging⁶

BCG, Bacillus Calmette-Guérin; CIS, carcinoma *in situ*; HR, high risk; NMIBC, non-muscle-invasive bladder cancer.

1. Madwani K, et al. *Int J Clin Exp Pathol*. 2025;18(2):89–95. 2. National Cancer Institute. Bladder cancer treatment (PDQ®) – Health Professional Version. Accessed August 14, 2026. <https://www.cancer.gov/types/bladder/stages> 3. Kulkarni GS, et al. *Clin Genitourin Cancer*. 2025;23(3):102313. 4. Kvikstad V, et al. *PLoS One*. 2024;19(1):e0297141. 5. Kwong JCC, et al. *BJU Int*. 2025;136:236–244. 6. Muvhar B, et al. *Res Rep Urol*. 2025;17:69–85.



Treatment options for intermediate-risk NMIBC



Intravesical BCG is a treatment option for patients with intermediate-risk NMIBC based on individual risk factors and guideline recommendations¹



Intravesical chemotherapy is an alternative to BCG therapy, with various agents and regimens used in clinical practice²



Mitomycin intravesical solution is FDA-approved for recurrent low-grade intermediate-risk NMIBC following prior TURBT³

For more information on current treatments, please refer to local treatment guidelines

BCG, Bacillus Calmette-Guérin; FDA, Food and Drug Administration; NMIBC, non-muscle invasive bladder cancer; TURBT, transurethral resection of bladder tumor.

1. Tan WS, et al. *Eur Urol Oncol*. 2022;5(5):505–516. 2. Grabe-Henye K, et al. *Front Oncol*. 2023;13:1170124. 3. ZUSDURI® (mitomycin). Prescribing Information. UroGen Pharma, Inc. 2025.



Current treatment options for high-risk NMIBC

	BCG	Intravesical chemotherapy	Radical cystectomy
Description	BCG is an intravesical treatment that triggers the immune system to attack bladder cancer cells ¹	Works by inhibiting DNA synthesis in cancer cells ^{3,4}	Involves the removal of the entire bladder , nearby organs, and regional lymph nodes ⁹
Administration	Induction phase followed by maintenance for up to 3 years ²	Administered weekly for induction ^{5,6} ; maintenance dosing varies between therapies ^{7,8}	One-time surgery ⁹
For more information on current treatments, please refer to local treatment guidelines			

BCG, Bacillus Calmette-Guérin; NMIBC, non-muscle-invasive bladder cancer.

1. American Cancer Society. Accessed September 28, 2026. <https://www.cancer.org/cancer/bladder-cancer/treating/intravesical-therapy.html> 2. Lamm DL, et al. *J Urol*. 2000;163(4):1124–1129. Cited by Kamat AM, et al. *Nat Rev Urol*. 2015;12:225–235.

3. Schäfer A, et al. *PLoS One*. 2010;5(11):e14060. 4. Snodgrass RG, et al. *J Biol Chem*. 2010;285(25):19068–19075. 5. Au JL, et al. *J Natl Cancer Inst*. 2001;93(8):597–604. 6. Han MA, et al. *Cochrane Database Syst Rev*. 2021;6:CD009294.

7. Gacci M, et al. *Urol Int*. 2006;76(2):106–111. Cited by Di Lorenzo G, et al. *Cancer*. 2010;1893–1900. 8. Kleinmann N, et al. *Lancet*. 2020;21(6):776–785. 9. Aminoltejeri K, et al. *Transl Androl Urol*. 2020;9(6):3073–3081.

Clinical barriers to BCG treatment in NMIBC



High AE burden, low BCG completion rates, and an ongoing BCG shortage may limit the optionality for BCG as a first-line treatment option for patients with NMIBC^{1–8}



High AE burden with BCG

- **BCG** is associated with a **substantial AE burden**¹
- **Local toxicities** such as dysuria and urinary frequency **occur** in most patients, and although less common, **systemic AEs can be serious and potentially life-threatening**^{1,2}



Low BCG regimen completion rates

- **Completion of adequate BCG therapy can be low in clinical practice**, with completion rates of <20% reported for the full maintenance regimen as originally described in the SWOG regimen, **largely due to AEs and tolerability issues**^{2–5}

An ongoing BCG shortage in the US has necessitated the use of alternative dosing and treatment considerations for patients with NMIBC⁶



Worldwide BCG shortage since 2012^{7,8}



In the event of a shortage, BCG **induction + maintenance** to be prioritized for **patients at high risk of recurrence** according to NCCN Guidelines⁶



Intravesical chemotherapy may be used as a **BCG alternative**⁶



NCCN Guidelines provide recommendations for **dose splitting** in the event of a BCG shortage⁶

Despite BCG therapy, patients with intermediate- and high-risk NMIBC remain at risk of recurrence and disease progression in both clinical trial and real-world settings^{9,10} ([Click here to see the data](#))

AE, adverse event; BCG, Bacillus Calmette-Guérin; NCCN, National Comprehensive Cancer Network® (NCCN®); NMIBC, non-muscle-invasive bladder cancer; SWOG, Southwest Oncology Group Study; US, United States.

