VGO NORTE INTERNATIONAL GU DEBATES

Clinical Vignette

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Clinical Case: 68-Year-Old Male

- **Medical History:** Smoking, Prostatic adenomectomy 2022
- **Presentation:** Episodes of gross hematuria for 1 year.
- **CT Urogram:** Soft tissue mass occupying bladder lumen (5.8 x 3.7 x 3.5 cm) originating from the anterior – right anterolateral bladder wall



Diagnostic Tools in NMIBC

Key Diagnostic Modalities & EAU Guidelines Recommendations

Cystoscopy

Gold standard for diagnosis and follow-up of bladder tumors.

- **Flexible Cystoscopy:** Preferred in office settings for superior patient comfort and mapping.
- **Enhanced Imaging (PDD / NBI):** Recommended when standard white-light cystoscopy is normal but cytology is positive.
- Mandatory prior to definitive resection (TURBT).

CT Urography

Upper Tract Evaluation: Imaging modality of choice to rule out UTUC.

- **Indications:** High-risk tumors, multifocal lesions, or unexplained positive cytology.
- Evaluates renal pelvis, ureters, and bladder involvement.
- Detects synchronous upper tract lesions and regional lymphadenopathy.

Urine Cytology

High-Grade Detection: High sensitivity for HG tumors and CIS.

- **Low Sensitivity:** Limited diagnostic value for Low-Grade (LG) lesions.
- Standardized reporting using *The Paris System*.
- **Positive Cytology + Negative Cystoscopy:** Mandates workup (PDD/NBI, CTU) to exclude hidden CIS/UTUC.

Genetic Biomarkers

Non-Invasive Diagnostics: Urinary biomarker tests for initial evaluation and recurrence monitoring.

- **Bladder EpiCheck:** DNA methylation analysis with high sensitivity for detecting high-grade recurrences.
- **UroMonitor:** Detects urinary tumor DNA mutations (TERT, FGFR3) for non-invasive NMIBC surveillance.
- High negative predictive value (NPV); reduces the frequency of follow-up cystoscopies.

EAU Guidelines Consensus: White-light cystoscopy combined with urine cytology remains the cornerstone of initial diagnosis. Enhanced cystoscopy (PDD/NBI) and CT Urography are mandatory in high-risk profiles or discordant findings (positive cytology with normal cystoscopy).

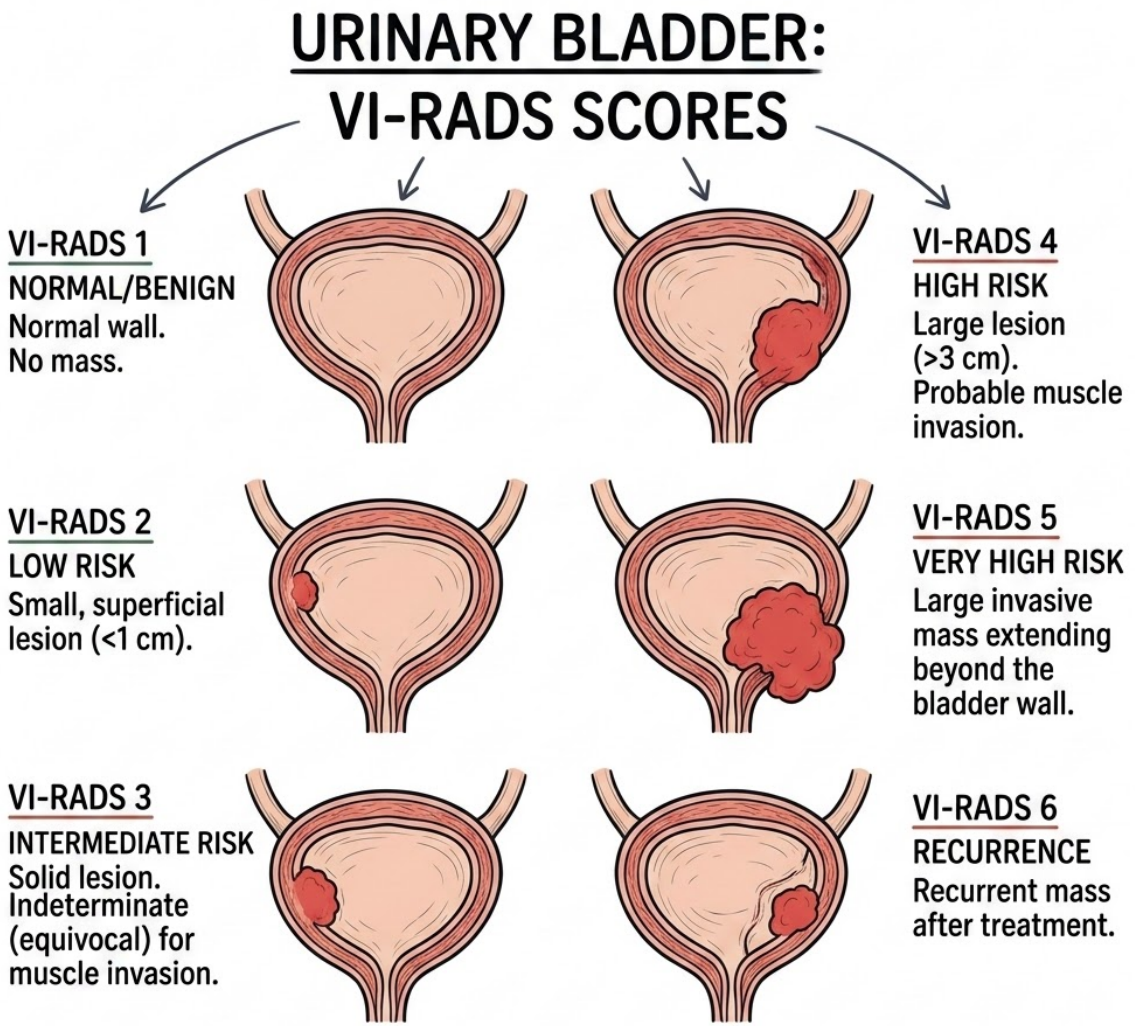
mpMRI Evaluation: VI-RADS System

Classification and Invasion Schema

VI-RADS 1-2
Mucosa / Lámina Propia (Capa Interna)
NMIBC

VI-RADS 3
Detrusor Muscle (Equivocal invasion)
Equívoco

VI-RADS 4-5
Detrusor Muscle / Perivesical Fat
MIBC



EAU Guidelines on Non-Muscle-Invasive Bladder Cancer (NMIBC)

mpMRI Evaluation: VI-RADS System

According to EAU Guidelines 2026, a VI-RADS score ≥ 4 predicts muscle invasion with a sensitivity of 78% and specificity of 94%.

