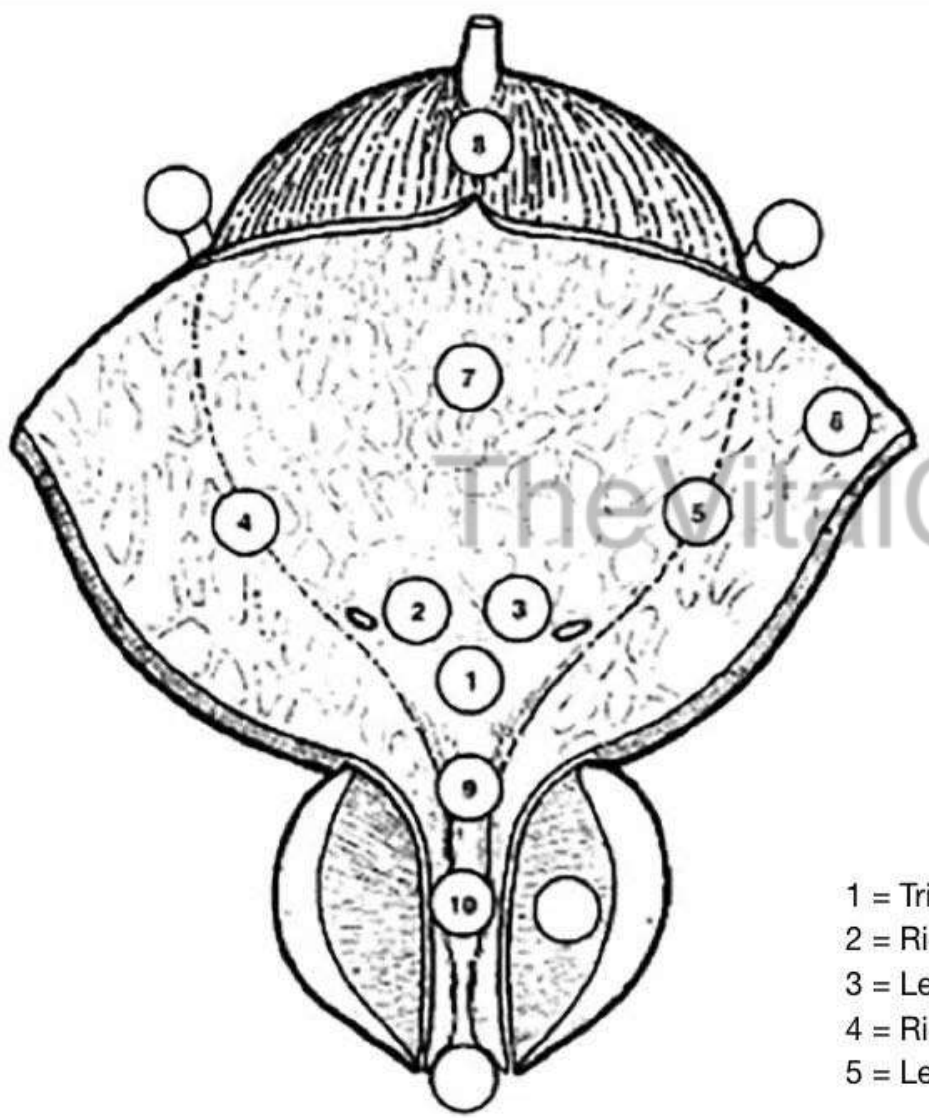
Management of NMIBC

Ta	Noninvasive papillary carcinoma
Tis	Urothelial carcinoma in situ: “flat tumor”
T1	Tumor invades lamina propria (subepithelial connective tissue)

TURBT

- Maximal TURBT – Resection of all visible tumor with detrusor muscle
- Piecemeal vs En-bloc resection – No difference
- Monopolar vs bipolar resection
  - Bipolar resection reduces complication of bladder perforation by avoiding obturator nerve stimulation
- Random bladder biopsies to be taken from normal appearing mucosa
- Prostatic urethra biopsy (involved in 11%)
  - When tumor is located in trigone / bladder neck
  - When planning for partial cystectomy

Figure 5.1: Bladder diagram



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

Enhanced cystoscopy

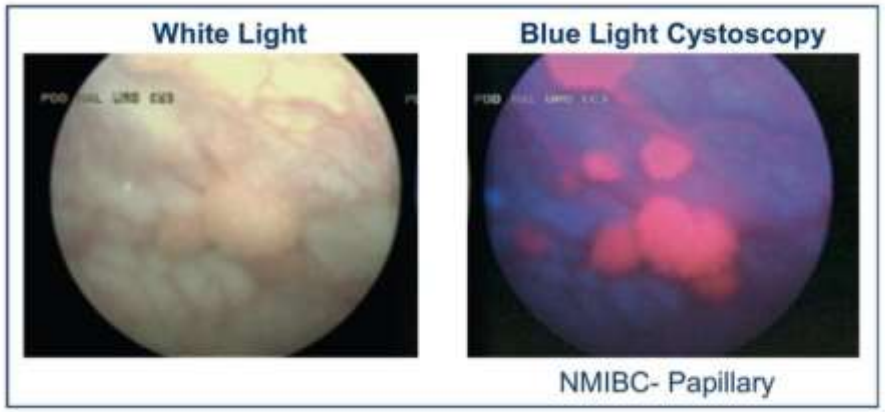


Fig. 136.7. White light cystoscopy reveals apparent normal-appearing mucosa juxtaposed with blue light cystoscopy demonstrating visual evidence of bladder cancer. Blue light cystoscopy reveals accumulation of hexaminolevulinate in the same area, ultimately found to contain non-muscle-invasive bladder cancer (NMIBC). (Image courtesy Dr. Siamak Daneshmand.)