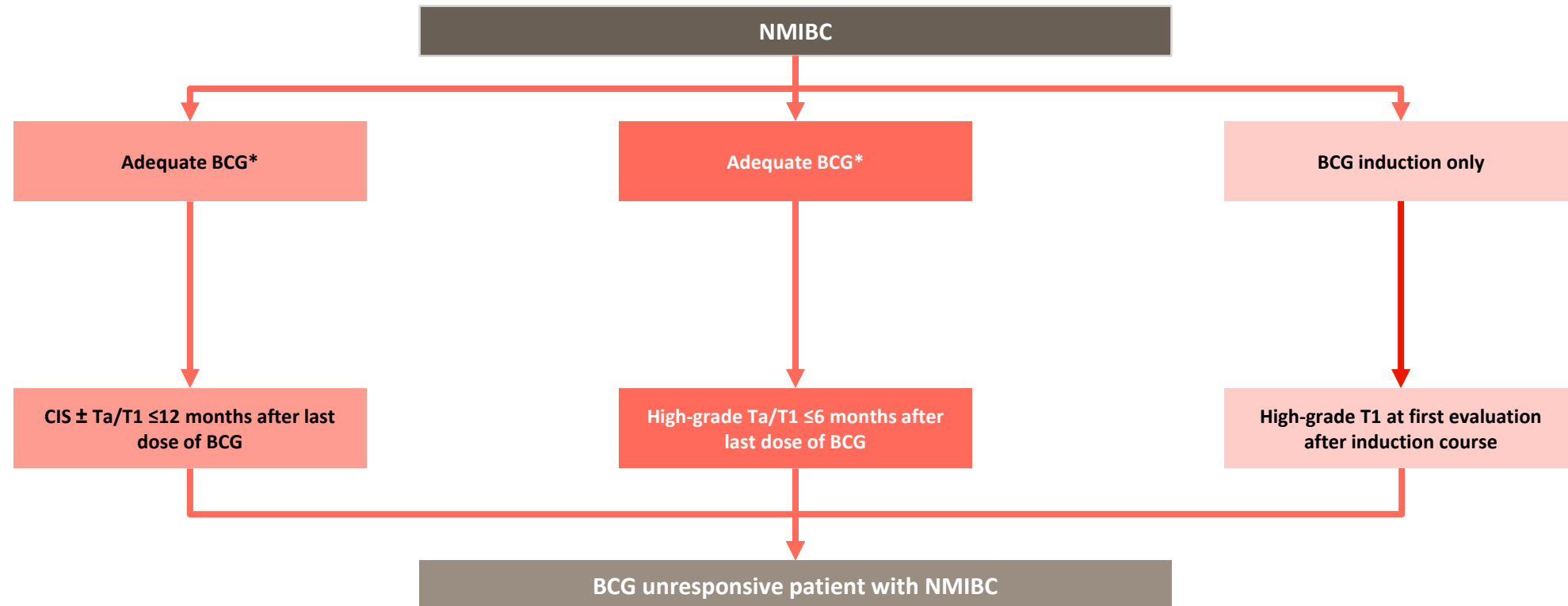
1. Maroof H, et al. *Cancer Pathog Ther.* 2023;2(2):74–80. 2. Lamm DL, et al. *J Urol.* 2000;163(4):1124–1129. 3. Tempo J, et al. *BMC Urol.* 2023;23(1):194. 4. Grabe-Heyne K, et al. *Front Oncol.* 2023;13:1170124. 5. van der Meijden AP, et al. *Eur Urol.* 2003;44(4):429–434. 6. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Bladder Cancer V.3.2026. © National Comprehensive Cancer Network, Inc. 2026. All rights reserved. Accessed September 28, 2026. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 7. Bandari J, et al. *Eur Urol Focus.* 2018;4(4):481–484. Cited by NCCN Guidelines.