2026

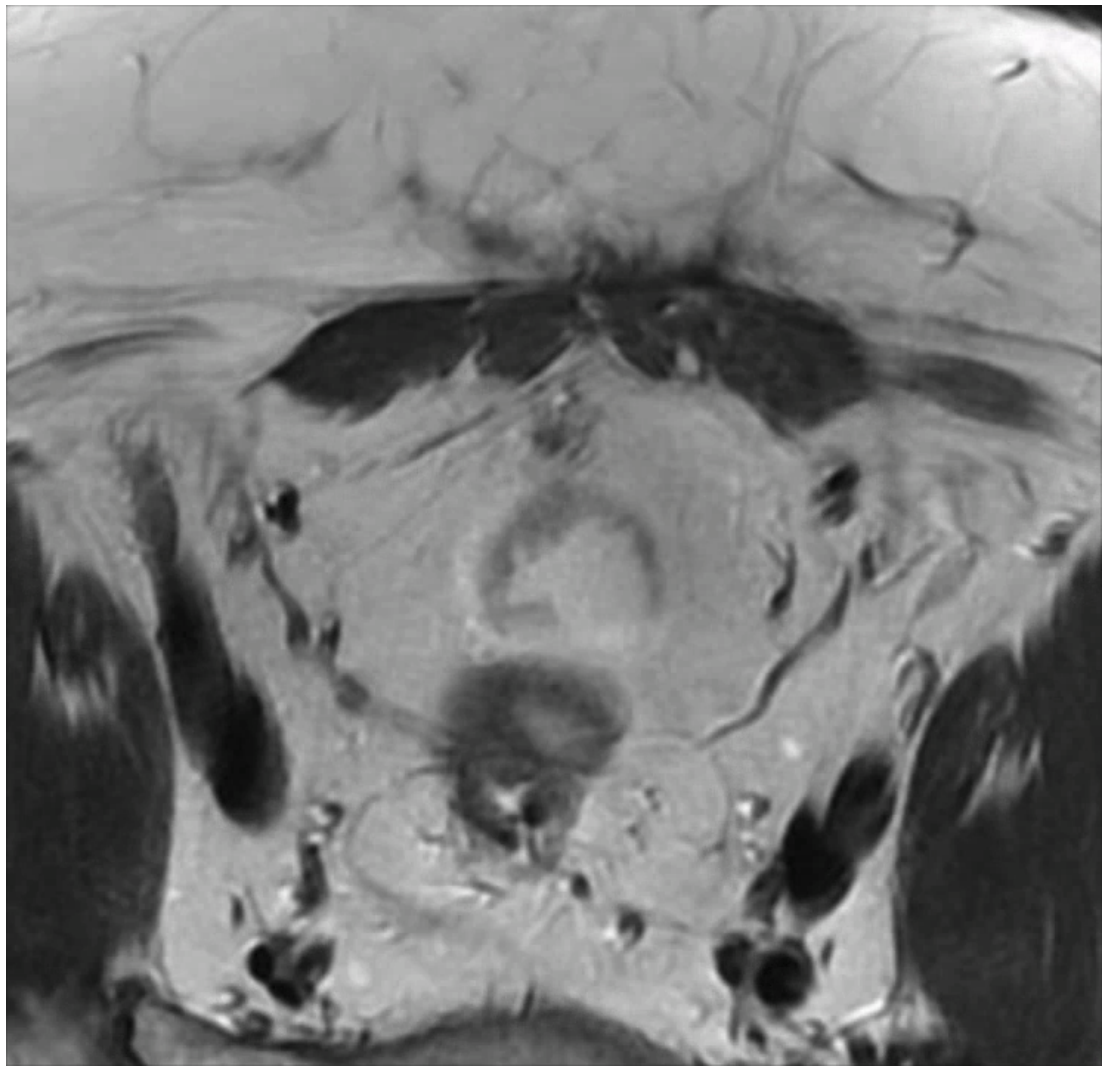
If a magnetic resonance imaging (MRI) is performed for local staging of bladder cancer (BC), it should be done before transurethral resection of bladder tumour (TURBT).	Strong

Utility: Predict invasion

EAU Guidelines on Non-Muscle-Invasive Bladder Cancer (NMIBC)