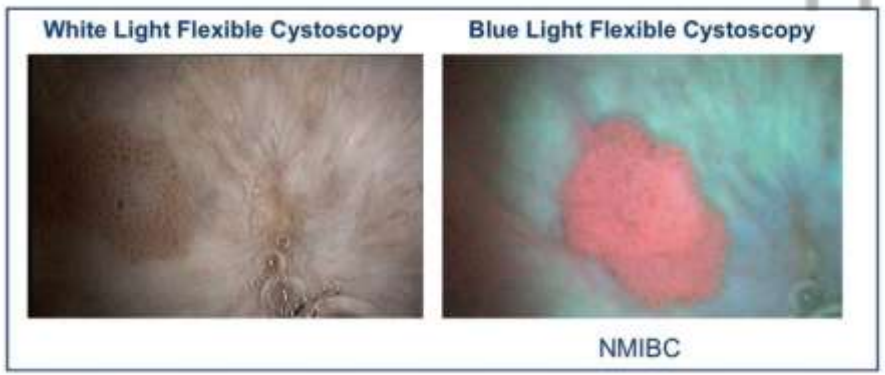
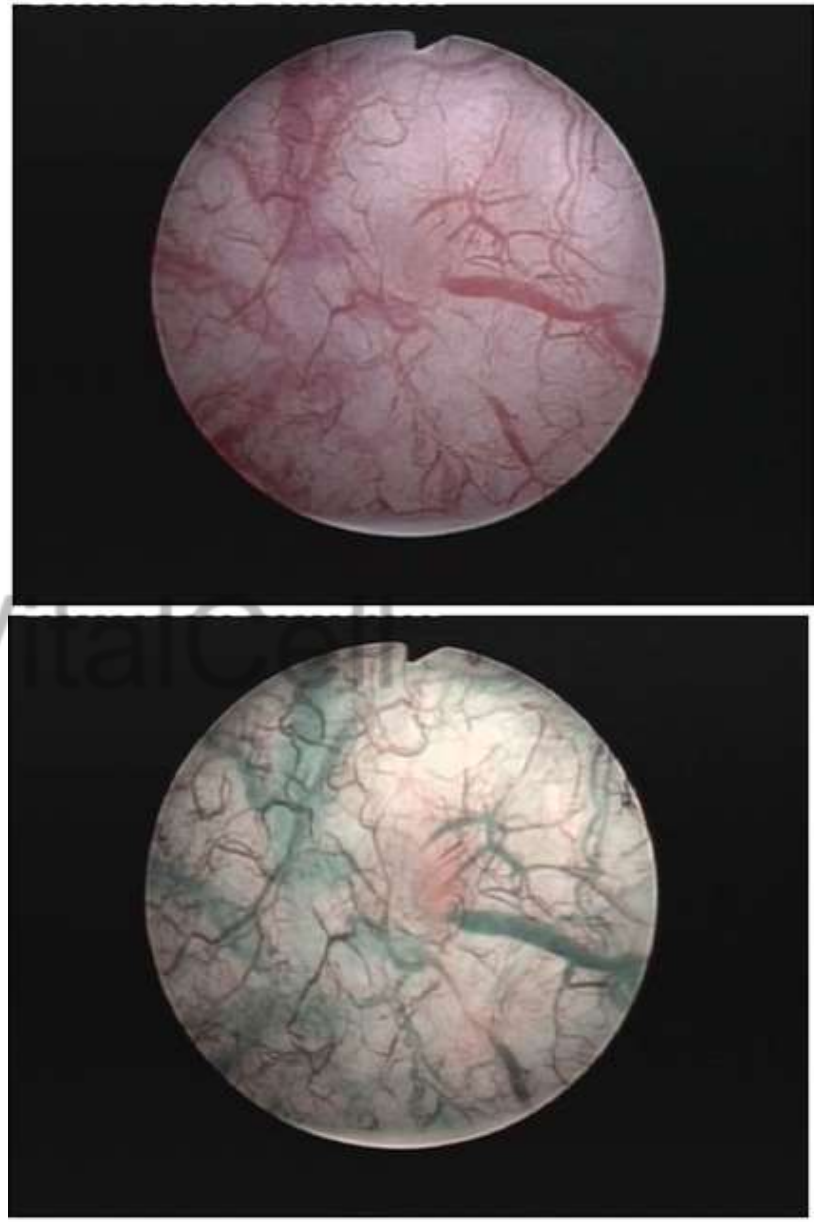


Fig. 136.8. White and blue light cystoscopy of non–muscle-invasive bladder cancer (NMIBC) using flexible cystoscopy after administration of hexaminolevulinate. (Image courtesy Dr. Siamak Daneshmand.)

Photodynamic diagnosis (PDD) / Fluorescence cystoscopy / blue light cystoscopy



Narrow band imaging

More sensitive than conventional white light cystoscopy especially for CIS lesions (90% vs 70%)

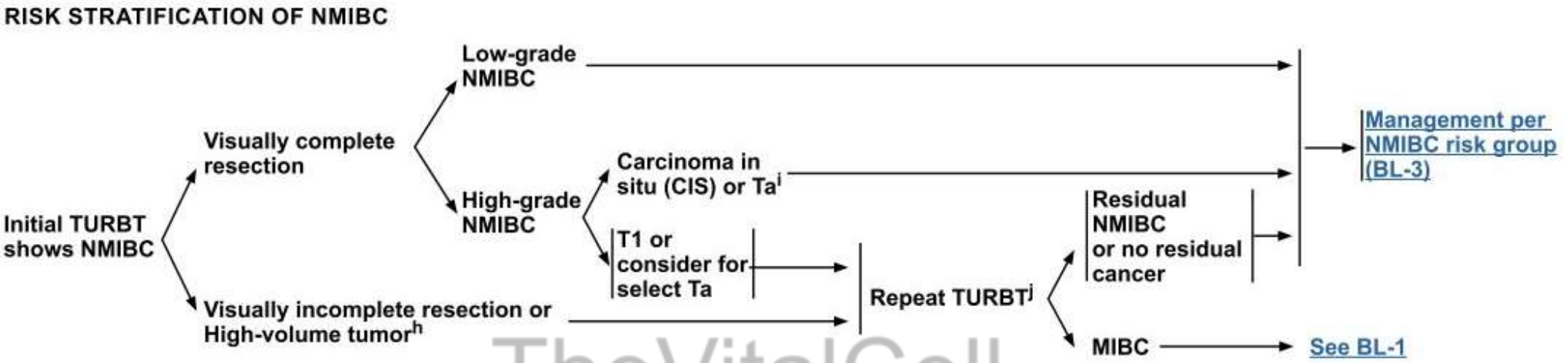
Indication for Re-TURBT

- Initial incomplete TURBT – due to extensive tumor / intra-op complications
- Absence of muscularis propria in initial TUR
- High grade / T1 lesions even in the presence of muscle in initial TUR
  - 51% chance of persistent disease and 8% risk of understaging in High grade / T1 lesions
- Done 6 weeks after initial resection

Risk stratification – EAU / WHO

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 T1G1, no CIS with all 3 risk factors • Ta HG/G3 or T1 LG, no CIS with at least 2 risk factors • T1G2 no CIS with at least 1 risk factor
Very High Risk	**Stage, grade with additional clinical risk factors:** • Ta HG/G3 and CIS with all 3 risk factors • T1G2 and CIS with at least 2 risk factors • T1 HG/G3 and CIS with at least 1 risk factor • T1 HG/G3 no CIS with all 3 risk factors