8. Chun B, et al. *Urol.* 2023;177:74–80. 9. Shore ND, et al. *Nat Med.* 2025;31:2806–2814. 10. Scilipoti P, et al. *Eur Urol Focus.* 2026;12(1):70–78.

Definition of BCG-unresponsiveness in NMIBC¹



Patients can meet the FDA definition of BCG unresponsive in a variety of ways



*Adequate BCG defined as at least five of six doses of an initial induction course plus at least two of three additional doses of maintenance therapy OR at least two of six doses of a second induction course.

BCG, Bacillus Calmette-Guérin; FDA, Food and Drug Administration; NMIBC, non-muscle-invasive bladder cancer.

1. FDA. BCG-unresponsive non-muscle invasive bladder cancer: developing drugs and biologics for treatment: guidance for industry. February 13, 2018. Accessed September 28, 2026. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bacillus-calmette-guerin-unresponsive-nonmuscle-invasive-bladder-cancer-developing-drugs-and>



Treatment approaches for BCG-unresponsive NMIBC

Treatment options may vary according to disease characteristics and patient eligibility.^{1–6}

Definitive treatment	Alternative treatment options				
Radical cystectomy ¹	BCG + IL-15 receptor agonist ²	Alternative Intravesical chemotherapy ³	Adenoviral vector-based gene therapy ⁴	PD-1 ICI ⁵	Traditional intravesical chemotherapy ⁶
Involves the removal of the entire bladder , nearby organs, and regional lymph nodes	IL-15 receptor agonist + BCG immunotherapy	Intravesical chemotherapy instillation or insertion	Adenoviral vector-based gene therapy	PD-1 ICI	Used as a bladder-preserving salvage therapy in selected patients with recurrent or high-risk NMIBC following BCG failure
Definitive, one-time surgery	Administered by intravesical instillation with BCG	Intravesical therapy instilled/inserted into bladder	Administered by intravesical instillation	Administered systemically	Administered by intravesical instillation; schedules vary between therapies

For more information on current treatments, please refer to local guidelines

BCG, Bacillus Calmette-Guérin; CIS, carcinoma *in situ*; ICI, immune checkpoint inhibitor; IL-15, interleukin-15; NMIBC, non-muscle-invasive bladder cancer; PD-1, programmed cell death protein 1.
 1. Aminoltehari K, et al. *Transl Androl Urol*. 2020;9(6):3073–3081. 2. Chamie K, et al. *NEJM Evid*. 2023;2(1):EVIDo2200167. 3. Daneshmand S, et al. *J Clin Oncol*. 2025;43(33):3578–3588.
 4. Boorjian SA, et al. *Lancet Oncol*. 2021;22(1):107–117. 5. Balar AV, et al. *Lancet Oncol*. 2021;22(7):919–930. 6. Garneau CA, et al. *Can Urol Assoc J*. 2024;18(2):33–40.

Repeat TURBT: Rationale and clinical evidence



The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) **recommend repeat TURBT** as a strategy for select patients with NMIBC to ensure adequate staging and ensure complete tumor removal^{1,2}

Repeat TURBT should be considered for patients with:¹

- Incomplete or inadequate initial resection
- High-volume disease (large and/or multifocal tumors)
- High-grade Ta, particularly if large and/or muscle is absent
- Any T1 disease

In patients with NMIBC, repeat TURBT was associated with improved outcomes compared with no repeat TURBT in a meta-analysis of multiple studies:²

- Lower risk of recurrence: RFS HR 0.78 (95% CI: 0.62–0.97; 5 studies, n=5,522)
- Lower risk of death: OS HR 0.86 (95% CI: 0.81–0.93; 5 studies, n=11,371)

31.4%

Of patients with T1 NMIBC who underwent conventional TURBT in the 2010s had **residual tumor detected** at repeat TURBT, based on a meta-analysis of 13 studies (n=1,398)²

2.8%

Of patients with T1 NMIBC who underwent conventional TURBT in the 2010s were **upstaged** at repeat TURBT, based on a meta-analysis of 11 studies (n=1,259)²

CI, confidence interval; HR, hazard ratio; NCCN, National Comprehensive Cancer Network® (NCCN®); NMIBC, non-muscle-invasive bladder cancer; OS, overall survival; RFS, recurrence-free survival; TURBT, transurethral resection of bladder tumor.