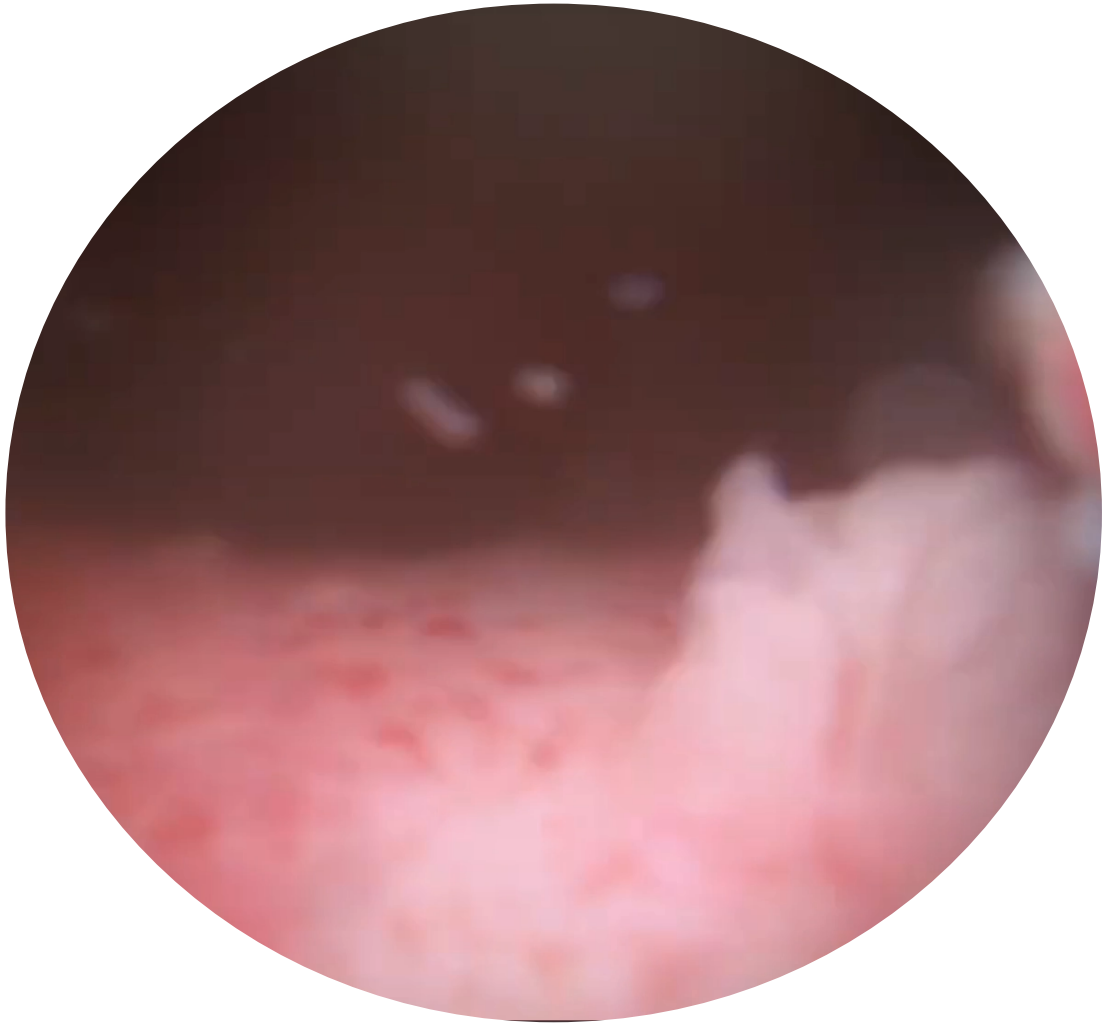
MRI Bladder

1. VIRADS 2 of 5cm anterior wall.
2. VIRADS 1 of 1cm two lesions in lateral left wall.
3. VIRADS 1 of 1cm in the bladder neck.



TURB

Piecemeal Resection



En Bloc Resection

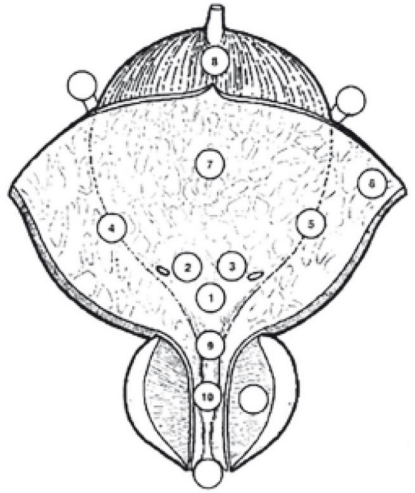


TURB

- TURB 04/2025 Incomplete resection. 7cm tumor in anterior wall. AP: Urothelial carcinoma T1 G3 High Grade + CIS peritumoral

- Re-TURB 05/2025 Complete resection. AP Urothelial carcinoma T1 G2. Muscular free of disease. Multiple bladder biopsies negatives

Figure 5.1: Bladder diagram



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



EAU 2021 Prognostic Risk Stratification

Risk group	
Low Risk	• A primary, single, TaT1 LG/G1 tumour < 3 cm in diameter without CIS in a patient ≤ 70 years • A primary Ta LG/G1 tumour without CIS with at most ONE of the additional clinical risk factors
Intermediate Risk	• Patients without CIS who are not included in either the low-, high-, or very high-risk groups
High Risk	• All T1 HG/G3 without CIS, EXCEPT those included in the very high-risk group • All CIS patients, EXCEPT those included in the very high-risk group
	Stage, grade with additional clinical risk factors: • Ta LG/G2 or T1 G1, no CIS with all three risk factors • Ta HG/G3 or T1 LG, no CIS with at least two risk factors • T1 G2 no CIS with at least one risk factor
Very High Risk	**Stage, grade with additional clinical risk factors:** • Ta HG/G3 and CIS with all three risk factors • T1 G2 and CIS with at least two risk factors • T1 HG/G3 and CIS with at least one risk factor • T1 HG/G3 no CIS with all three risk factors

EAU 2021 Prognostic Risk Stratification: Clinical application

Risk Group	Clinicopathological Criteria	Standard Management
Low Risk	Primary, solitary, Ta G1/LG, <3 cm, no CIS	Single post-TURB instillation
Intermediate Risk	Neither low nor high risk (multiple/recurrent LG)	Chemotherapy / 1-yr BCG
High Risk	T1G2/HG without very high risk factors or isolated CIS	BCG induction + 1-3 yrs maint.
Very High Risk	**T1G3/HG + concomitant CIS, multiple >3 cm tumors or persistent T1 on Re-TURB**	**Intensive BCG (3 yrs) vs Early Radical Cystectomy**