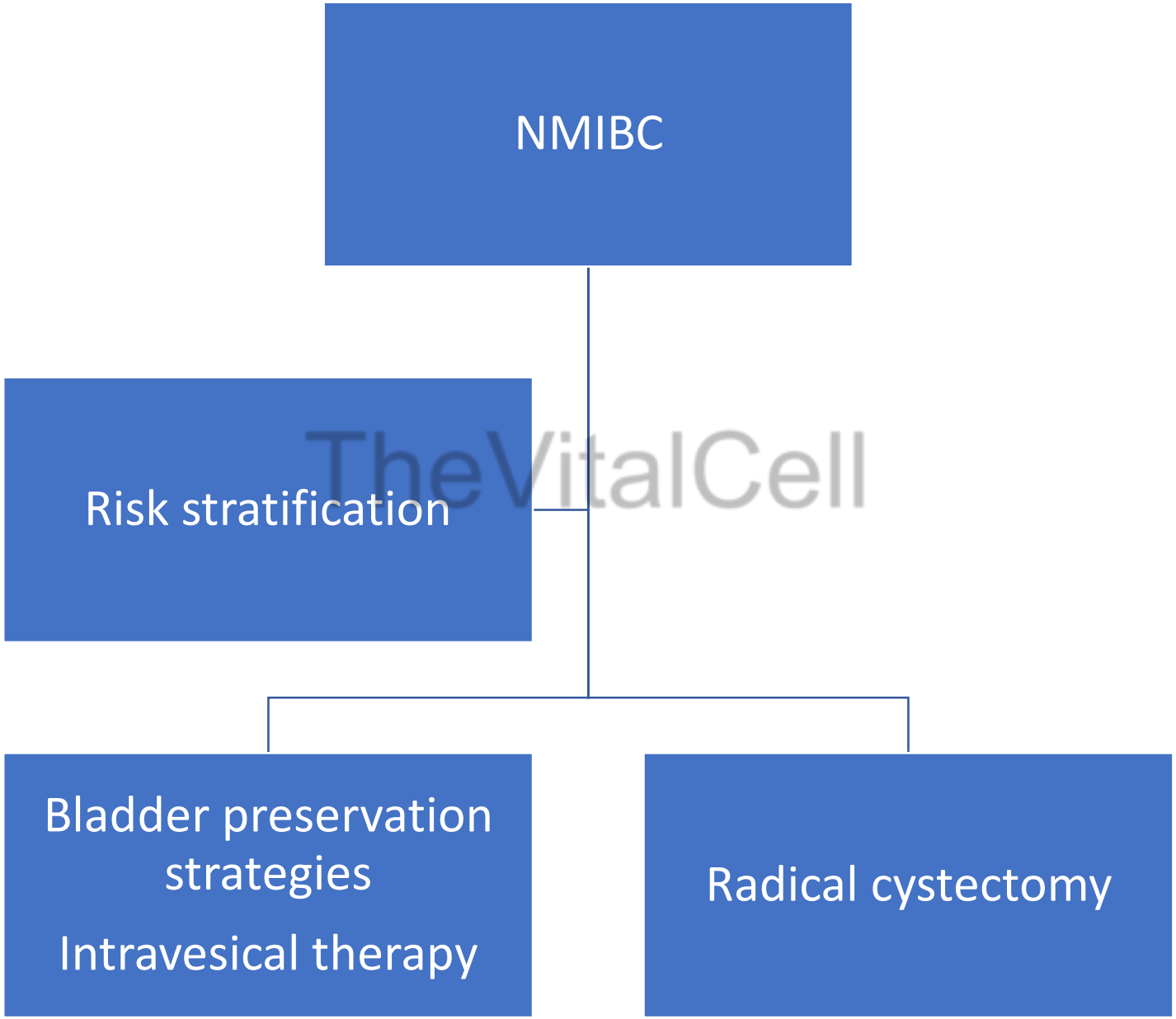
Risk stratification – AUA / NCCN



AUA Risk Stratification for Non-Muscle Invasive Bladder Cancer*

Low Risk	Intermediate Risk	High Risk
• Papillary urothelial neoplasm of low malignant potential • Low grade urothelial carcinoma ▸ Ta and ▸ ≤3 cm and ▸ Solitary	• Low grade urothelial carcinoma ▸ T1 or ▸ >3 cm or ▸ Multifocal or ▸ Recurrence within 1 year • High grade urothelial carcinoma ▸ Ta and ▸ ≤3 cm and ▸ Solitary	• High grade urothelial carcinoma ▸ CIS or ▸ T1 or ▸ >3 cm or ▸ Multifocal • Very high risk features (any): ▸ BCG unresponsive[k] ▸ Variant histologies[l] ▸ Lymphovascular invasion ▸ Prostatic urethral invasion

•The recurrence and progression rates of papillary urothelial neoplasm of low malignant potential (PUNLMP) are expected to be higher than urothelial papilloma and lower than low grade noninvasive urothelial carcinoma



Intravesical therapy

Chemotherapy

Immunotherapy

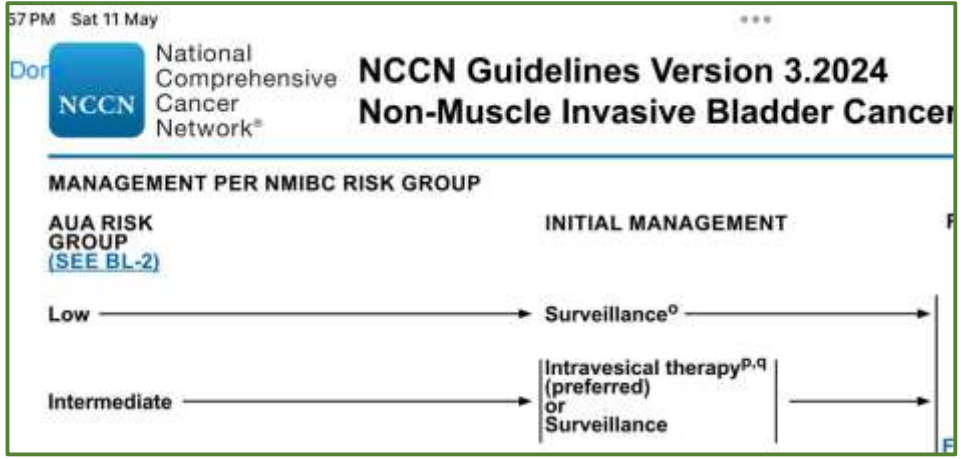
Intravesical chemotherapy

- Why?

Table 6.2: Probabilities of disease progression in 1, 5 and 10 year(s) for the new EAU NMIBC risk groups [65]*

Risk group	***Probability of Progression and 95% Confidence Interval (CI)***		
	1 Year	5 Years	10 Years
New Risk Groups with WHO 2004/2016			
Low	0.06% (CI: 0.01%–0.43%)	0.93% (CI: 0.49%–1.7%)	3.7% (CI: 2.3%–5.9%)
Intermediate	1.0% (CI: 0.50%–2.0%)	4.9% (CI: 3.4%–7.0%)	8.5% (CI: 5.6%–13%)
High	3.5% (CI: 2.4%–5.2%)	9.6% (CI: 7.4%–12%)	14% (CI: 11%–18%)
Very High	16% (CI: 10%–26%)	40% (CI: 29%–54%)	53% (CI: 36%–73%)

Intravesical chemotherapy



- What drugs?

1. Mitomycin – standard of care
2. Gemcitabine – 4yr recurrence rate – 34%
3. Epirubicine
4. Valrubicine
5. Thiotepa
6. Saline

No trials with head to head comparison of drugs

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

Intravesical chemotherapy

- When?
- Single, immediate, postoperative intravesical instillation of chemotherapy
  - Reduces 5yr recurrence rate by 14% (from 59% - 45%)
  - Intermediate risk category is a diverse group.
  - 2006 EORTC recurrence score <5 / <1 recurrence per year benefitted from SI
- Dosage – Mitomycin C 40mg in 20cc distilled water instilled over 1 hour, within 6 hours of TUR, with alkaline urine (oral sodabicarb), with oral fluid restriction.
- Mechanism of action – prevents tumor cell implantation – not effective if given after 24 hours.

2006 EORTC recurrence score calculator

Table 1: Disease recurrence and progression scores

FACTOR	RECURRENCE	PROGRESSION
NUMBER OF TUMORS		
Single	0	0
2-7	3	3
>8	6	3
Tumor diameter		
< 3 cm	0	0
> 3 cm	3	3
Prior recurrence rate		
Primary	0	0
< 1 recurrence/year	2	2
> 1recurrence/year	4	2
Category		
Ta	0	0
T1	1	4
Concurrent CIS		
No	2	2
Yes	4	2
Grade (WHO 1973)		
G1	0	0
G2	1	0
G3	2	5
Total score	0-17	0-23

Intravesical chemotherapy

- How?