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MIBC overview



MIBC is characterized by tumor invasion of the muscularis propria and is associated with a high risk of metastasis.^{1,2}
Despite treatment with curative intent, 5-year OS is ~50% for patients with MIBC³

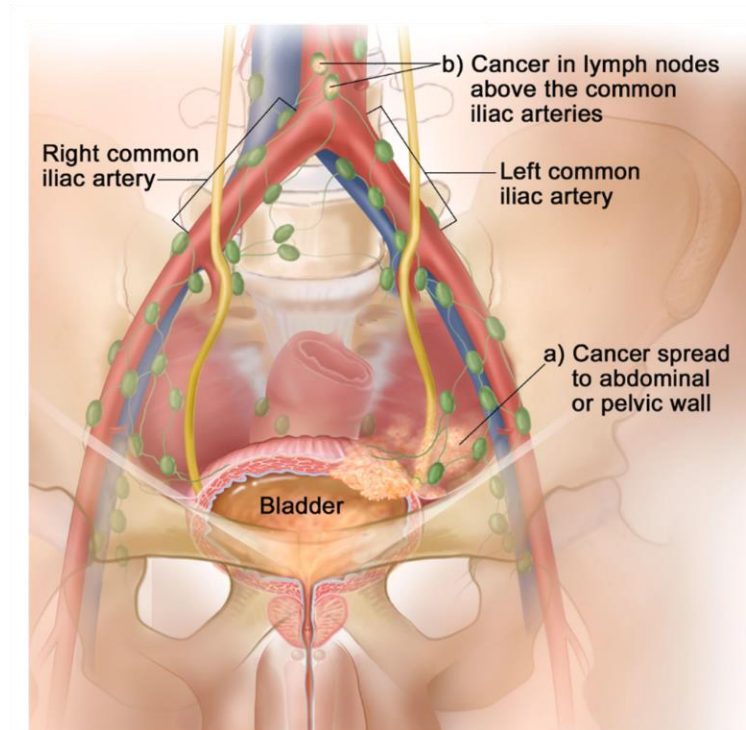
MIBC develops through flat dysplasia and CIS³

Approximately **20% of bladder cancer patients present with MIBC** at the time of diagnosis⁴

Bladder cancer that has **invaded deeply into the muscularis propria** increases the risk of **progression** and eventually **death**¹

The **5-year survival rate** for bladder cancer that has spread to nearby muscles/lymph nodes is **41.8%**^{5*}

Bladder wall invasion¹



*Among patients initially diagnosed with regionally isolated bladder cancer.

CIS, carcinoma *in situ*; MIBC, Muscle-invasive bladder cancer; OS, overall survival.

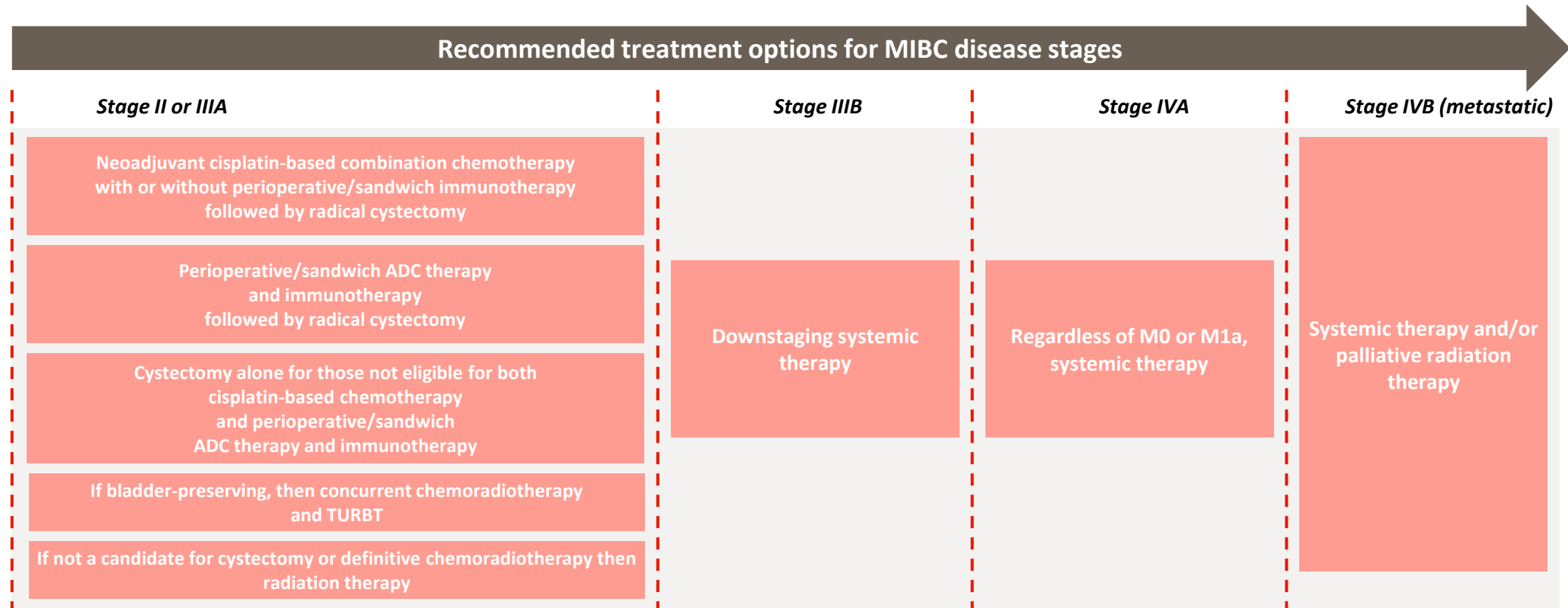
1. National Institutes of Health. Bladder cancer treatment (PDQ®)-health professional version. Accessed August 12, 2026. <https://www.cancer.gov/types/bladder/hp/bladder-treatment-pdq> 2. Bosveld J, et al. *BJU Int.* 2025;135:766–774.