Depth
- Ta: invades chorion
- T1: invades muscularis propria

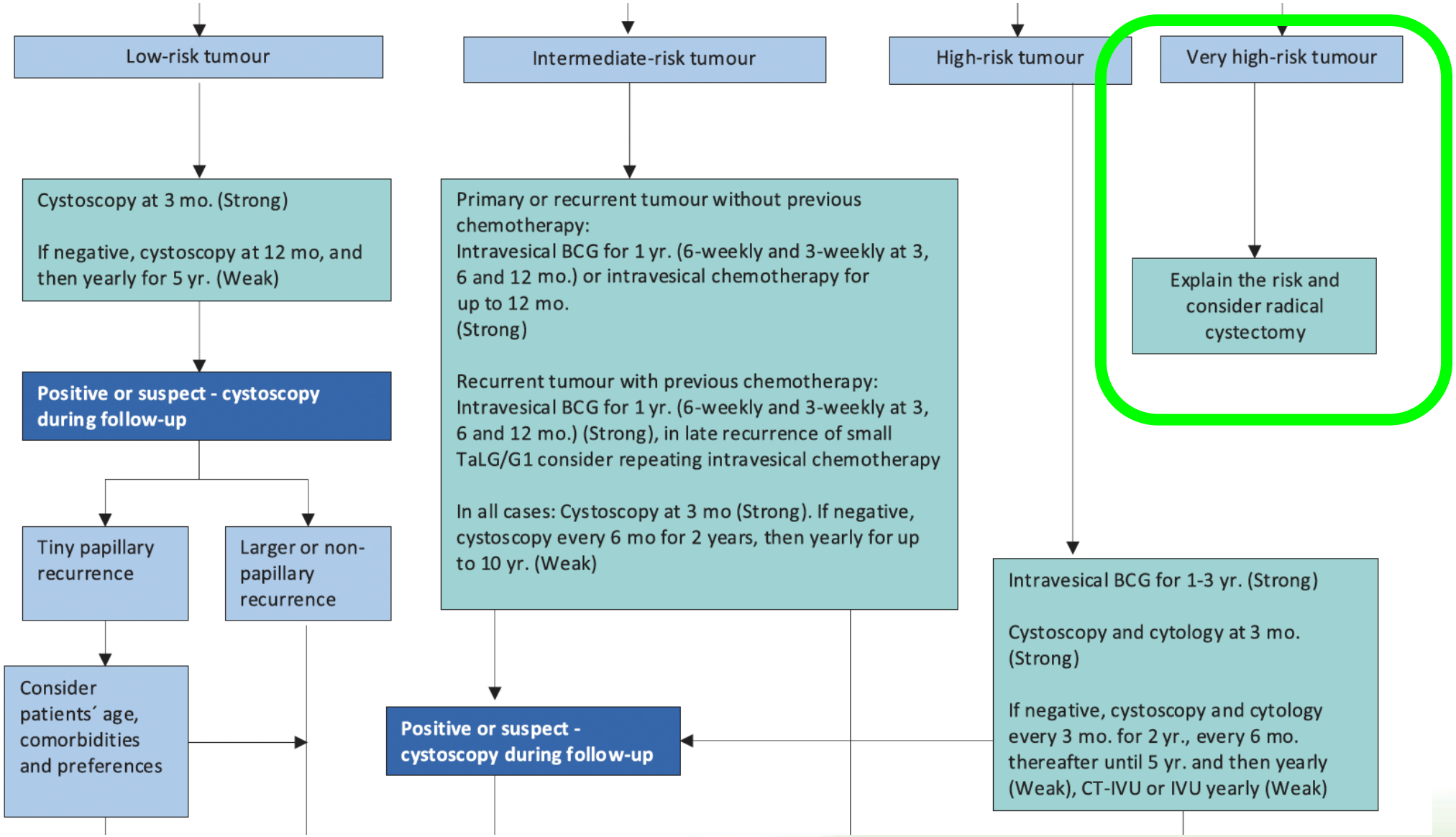
Histological Grade
- Low Grade (G1)
- High Grade (G2/G3)

CIS
- With concomitant CIS
- Without concomitant CIS

Risk Factors
- Multiple tumors
- Larger than 3 cm
- Age > 70 years

EAU Guidelines on Non-Muscle-Invasive Bladder Cancer (NMIBC)

Algorithm NMIBC EAU 2026



Therapeutic Options

Radical Cystectomy

Considered the "Gold Standard" in oncology for very high-risk tumors. Guidelines strongly recommend thoroughly discussing this surgical option early on due to the extremely high probability of invasive progression and potential impact on overall survival.

BCG Preservation

For patients who refuse surgery or have contraindications, the main alternative consists of full-dose intravesical BCG instillations for 1 to 3 years. The patient in this case has opted for initial conservative management with BCG.

EAU Guidelines on Non-Muscle-Invasive Bladder Cancer (NMIBC)

Intravesical BCG: Oncological Efficacy & Regimens

Level of Evidence: 1a

−32% vs. Chemotherapy
Recurrence Risk Reduction
Absolute reduction vs. Mitomycin C maintenance.

−27%
Progression Odds Reduction
Achieved only when maintenance is delivered.

72–93%
Complete Response in CIS
59% reduction in odds of treatment failure.

Oncological

Gold Standard: Unmatched in high-risk disease; significantly outperforms TURBT alone or TURBT + intravesical chemotherapy.

Induction Insufficiency: 6-week induction alone fails to impact long-term progression without structured maintenance.

Optimal 3-Year Schedule

High-Risk Protocol: 3-year maintenance (3-weekly courses at mo 3, 6, 12, 18, 24, 30, 36) proves superior to 1 year.

NIMBUS Trial Warning: Reduced instillation frequency is oncologically inferior; full schedule must be prioritized.

SWOG Maintenance Schedule



Induction

Consists of 6 consecutive weekly instillations. Completing this phase is crucial to trigger the initial antitumor immune response in the bladder mucosa.



Maintenance

3 consecutive weekly instillations at months 3, 6, 12, 18, 24, 30, and 36. In high/very high-risk tumors, the goal is to complete 3 years of therapy.



Clinical Benefit

This rigorous schedule has proven to be the most effective in reducing recurrence rates and delaying progression to muscle-invasive disease.

EAU Guidelines on Non-Muscle-Invasive Bladder Cancer (NMIBC)

Contraindications & Toxicity Management Algorithm

Absolute Contraindications

- **Post-TURBT Interval:** First 14 days following bladder resection.
- **Active Bleeding:** Gross macroscopic haematuria present.
- **Traumatic Catheterisation:** Immediate risk of intravascular entry.
- **Active Infection:** Symptomatic bacterial UTI.

Safe to Proceed (Non-Contraindications)

Do NOT delay treatment for: Asymptomatic bacteriuria, microscopic haematuria, isolated leukocyturia, or a positive PPD skin test.

Local Irritative Cystitis (Mild/Moderate)

Common

Action: Symptomatic treatment (Phenazopyridine, NSAIDs, anticholinergics). If persistent >48h, pause BCG and start empirical fluoroquinolones.

Granulomatous Prostatitis / Epididymo-orchitis

Severe Local

Action: Discontinue BCG instillations. Initiate Isoniazid (300 mg/d) + Rifampicin (600 mg/d) for 3 months. Urge infectious disease consult.

Systemic BCG Sepsis / High Fever (>38.5°C >48h)

Medical Emergency

Action: Permanent discontinuation of BCG. Hospitalize immediately. Triple therapy: INH + Rifampicin + Ethambutol (1.2 g/d) + High-dose systemic steroids.

Risk of Recurrence and Progression in NMIBC

Impact of BCG treatment at 5 years according to EAU risk stratification

Risk Group	Recurrence (w/o BCG)	Recurrence (w/ BCG)	Progression (w/o BCG)	Progression (w/ BCG)
Low Risk	~ 30%	~ 15 - 20%	< 1%	< 1%
Intermediate Risk	45 - 50%	**25 - 30%**	~ 5%	**2 - 3%**
High Risk	60 - 70%	**35 - 45%**	10 - 20%	**5 - 10%**
Very High Risk	> 70%	**40 - 50%**	**40 - 50%**	**15 - 20%**

Recurrence Reduction

Intravesical immunotherapy with **maintenance BCG** significantly reduces recurrence rates in intermediate and high-risk tumors compared to resection alone or intravesical chemotherapy.