Method of administration

- Place a 3-way catheter in the OR attached to an irrigant fluid, which is left turned off.
- Administer the chemotherapy agent through the main catheter port, clamp with hemostat and attach to a drainage bag .The system is thus closed.
- Staff should be notified to unclamp after 1 hour.
- Run 1 liter of saline through the irrigant port over next 30–60 minutes,
- Remove and discard the Foley along with urinary drainage bag into biohazard container.[2]

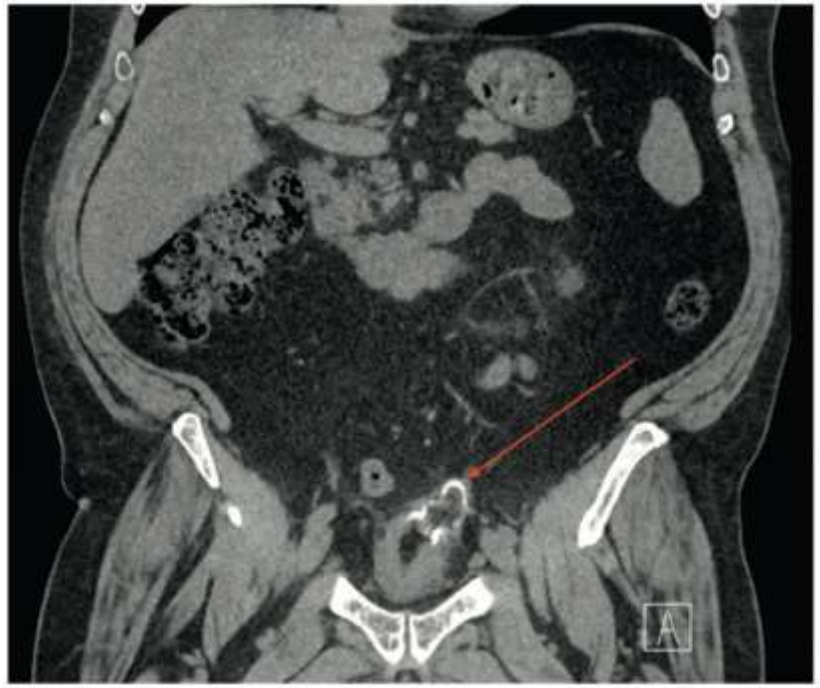


Fig. 136.9. CT image taken from image of a 59-year-old male who received perioperative administration of mitomycin C at time of transurethral resection of bladder tumor in the setting of extravesical perforation. This patient subsequently developed calcified, necrotic tissue associated with non-healing bladder ulcer (as pictured in image with *red arrow* pointing to calcified region) and ultimately required radical cystectomy with ileal neobladder secondary to refractory symptoms.

Device assisted intravesical chemotherapy

1. Hyperthermic intravesical chemotherapy
2. Microwave induced hyperthermia effect
3. Conductive chemohyperthermia
4. Electromotive drug administration

So far not shown any significant advantage over the conventional metheod.

Intravesical chemotherapy

Systematic Review on the Utilization of Maintenance Intravesical Chemotherapy in the Management of Non-Muscle Invasive Bladder Cancer

William B. Tabayoyong[1], Ashish M. Kamat[1], Michael A. O'Donnell[2], James M. McKiernan[3], Mohamed D. Ray-Zack[4], Joan Palou[5], Maurizio Brausi[6], Peter C. Black[7], Stephen B. Williams[4]

Conclusion: Although maintenance intravesical chemotherapy is suggested as a treatment option for patients with NMIBC by some guidelines, the majority of evidence suggested that it provided no significant advantage over induction therapy alone with respect to recurrence, progression, or survival

Intravesical immunotherapy – BCG

- Why?

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INTRACAVITARY BACILLUS CALMETTE-GUERIN IN THE TREATMENT OF SUPERFICIAL BLADDER TUMORS

A. MORALES,* D. EIDINGER AND A. W. BRUCE

From the Departments of Urology, and Microbiology and Immunology, Queen's University, Kingston, Ontario, Canada

- In 1976, Morales and colleagues published a landmark paper on the favourable effect of intravesical BCG on outcomes in recurrent superficial bladder cancer in nine patients.
- The first controlled trial showing similar results was published in 1980.
- BCG received FDA approval for the treatment of superficial bladder cancer in 1990.

Long-Term Efficacy Results of EORTC Genito-Urinary Group Randomized Phase 3 Study 30911 Comparing Intravesical Instillations of Epirubicin, Bacillus Calmette-Guérin, and Bacillus Calmette-Guérin plus Isoniazid in Patients with Intermediate- and High-Risk Stage Ta T1 Urothelial Carcinoma of the Bladder

Richard J. Sylvester [a], Maurizio A. Brausi [b], Wim J. Kirkels [c], Wolfgang Hoeltl [d], Fernando Calais Da Silva [e], Philip H. Powell [f], Stephen Prescott [g], Ziya Kirkali [h], Cees van de Beek [i], Thierry Gorlia [a], Theo M. de Reijke [j],

EORTC Genito-Urinary Tract Cancer Group

32% relative risk reduction with the use of BCG maintenance compared with intravesical chemotherapy.

Intravesical bacillus Calmette–Guérin is superior to mitomycin C in reducing tumour recurrence in high-risk superficial bladder cancer: a meta-analysis of randomized trials

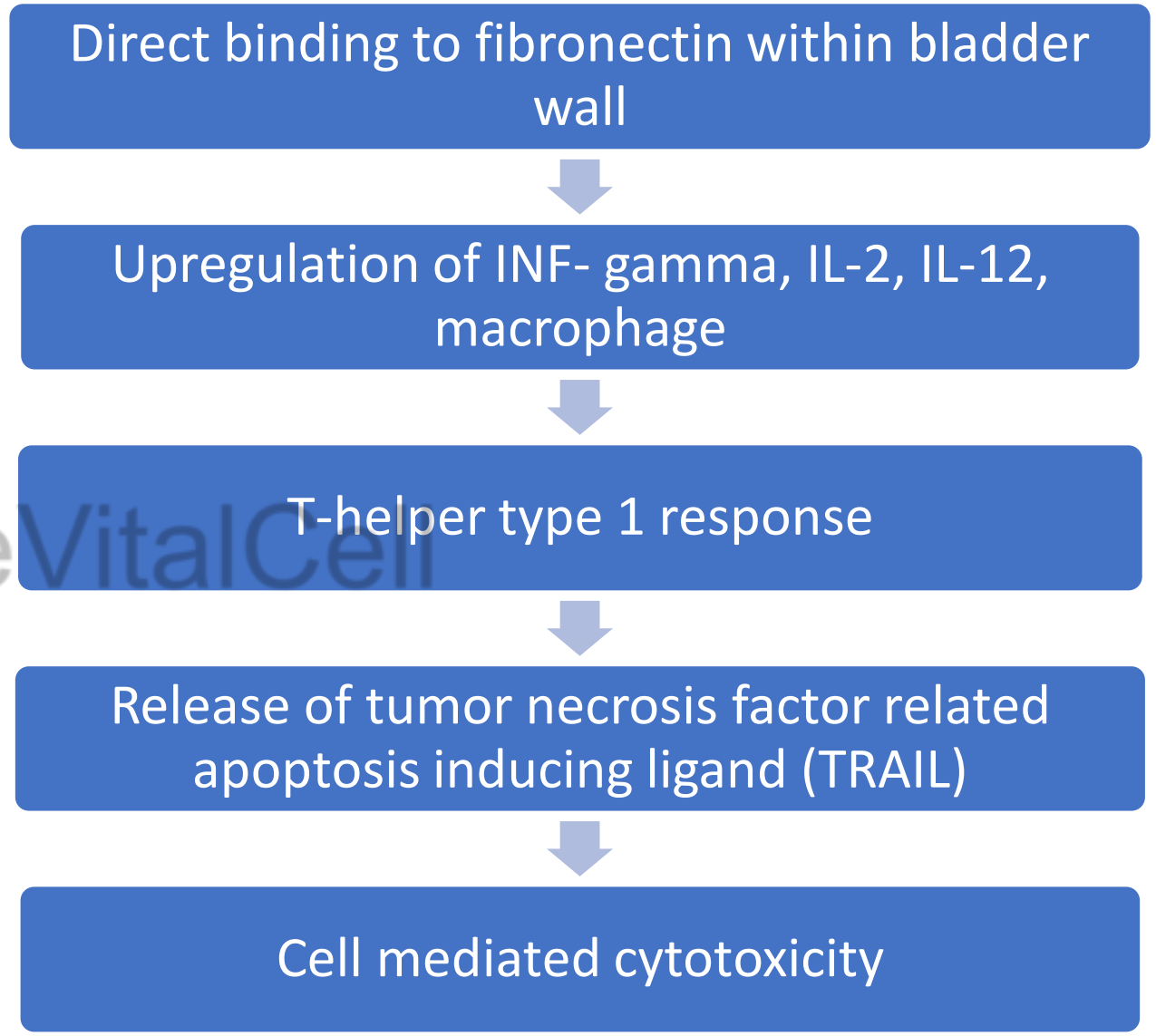
M.D. SHELLEY, T.J. WILT*, J. COURT, B. COLES, H. KYNASTON† and M.D. MASON