3. Valderrama BP, et al. *Clin Transl Oncol.* 2022;24(4):613–624. 4. Attanasio G, et al. *Front Oncol.* 2025;15:1546160. 5. National Cancer Institute SEER. Cancer stat facts: bladder cancer. Accessed September 28, 2026. <https://seer.cancer.gov/statfacts/html/urinb.html>

NCCN treatment recommendations for MIBC



Chemoradiotherapy is included by **NCCN Guidelines** as a bladder-preserving treatment option for patients with MIBC



ADC, antibody-drug conjugate; MIBC, muscle-invasive bladder cancer; NCCN, National Comprehensive Cancer Network®; TURBT, Transurethral resection of bladder tumor.

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MIBC treatment overview: Perioperative systemic therapy plus radical cystectomy



Treatment of cystectomy-eligible MIBC has evolved beyond surgery alone to incorporate perioperative systemic therapy regimens administered before and/or after radical cystectomy¹

Perioperative treatment approaches

Cisplatin-based neoadjuvant chemotherapy, followed by radical cystectomy¹

Cisplatin/gemcitabine plus immunotherapy, followed by radical cystectomy, followed by immunotherapy¹

ADC therapy plus immunotherapy, followed by radical cystectomy, followed by ADC plus immunotherapy regardless of cisplatin eligibility¹

Morbidity and quality of life with radical cystectomy

Radical cystectomy is associated with **high morbidity** and can have a significant impact on **quality of life**²

There is a **~60% (n=514) complication incidence** after surgery^{3*}

High rates of surgical complications within 90 days from open (**69%**, n=152) and robotic cystectomy (**67%**, n=150)⁴

Significant **quality of life impact** relating to poor urinary and sexual function after surgery⁵

*514/858 experienced at least one complication within 3 months.³

ADC, antibody-drug conjugate; MIBC, muscle-invasive bladder cancer.

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5. Kaufmann E, et al. *JU Open Plus*. 2023;1(11):e00071.

MIBC treatment overview: TMT



Bladder-sparing treatment is typically reserved for patients who have limited risk factors or are ineligible or refusing to undergo cystectomy^{1,2}



TMT consists of **maximal TURBT** and concurrent **chemoradiation**²



TMT may be considered for patients with MIBC, who can achieve maximal TURBT, with favorable tumor characteristics, no untreated hydronephrosis, and good bladder capacity/function²

TMT may be an alternative to radical cystectomy in patients who failed BCG with recurrent high-grade T1 tumors²

~**75%** of long-term survivors may maintain a **functional bladder** with TMT^{3*}

TMT led to **complete response** in **69%** of patients and **5-year OS** was reported to be **57%**^{4†}

In patients surviving at least 2 years, Grade 3 late genitourinary toxicity was **5.7%** and Grade 3 late GI toxicity was **1.9%**^{5‡}

*Data from 1986 to 2000; n=32.3. †Data from 1988 to 2007; n=468.5. ‡Data from 1990- to 2002; n=157.6.

BCG, Bacillus Calmette-Guérin; GI, gastrointestinal; MIBC, muscle-invasive bladder cancer; OS, overall survival; TMT, trimodal therapy; TURBT, transurethral resection of bladder tumor.