Progression Prevention

In **high and very high-risk** patients, adequate BCG treatment is critical to prevent progression to muscle-invasive disease, reducing relative risk by up to **37-45%**.

EAU Guidelines on Non-Muscle-Invasive Bladder Cancer (NMIBC)

Follow-up Protocol



Very High-Risk Monitoring

Follow-up must be thorough and lifelong:

- Cystoscopy and urinary cytology every 3 months during the first 2 years.
- Semi-annual evaluations up to year 5, and annually for life.
- Annual upper tract anatomical evaluation via CT Urogram up to year 5, then biannual.
- Random bladder biopsies if cytology is positive without visible bladder lesion.

EAU Guidelines on Non-Muscle-Invasive Bladder Cancer (NMIBC)

Patient Chronological Summary

04/2025
Diagnosis
Hematuria, UroCT, MRI VI-RADS 2/3.

04/25/2025
1st Bladder TUR
Incomplete.
PA: High Grade + CIS.

05/13/2025
Re-TUR Bladder
PA: pT1, muscle clear.

06/2025
BCG Induction
Induction treatment (6 weeks).

09/2025
Follow-up
Under anesthesia (Cystoscopy + BMB).
Complete response.

10/2025
Maintenance
Start of BCG (3-year SWOG schedule).

04/2026
Follow-up
negative cytology
uromonitor negative
UroCT SHP

06/2026
Cystoscopy
Flexible follow-up (negative / scar).



The Great Reality: 50 Years with BCG…

The Great Question: Can we improve BCG results?

- By replacing it?
- By combining it?

IMMUNOTHERAPY + BCG

CREST Trial

Global Phase 3

Sasanlimab (anti-PD-1) in NMIBC

Trial Design

Population: High/very high-risk NMIBC, BCG-naïve.

Drug: Subcutaneous Sasanlimab + intravesical BCG.

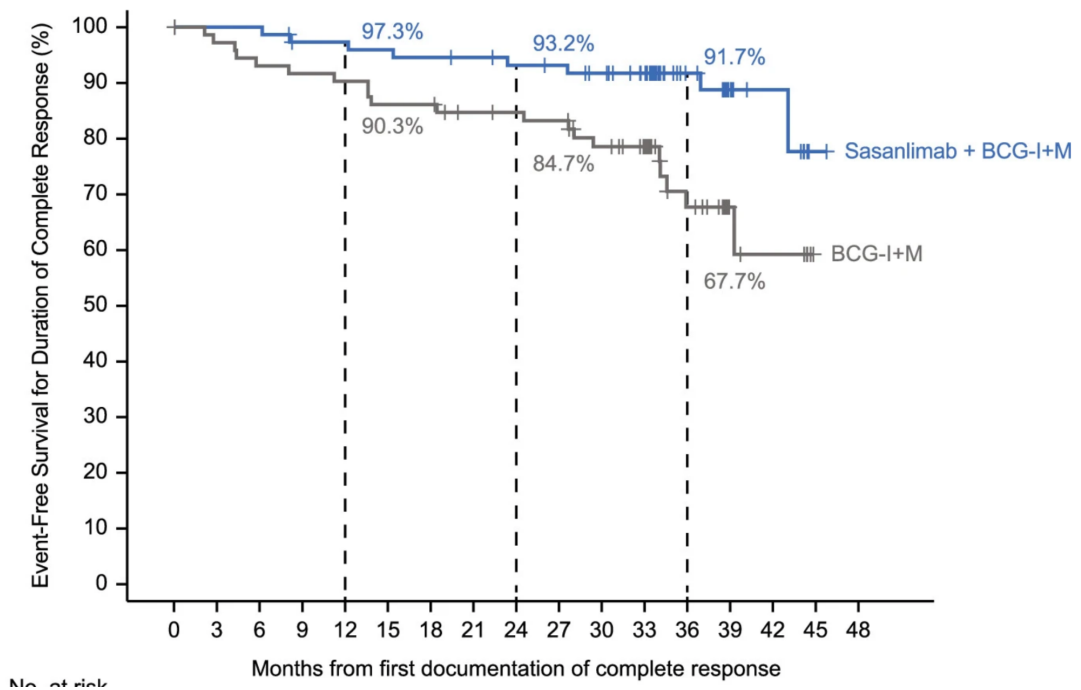
Comparator: Standard BCG induction & maintenance.

Key Results

Efficacy: 32% event risk reduction (HR 0.68).

36-month EFS: 82.1% (Combo) vs. 74.8% (BCG). Great response CIS subgroup

Condition: Combined maintenance is strictly necessary.



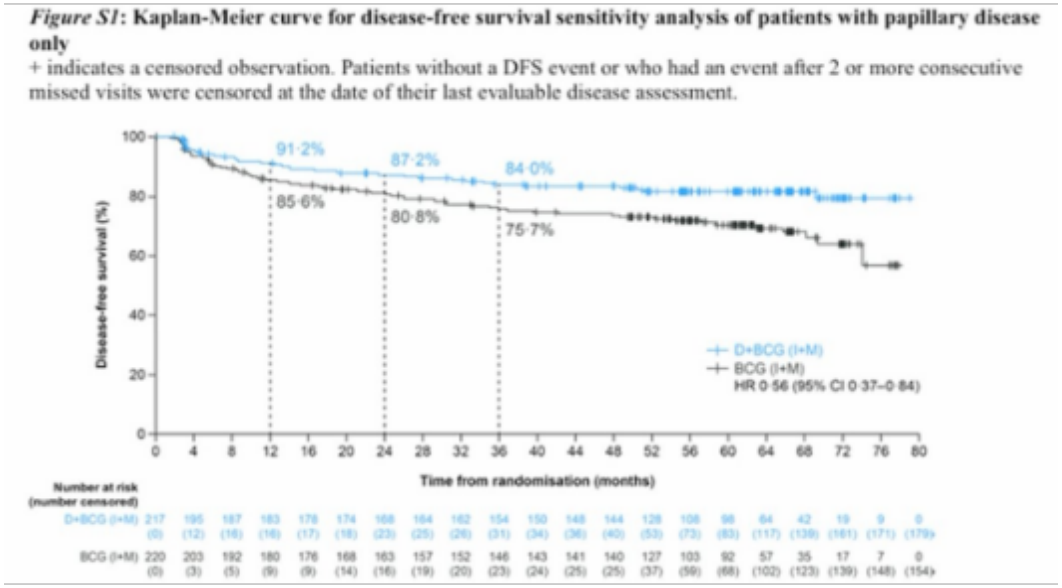
Sasanlimab + BCG (Very High-Risk + CIS Subgroup)

IMMUNOTHERAPY + BCG

POTOMAC Trial

FDA Approval 2026

Durvalumab (anti-PD-L1) in NMIBC



Kaplan-Meier Curve: Durvalumab + BCG (Very High-Risk Subgroup)

Trial Design

Population: High/very high-risk NMIBC, BCG-naïve.