*Cochrane Prostatic Diseases and Urologic Cancers Group, Velindre NHS Trust and †Urology Department, University Hospital of Wales, Cardiff, UK, and * Minneapolis VA Center for Chronic Disease Outcomes Research, USA*

Accepted for publication 10 September 2003

Intravesical immunotherapy – BCG

Mechanism of action



BCG dosage

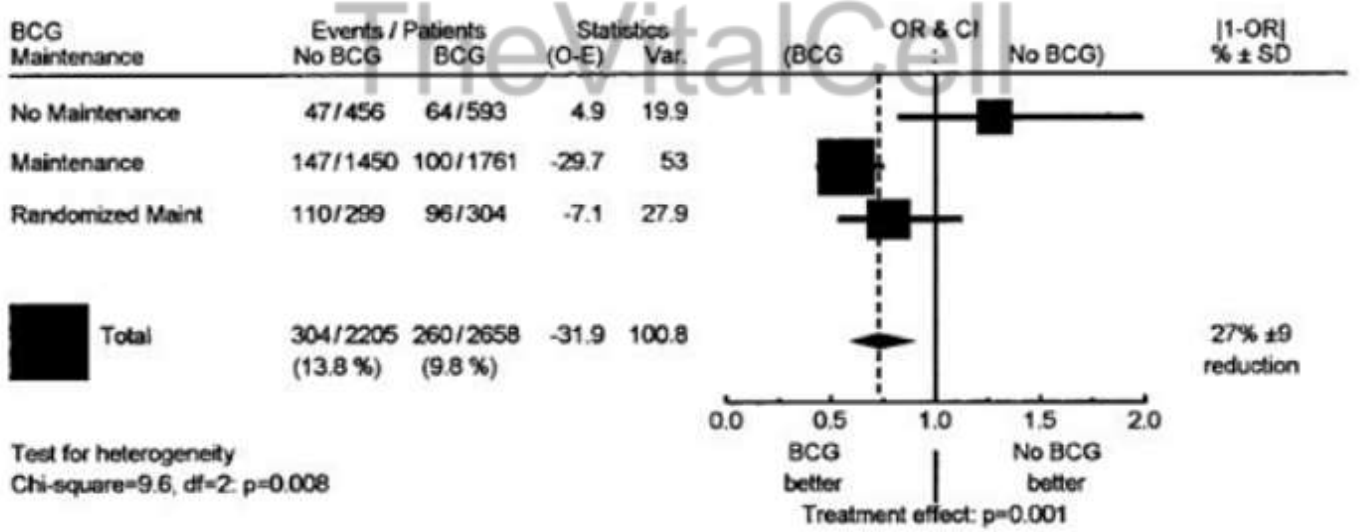
- Given 2-4 weeks after TURBT – allowing time for bladder re-epithelisation.
- 1 vial = 40mg
- 80 mg in 50ml saline instilled over 2 hours
- Limit fluid consumption to less than 250ml (1 glass) 4 hours before instillation, to prevent dilution.
- Other dosage – 40mg / 120mg, half dose / one third dose.

  - evaluated for BCG shortage scenario
- CUETO group study
  - For intermediate risk disease – no difference in efficacy between std. and reduced dose
  - For High risk, multifocal disease – reduced dose is inferior.
- Pre instillation urine cytology / culture – not mandatory
- Pre instillation oral fluroquinolones – reduces systemic toxicity and improves efficacy

BCG therapy – Induction only or maintenance needed?

BCG reduces progression only when maintenance is used

Meta-analysis of 24 RCT of BCG with 4863 patients



Forest plot of progression of BCG maintenance vs no maintenance

Sylvester RJ et al. J Urol. 2002;168:1964–70

BCG Regime (Induction + Maintenance)

Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study

D L Lamm [1], B A Blumenstein, J D Crissman, J E Montie, J E Gottesman, B A Lowe, M F Sarosdy, R D Bohl, H B Grossman, T M Beck, J T Leimert, E D Crawford

6-week induction course of BCG followed by maintenance with 3 weekly instillations at months 3, 6, 12, 18, 24, 30, and 36.

Results: No toxicities above grade 3 were noted in the 243 maintenance arm patients. The policy of withholding maintenance BCG from patients with increased side effects may have diminished the opportunity to observe severe toxicity. Estimated median recurrence-free survival was 35.7 months (95% confidence interval 25.1 to 56.8) in the no maintenance and 76.8 months (64.3 to 93.2) in the maintenance arm (log rank $p<0.0001$). Estimated median time for worsening-free survival, defined as no evidence of progression including pathological stage T2 disease or greater, or the use of cystectomy, systemic chemotherapy or radiation therapy, was 111.5 months in the no maintenance and not estimable in the maintenance arm (log rank $p = 0.04$). Overall 5-year survival was 78% in the no maintenance compared to 83% in the maintenance arm.

- RFS advantage of 41 months
- 5yr OS advantage of 5%

BCG maintenance – 1 year vs 3 years

Final Results of an EORTC-GU Cancers Group Randomized Study of Maintenance Bacillus Calmette-Guérin in Intermediate- and High-risk Ta, T1 Papillary Carcinoma of the Urinary Bladder: One-third Dose Versus Full Dose and 1 Year Versus 3 Years of Maintenance

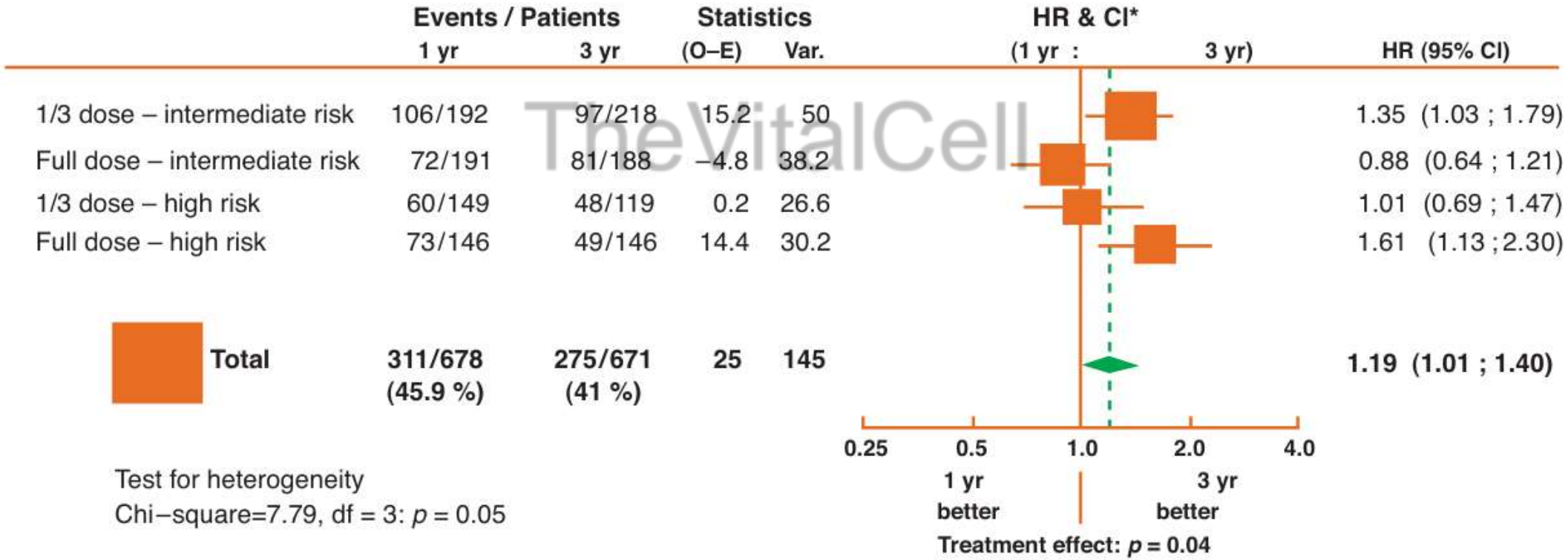


Fig. 5 – Disease-free interval: 1 yr of maintenance versus 3 yr of maintenance according to dose and risk group. HR = hazard ratio; CI = confidence interval; df = degrees of freedom.