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Bladder Cancer V.3.2026. © National Comprehensive Cancer Network, Inc. 2026. All rights reserved. Accessed September 28, 2026. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 2. Oberoi JK, et al. *Urol Oncol*. 2026;44(9):343–356. 3. Zietman AL, et al. *J Urol*. 2003;170(5):1772–1776.

4. Mak RH, et al. *J Clin Oncol*. 2014;32(34):3801. 5. Efstathiou JA, et al. *J Clin Oncol*. 2009;27(25):4055.

mUC overview



mUC involves the spread of bladder cancer to distant sites and is associated with poor long-term survival^{1,2}

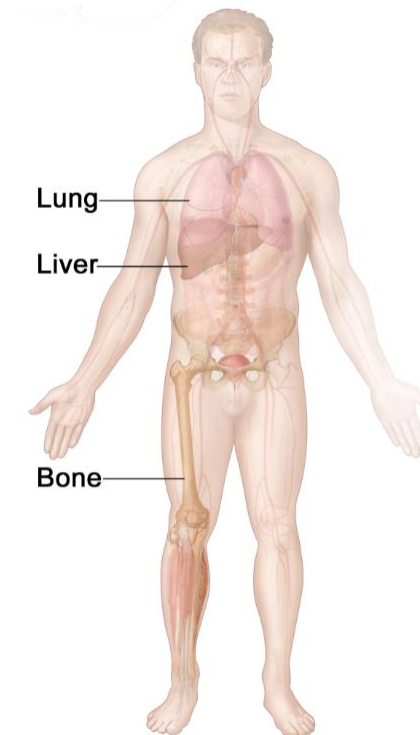
6% of bladder cancer patients are initially diagnosed with mUC
(ie, cancer that has metastasized beyond regional lymph nodes)²

Common metastatic sites include bone (38.3%), lymph nodes (36.8%), lung (33.5%), liver (22.6%), and brain (2.6%)^{3*}

5-year survival for patients with metastatic bladder cancer as an initial diagnosis is **9.6%**²

Median OS **~20 months** with systemic treatment[†]
and **~6 months** without treatment⁵

Bladder cancer metastasis⁴



*Data from 2000 to 2020; Organotropic metastasis rates in urothelial carcinoma (patients with metastasis to the indication organ/patients with metastasis); Bone (1,608/4,194), lymph nodes (792/2,153), lung (1,399/4,181), liver (948/4,190), brain (109/4,175). [†]Based on survival time of 139 with mUC treated with chemotherapy. MIBC, muscle-invasive bladder cancer; mUC, metastatic urothelial carcinoma; OS, overall survival.

1. Amin MB, et al. AJCC Cancer Staging Manual. 2017. Accessed September 28, 2026. Cited by the National Cancer Institute. 2. National Cancer Institute SEER. Cancer stat facts: bladder cancer. Accessed September 28, 2026. <https://seer.cancer.gov/statfacts/html/urinb.html>.

3. Park HK. *Curr Oncol*. 2023;30(10):9078–9089. 4. Chin J, et al. *Intro Cancer Met*. 2017;177–198. 5. Mahmoudpour SH, et al. *Urol Oncol*. 2024;42(12):451.e11–451.e18.

mUC guidelines



NCCN Guidelines include systemic/radiation therapy as a treatment option for patients with metastatic disease

NCCN Guideline recommendations for mUC		
Diagnosis	Additional workup	Treatment
Metastatic: Stage IVB any T, any N, M1b	Bone scan or MRI if clinical suspicion or symptoms of bone metastases Chest CT Consider CNS imaging GFR estimation to assess cisplatin eligibility Consider biopsy if technically feasible Molecular testing	Systemic therapy and/or palliative radiation therapy*

*See source for list of recommended systemic therapies.

CNS, central nervous system; CT, computed tomography; GFR, glomerular filtration rate; MRI, magnetic resonance imaging; mUC, metastatic urothelial carcinoma; NCCN, National Comprehensive Cancer Network*; TNM, tumor, node, metastasis.