Drug: Intravenous Durvalumab + intravesical BCG.

Comparator: Standard BCG monotherapy.

Clinical Impact

Efficacy: 31-32% event risk reduction (EFS).

24-month EFS: 87% (Combo) vs. 82% (BCG).

Preservation: Cystectomy rate reduced (25% to 8%).

Novel Intravesical Devices

TAR-200

SUNRISE Study

Investigational Phase

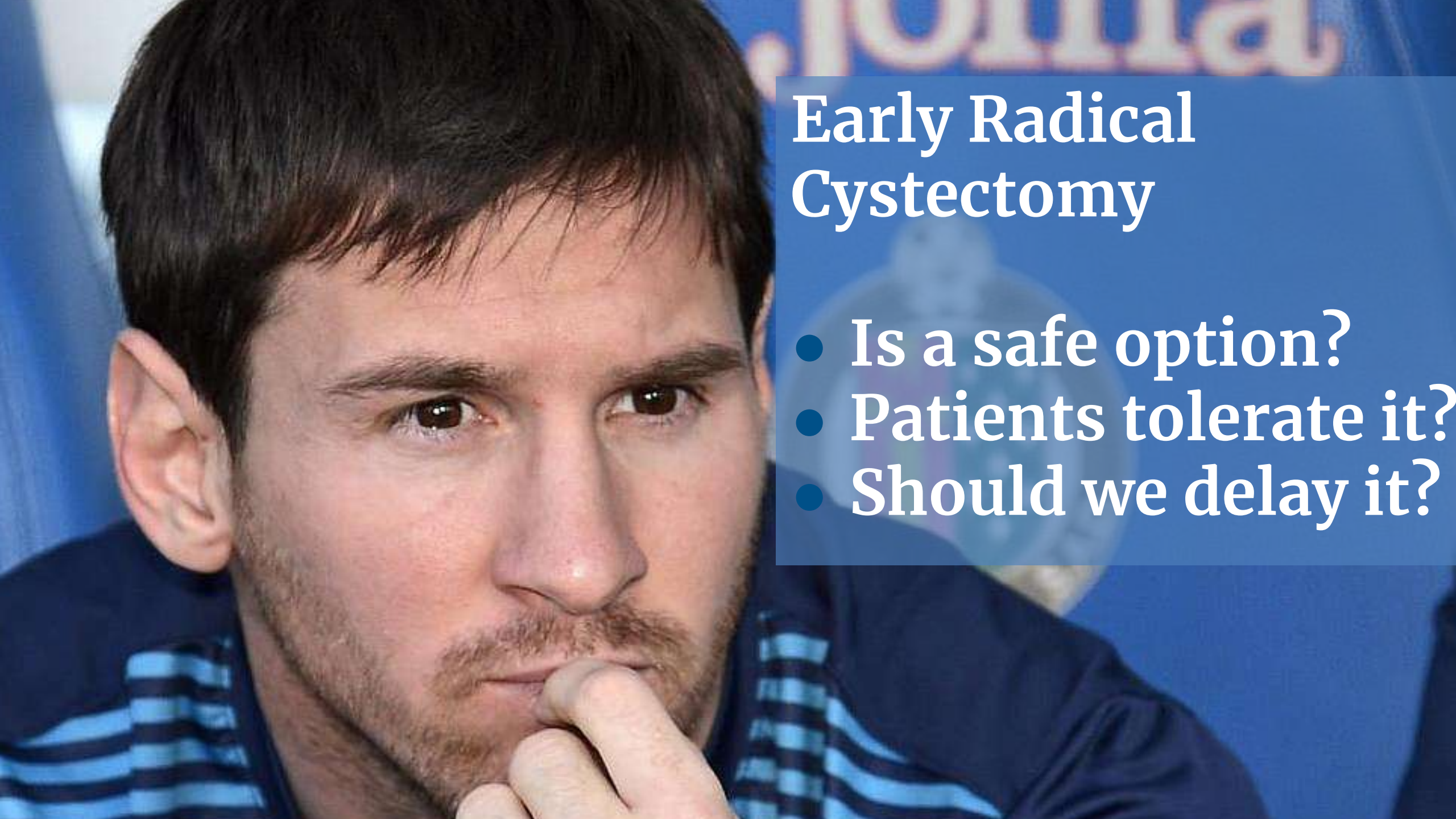
Device Overview

- **Mechanism:** Continuous intravesical release system (micro-osmotic pretzel) delivering gemcitabine directly to bladder mucosa over weeks.
- **Target Population:** Non-muscle-invasive bladder cancer (NMIBC), especially BCG-unresponsive.

Key Advantages

- **Sustained Exposure:** Overcomes rapid drug voiding of traditional intravesical instillations.
- **Outpatient Procedure:** Simple in-office catheter insertion and removal.
- **Bladder Preservation:** Promising organ-sparing alternative to radical cystectomy.





Early Radical Cystectomy

- Is a safe option?
- Patients tolerate it?
- Should we delay it?

CISTO Study: Radical Cystectomy vs. Bladder-Sparing Therapy in NMIBC

Gore et al. • N = 570 Patients

36 US Sites (PCORI)
371 BST (65%) | 199 RC (35%)

12-Mo Physical Function
No Difference (P = 0.22)

Cancer-Specific Survival
99% BST vs. 96% RC (NS)

RC 90-Day Morbidity
30% Readmission | 2.5% Mortality

Patient-Reported QOL & Wellbeing (12 Months)

FAVORS BST
Sexual & Bowel
BCI Sex: 47.1 vs 32.6 (P<.001)

FAVORS RC
Emotional & Financial
Lower Anxiety & Less Cost

- **Physical Recovery:** RC patients experienced a significant dip at 3 months, fully recovering to baseline parity by 9–12 months.
- **Financial Toxicity:** Significantly higher in BST at 12 months due to repeated intravesical treatments and quarterly cystoscopies.