BCG maintenance – 1 year vs 3 years

- There were no significant differences in toxicity between one thirds and Full Dose BCG.
- Based on the primary end point of DFI, one thirds with 1 yr of maintenance is suboptimal compared with the standard FD during 3 yr.
- It is recommended to treat intermediate-risk patients with FD for 1 yr because there is no further improvement in outcome by continuing treatment to 3 yr.
- In high-risk patients, FD-3 yr BCG reduces recurrences as compared with FD-1 yr; however, there were no long term differences in progression or survival.
- The benefit of the two additional years of maintenance should thus be weighed against its additional costs, side effects, and inconvenience.

Contraindications to intravesical BCG

BOX 136.1 Contraindications to Bacille Calmette-Guérin (BCG) Therapy

ABSOLUTE CONTRAINDICATIONS

Immunosuppressed and immunocompromised patients[a]
Immediately after transurethral resection on the basis of the risk of intravasation and septic death
Personal history of BCG sepsis
Gross hematuria (intravasation risk)
Traumatic catheterization (intravasation risk)
Total incontinence (patient will not retain agent)

RELATIVE CONTRAINDICATIONS

Urinary tract infection (intravasation risk)
Liver disease (precludes treatment with isoniazid if sepsis occurs)
Personal history of tuberculosis (risk theorized but unknown)
Poor overall performance status
Advanced age

NO OR INSUFFICIENT DATA ON POTENTIAL CONTRAINDICATIONS

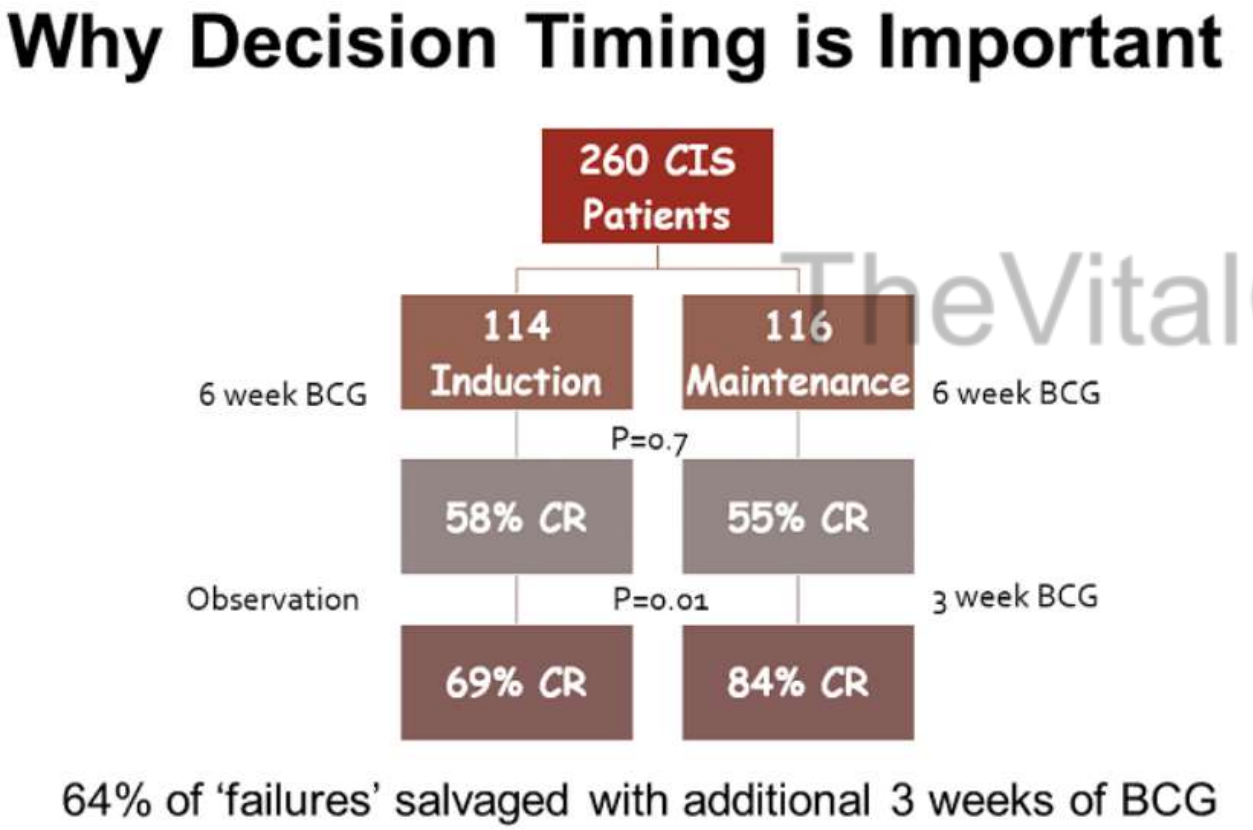
Patients with prosthetic materials have not been shown to have increased risk of infectious or other complications in limited literature (Rosevear et al., 2010)
Ureteral reflux
Anti–tumor necrosis factor medications (theoretically predispose to BCG sepsis)

BCG toxicity

Supplementary Table 1. Cleveland Clinic Approach to the Management of BCG Toxicity

Grade 1: Moderate symptoms <48 hours	Antispasmodics, NSAIDs
Mild to moderate irritative voiding symptoms, mild hematuria, fever <38.5°C	
Grade 2: Severe symptoms and/or >48 hours	Consider Dose reduction Oral Isoniazid + rifampicin till symptom resolution
Severe irritative voiding symptoms, hematuria, or symptoms lasting >48 hours	
Grade 3: Serious complications (hemodynamic changes, persistent high-grade fever)	Stop BCG Isoniazid + rifampicin BCG is uniformly resistant to pyrazinamide – no role Monitor LFT
Allergic Reactions, such as Joint Pain, Rash	
Solid Organ Involvement: Epididymis, Liver, Lung, Kidney, Bone, Joint, Prostate	

BCG failure definitions by IBCG (International Bladder Cancer Group)



Definition of adequate BCG treatment:
BCG induction 6 weeks + at least one BCG maintenance of 3 weeks

BCG failure definitions by IBCG (International Bladder Cancer Group)

BCG refractory:

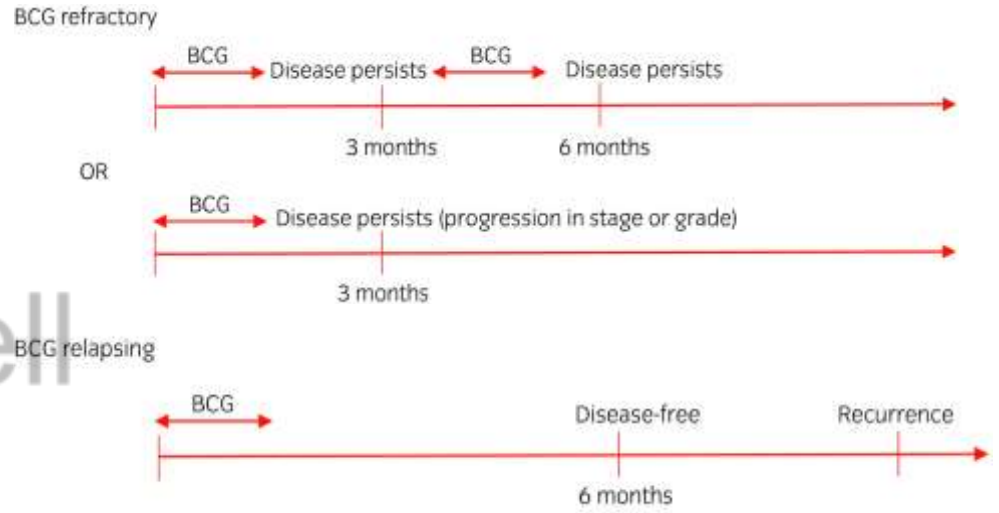
- Persistent HG disease at 6 mo despite adequate BCG treatment
- Also includes any stage/grade progression at 3 mo after iBCG

BCG relapsing:

- Recurrence of HG disease after achieving a disease-free state at 6 mo after adequate BCG
- Highest risk relapsing patients: within 6 mo of last exposure to BCG (eg those on maintenance therapy).

BCG unresponsive: BCG refractory + BCG relapsing within 6 months of last BCG

- Persistent high-grade disease at 6 mo cysto after iBCG + mBCG
- Progression of disease from Ta/Tis -> T1 at 3 mo cysto after iBCG alone
- Recurrence of HG disease while on BCG maintenance therapy



Management of BCG failure

Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study

Prof Arjun V Balar, MD • Prof Ashish M Kamat, MD • Girish S Kulkarni, MD • Prof Edward M Uchio, MD • Joost L Boormans, MD • Mathieu Roumiguié, MD • et al. Show all authors

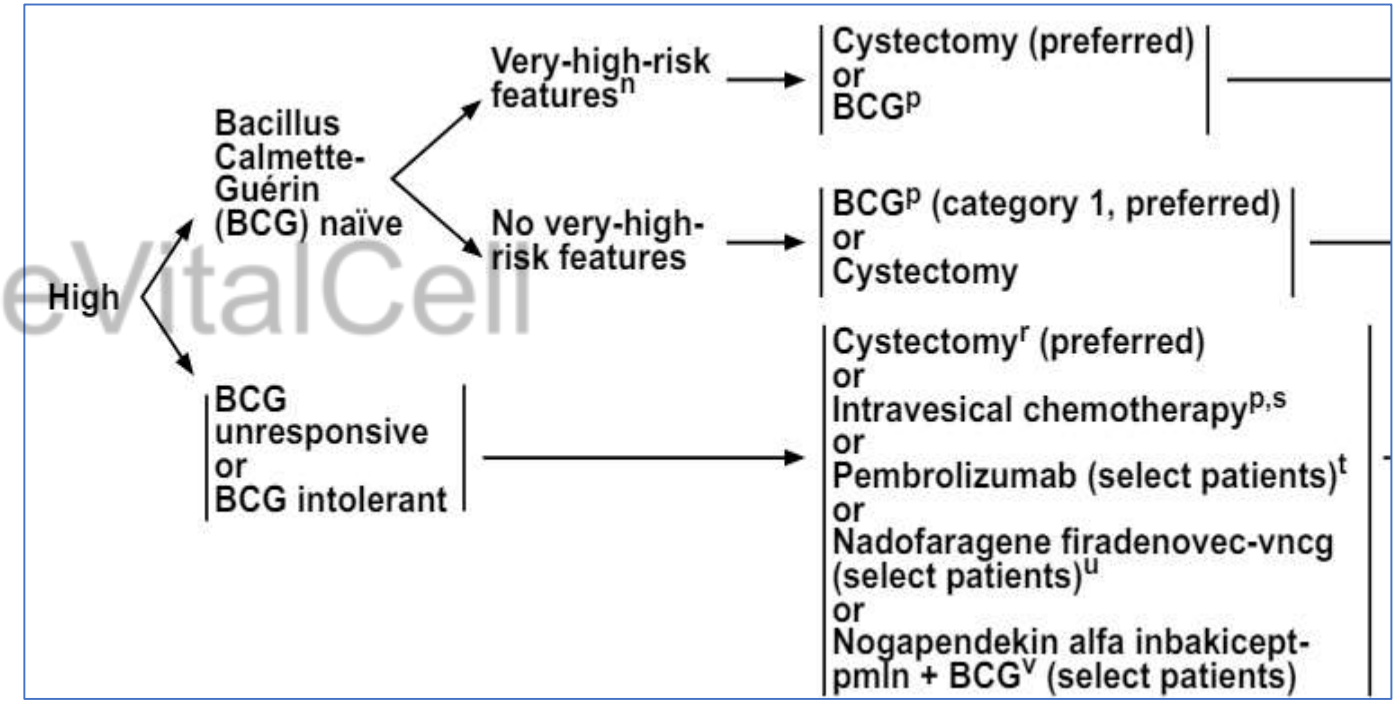
Published: May 26, 2021 • DOI: https://doi.org/10.1016/S1470-2045(21)00147-9 •

- IV Pembrolizumab 200mg Q3W
- Achieved 40% complete response rate and maintained in 48% of patients upto 12 months.
- FDA approved.

- Intravesical gene therapy
- Mechanism of action : Recombinant adenoviral-mediated interferon (IFN alpha) delivery

Cystectomy in NMIBC

- Reserved for residual high-grade cT1, subtype histology, lymphovascular invasion, concomitant CIS, and BCG-unresponsive disease.
- Cystectomy should be done within 3 months of diagnosis if no therapy is given.



Follow up of NMIBC

In Low risk NMIBC

Table 2: Low-Risk,[a] Non-Muscle Invasive Bladder Cancer

Test	Year						
	1	2	3	4	5	5–10	>10
Cystoscopy	3, 12	Annually				As clinically indicated	
Upper tract[b] and abdominal/ pelvic[c] imaging[d]	Baseline imaging	As clinically indicated					
Blood tests	N/A						
Urine tests	N/A						