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Current treatment options for mUC

	ADC + PD-1i combination therapy	PD-1i + platinum-based chemotherapy	ADC	PD-(L)1i monotherapy	Platinum-based chemotherapy ²	Biomarker-guided targeted therapy
FDA Approval information as of August 2026 ¹	Approved	Approved	Approved	Approved	Approved	Approved in patients identified with specific alterations
Administration	IV infusion ³ or SC injection (for PD-1 therapy) ⁵	IV infusion ⁴	IV infusion ³	IV infusion or SC injection ⁵	IV infusion ⁶	Oral ⁷
NCCN guidelines recommendations ⁸	1L preferred regimen 2L preferred (post-chemo/-immunotherapy)	1L other recommended regimen for eligible patients	2L (post-chemo) other recommended regimen 2L (post-immunotherapy) preferred regimen Post chemo + immunotherapy preferred regimen	1L (useful in certain circumstances for cis-ineligible) 2L (post-platinum/chemo) other recommended regimen	1L other recommended regimen	2L (post-chemo) other recommended regimen 2L (chemo-naïve, post-checkpoint inhibitor) preferred regimen 3L+ preferred regimen

1L+, first line and beyond; 1L/2L, first line, second line; 2L, second line; 3L+, third line and beyond; ADC, antibody-drug conjugate; cis, cisplatin; FDA, Food and Drug Administration; PD-1i, programmed cell death inhibitor; PD-L1i, programmed cell death ligand inhibitor; mUC, metastatic urothelial carcinoma; NCCN, National Comprehensive Cancer Network®; PD, programmed death; SC, subcutaneous.

1. Food and Drug Administration. Oncology (cancer)/hematologic malignancies approval notifications. Accessed September 28, 2026. <https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications> 2. National Cancer Institute. Cisplatin. Accessed September 28, 2026. <https://www.cancer.gov/about-cancer/treatment/drugs/cisplatin> 3. FDA approves ADC + PD-1i. Accessed September 28, 2026. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-enfortumab-vedotin-ejfv-pembrolizumab-locally-advanced-or-metastatic-urothelial-cancer> 4. van der Heijden MS, et al. *N Engl J Med*. 2023;389(19):1778–1789. 5. FDA approves PD-(L)1i. Accessed September 28, 2026. <https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-avelumab-urothelial-carcinoma-maintenance-treatment> 6. Kelland L. *Nat Rev Cancer*. 2007;7(8):573–584.

7. FDA approves biomarker-guided targeted therapy. Accessed September 28, 2026. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-erdafitinib-locally-advanced-or-metastatic-urothelial-carcinoma> 8. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Bladder Cancer V.3.2026. © National Comprehensive Cancer Network, Inc. 2026. All rights reserved. Accessed September 28, 2026. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Appendix

Bladder cancer cellular classification

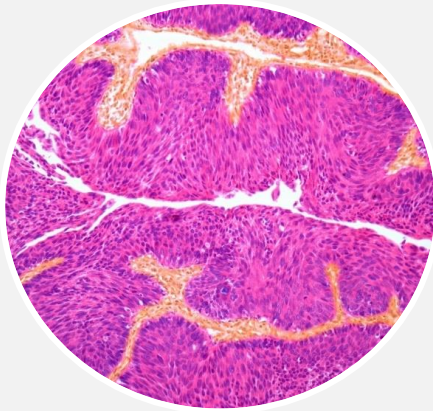


Urothelial cell carcinoma¹

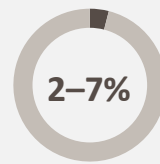


of all
bladder cancers

Begins in urothelial cells found in
the urinary tract

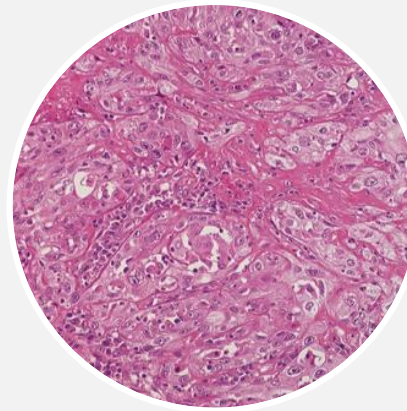


Squamous cell carcinoma¹

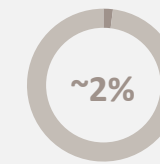


of all
bladder cancers

Develops in the bladder lining in response
to irritation and inflammation

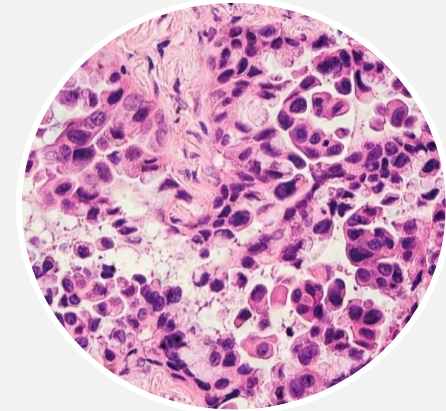


Adenocarcinoma¹



of all
bladder cancers

Develops from glandular cells



1. National Cancer Institute. Accessed September 28, 2026. <https://www.cancer.gov/types/bladder/hp/bladder-treatment-pdq> 2. Steve Gschmeissner. Getty Images. #160936354. (Left image). 3. MiyataY, et al. *Anticancer Res.* 2011;31(12):4465–4468. (Center image). 4. David A Litman. #404835043. Shutterstock. (Right image).