Urinary Health: Identical at 12 months (BCI: 85.3 BST vs. 83.8 RC), dispelling concerns of permanent functional decline.

Oncological Outcomes & Staging Divergence

12-MO RECURRENCE-FREE
64% vs 92%
BST vs. RC (wRR 1.44)

OCCULT MUSCLE INVASION
22%
Upstaged to ≥pT2 at RC

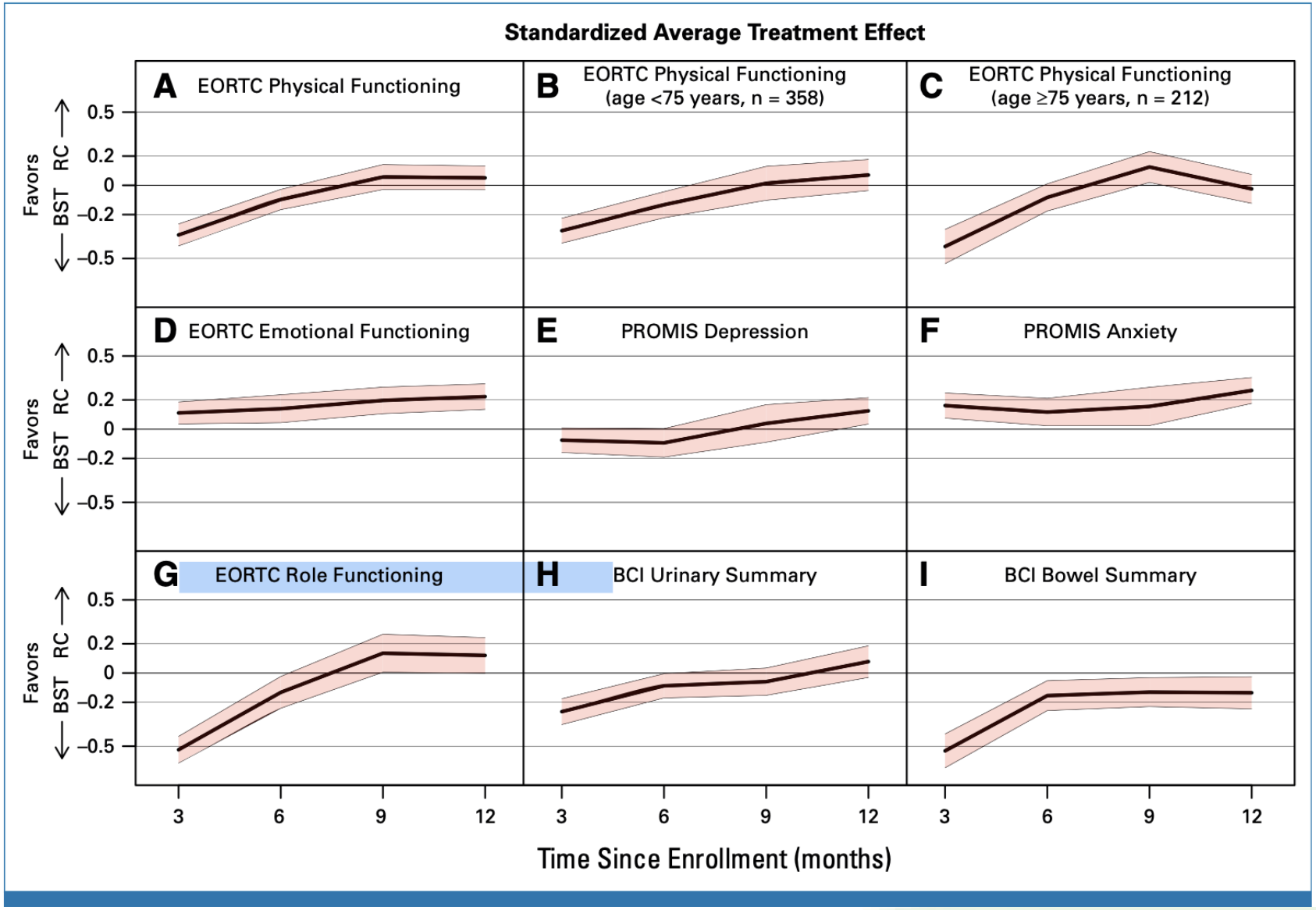
- **Delayed RC Rate:** Only 8.1% (27/371) in the BST arm required cystectomy within 12 months (only 1.2% due to muscle invasion).
- **Adverse Events:** Significantly higher with RC (62% vs. 38% for BST, wRR 1.61) with 4-fold higher serious life-threatening events.

Surveillance Safety: Excellent short-term cancer-specific survival (99% BST) validates initial bladder-sparing attempts under close monitoring.

Shared Decision-Making: RC provides definitive cancer control and eliminates recurring surveillance anxiety/costs without 12-month physical decline, but patients trade off acute 90-day surgical morbidity and long-term sexual/bowel quality of life.

Level 1 Evidence

CISTO Study


Standardized Average Treatment Effect
A EORTC Physical Functioning
B EORTC Physical Functioning (age <75 years, n = 358)
C EORTC Physical Functioning (age ≥75 years, n = 212)
D EORTC Emotional Functioning
E PROMIS Depression
F PROMIS Anxiety
G EORTC Role Functioning
H BCI Urinary Summary
I BCI Bowel Summary
Favors BST RC
0.5
0.2
0
−0.2
−0.5
3
6
9
12
Time Since Enrollment (months)

Scilipoti et al. • N = 1,491

Upfront Radical Cystectomy vs. BCG in HR & VHR NMIBC

European Multicenter
1,221 HR (90%) | 121 VHR (10%)

Real-World Upfront RC
Only 7.1% (87/1,221 patients)

Matched Cohort
1:1 PSM (87 BCG vs. 87 RC)

Follow-Up
Median 2.6 Years

5-Year Cancer-Specific Mortality (1:1 PSM)

BCG THERAPY
13%
5-Yr CSM

UPFRONT RC
16%
5-Yr CSM

Cox Hazard Ratio: 1.77 (95% CI 0.66–4.73). Initial bladder preservation with BCG does not compromise cancer-specific survival compared to upfront cystectomy.

Delayed RC: Progression Timing Dictates Survival

BEFORE PROGRESSION
11%
3-Yr CSM (cT1/CIS)

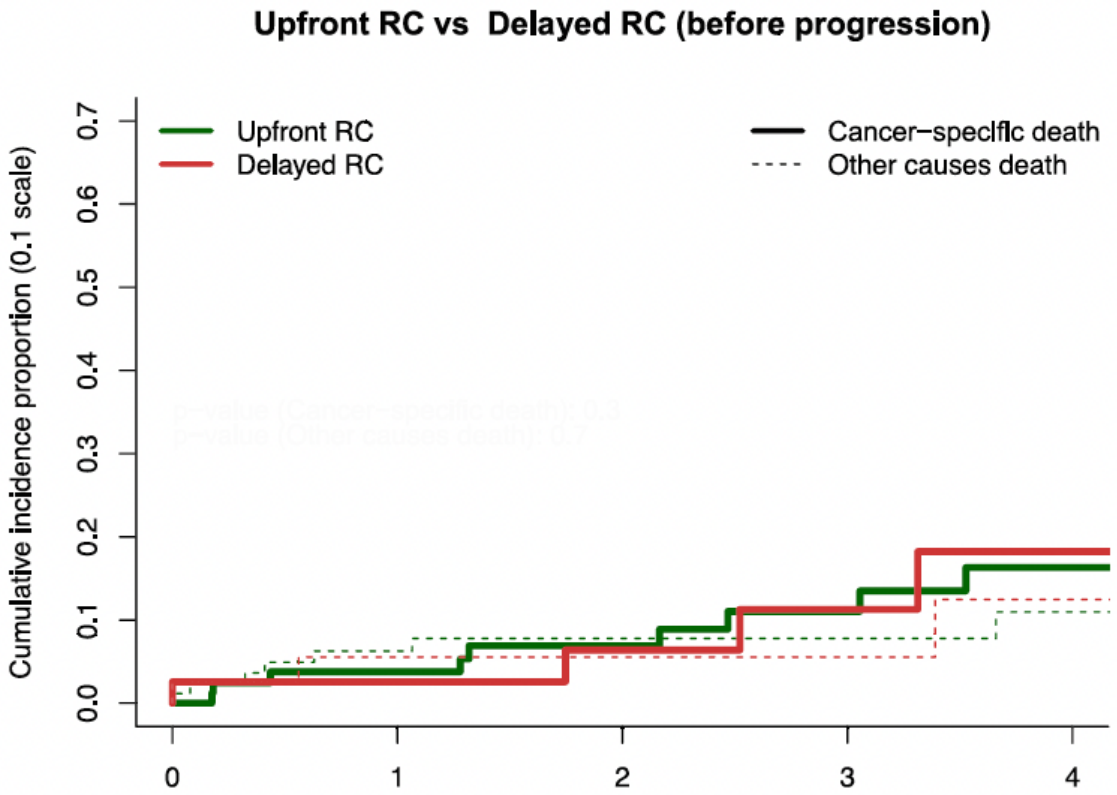
AFTER PROGRESSION
31%
3-Yr CSM (≥cT2)

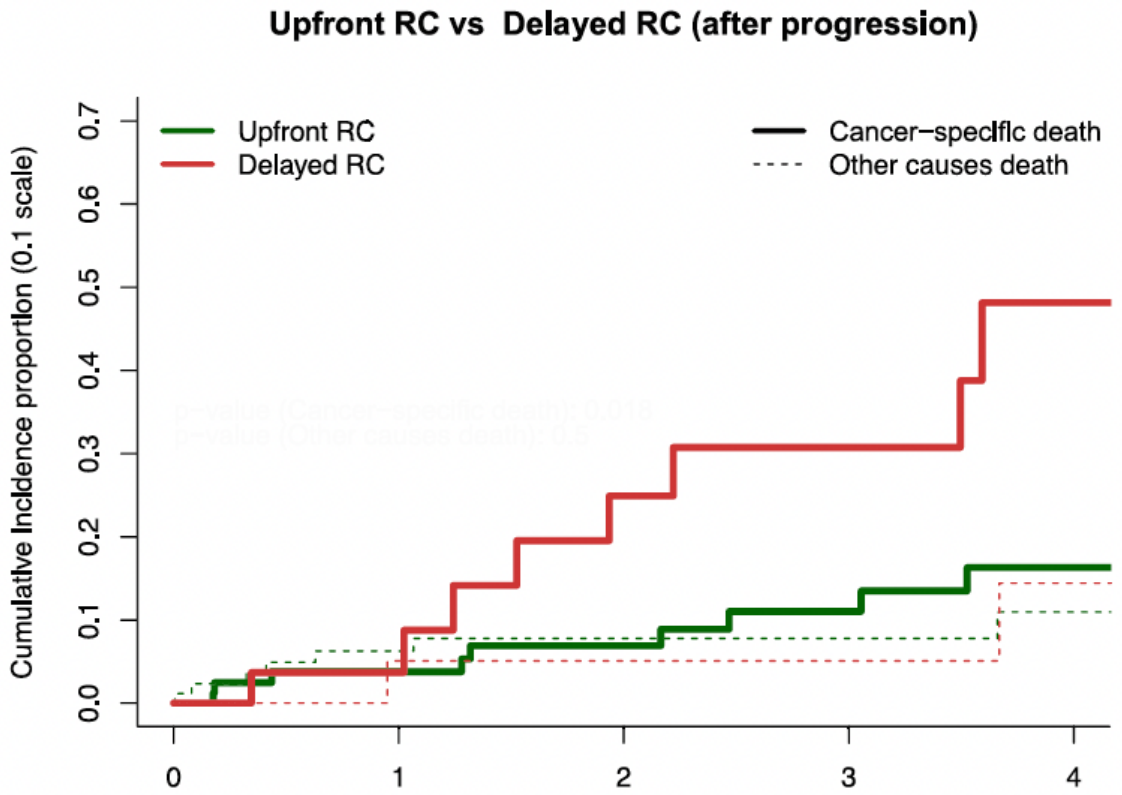
Progression Hazard: 73/1,134 (6.6%) required delayed RC; 47% had progressed to MIBC. Progression prior to salvage surgery triples mortality (HR: 0.32, 95% CI 0.13–0.83).

Clinical Takeaway: Bladder preservation with BCG is oncologically sound and non-inferior to upfront cystectomy, provided that surveillance is rigorous and delayed RC is performed *before* muscle invasion develops.

EAU Guidelines 2026

Upfront Radical Cystectomy vs. BCG in HR & VHR NMIBC





¿Preguntas?

Gracias por su atención.