Cellular classification/histopathology



Histological grade¹

Low-grade

- Rarely invades the muscular layer
- If invasive, has limited spread to local organs
- Low rate of death

High-grade

- Strong tendency to invade muscular layer
- Has a propensity to spread to adjacent organs, which decreases survival and increases complexity of care
- More likely to be treated with aggressive therapy

Differentiation²

NMIBC

- Bladder cancer has grown into the lamina and not into the muscle

MIBC

- Grown into the bladder's muscle wall and sometimes into the fatty layers or surrounding tissue outside the bladder

mUC

- Spread of bladder cancer cells from beyond the bladder to distant regions of the body

MIBC, muscle-invasive bladder cancer; mUC, metastatic urothelial carcinoma; NMIBC, non-muscle-invasive bladder cancer;

1. National Cancer Institute. Accessed September 28, 2026. <https://www.cancer.gov/types/bladder/hp/bladder-treatment-pdq>

2. ASCO. Accessed September 28, 2026. <https://www.cancer.net/cancer-types/bladder-cancer/view-all>

Tumor staging



Bladder cancer can be classified according to the AJCC TNM system¹

Bladder cancer staging²

T

Describes the extent of primary tumor growth (ie, growth through the bladder wall), and if growth extends into nearby tissues

N

Reflects cancer spread to lymph nodes adjacent to the bladder

M

Indicates if cancer has metastasized to distant sites

NMIBC

MIBC

Metastatic

AJCC TNM staging system, bladder cancer¹

Stage	T	N	M
Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a-b	N0	M0
Stage IIIA	T3a	N0	M0
	T3b	N0	M0
	T4a	N0	M0
	T1-T4a	N1	M0
Stage IIIB	T1-T4a	N2, N3	M0
Stage IVA	T4b	N0	M0
	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b

Also known as CIS¹

AJCC, American Joint Committee on Cancer; CIS, carcinoma *in situ*; MIBC, muscle-invasive bladder cancer; NMIBC, non-muscle-invasive bladder cancer; TNM, tumor, node, metastasis.

1. Amin MB, et al. AJCC Cancer Staging Manual. 2017. Accessed September 28, 2026. Cited by the National Cancer Institute. <https://www.cancer.gov/types/bladder/hp/bladder-treatment-pdq>

2. American Cancer Society. Accessed September 28, 2026. <https://www.cancer.org/cancer/bladder-cancer/detection-diagnosis-staging/staging.html>



Outcomes following BCG in patients with intermediate-risk and high-risk NMIBC

Despite BCG therapy, patients with intermediate- and high-risk NMIBC remain at risk of recurrence and disease progression in both clinical trial and real-world settings^{1,2}

CREST Phase 3 clinical trial (control arm)¹



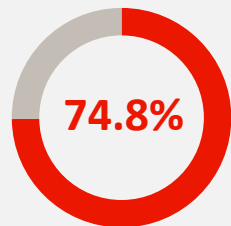
Phase 3, randomized trial in patients with BCG-naïve high-risk NMIBC



BCG induction + maintenance per protocol



N=349



36-month EFS* with BCG induction + maintenance

Scilipoti P, et al. multicenter real-world study²



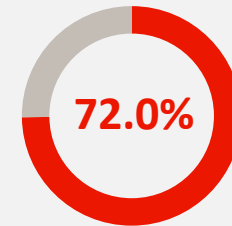
Retrospective, multicenter study across 24 centers in Europe in patients with BCG-naïve intermediate-risk and high-risk NMIBC



Patients treated with adequate BCG* between 2010–2024



N=1,226



5-year RFS with adequate BCG[†]

*EFS included high-grade recurrence, disease progression, persistence of CIS in patients with CIS at baseline, or death. †Adequate BCG defined as induction of BCG and at least two additional doses of maintenance therapy.

BCG, Bacillus Calmette-Guérin; CIS, carcinoma *in situ*; EFS, event-free survival; NMIBC, non-muscle invasive bladder cancer; RFS, recurrence-free survival.

1. Shore ND, et al. *Nat Med*. 2025;31:2806–2814. 2. Scilipoti P, et al. *Eur Urol Focus*. 2026;12(1):70–78.