Intermediate and high risk NMIBC

Table 3: Intermediate Risk,[a] Non-Muscle Invasive Bladder Cancer

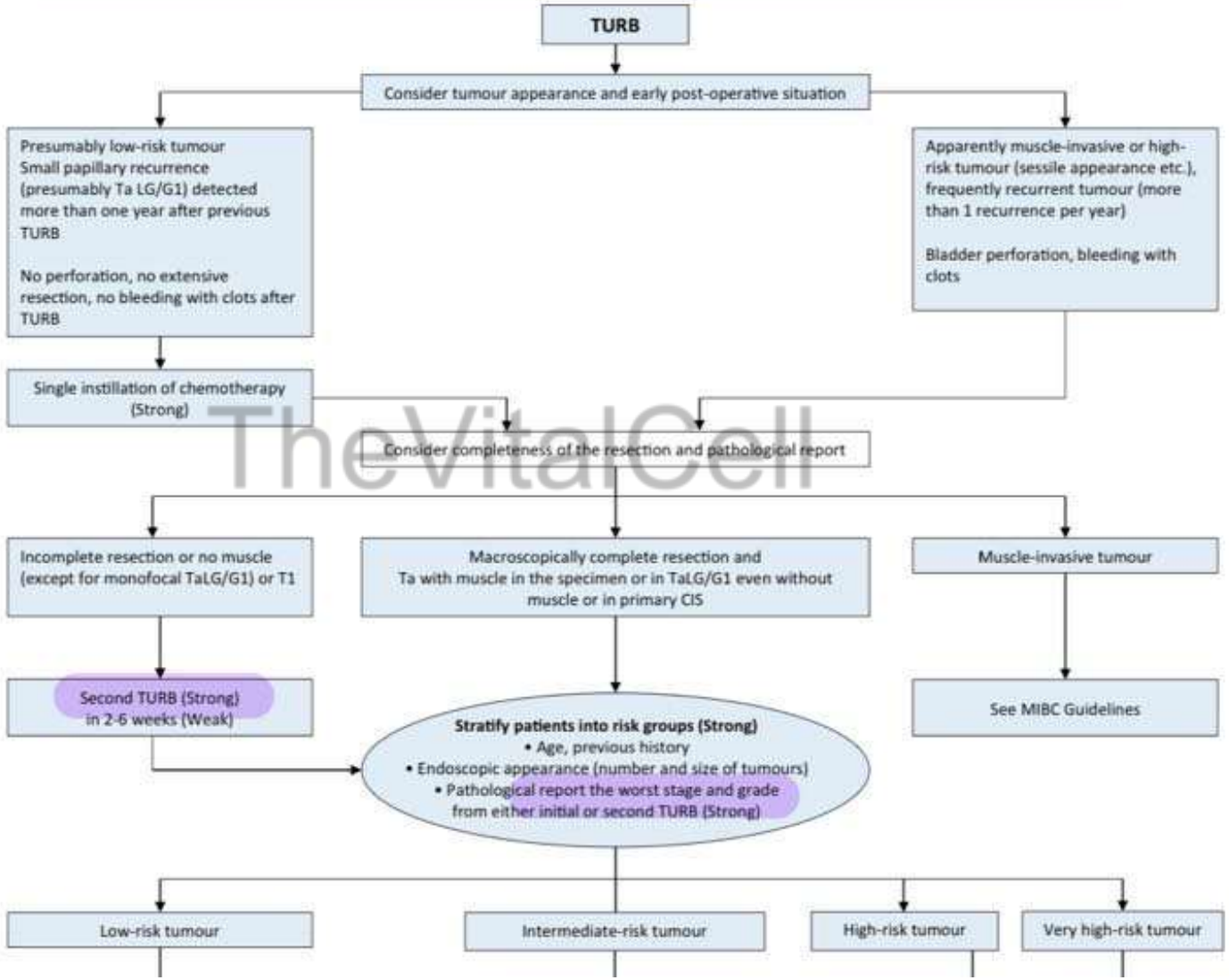
Test	Year						
	1	2	3	4	5	5–10	>10
Cystoscopy	3, 6, 12	Every 6 mo	Annually			As clinically indicated	
Upper tract[b] and abdomen/ pelvis[c] imaging[d]	Baseline imaging	As clinically indicated					
Blood tests	N/A						
Urine tests	Urine cytology 3, 6, 12	Urine cytology every 6 mo	Annually			As clinically indicated	

Table 4: High-Risk,[a] Non-Muscle Invasive Bladder Cancer

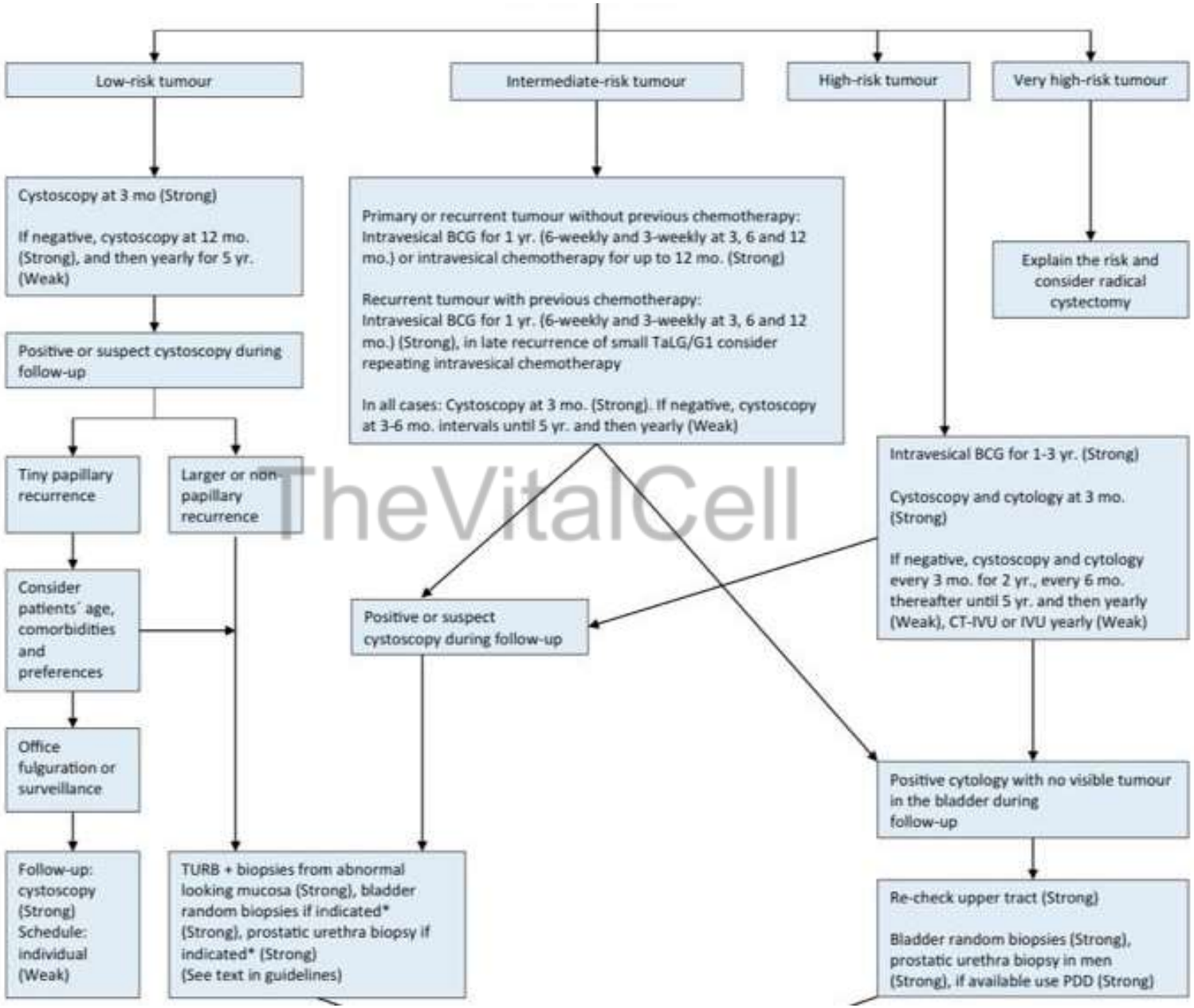
Test	Year						
	1	2	3	4	5	5–10	>10
Cystoscopy	Every 3 mo		Every 6 mo			Annually	As clinically indicated
Upper tract[b] imaging[d]	Baseline imaging, and at 12 mo	Every 1–2 y					As clinically indicated
Abdomen/ pelvis[c] imaging[d]	Baseline imaging	As clinically indicated					
Blood tests	N/A						
Urine tests	• Urine cytology every 3 mo • Consider urinary urothelial tumor markers (category 2B)		Urine cytology every 6 mo			Annually	As clinically indicated

Summary

Figure 7.1: Treatment strategy in primary or recurrent tumour(s) without previous BCG*

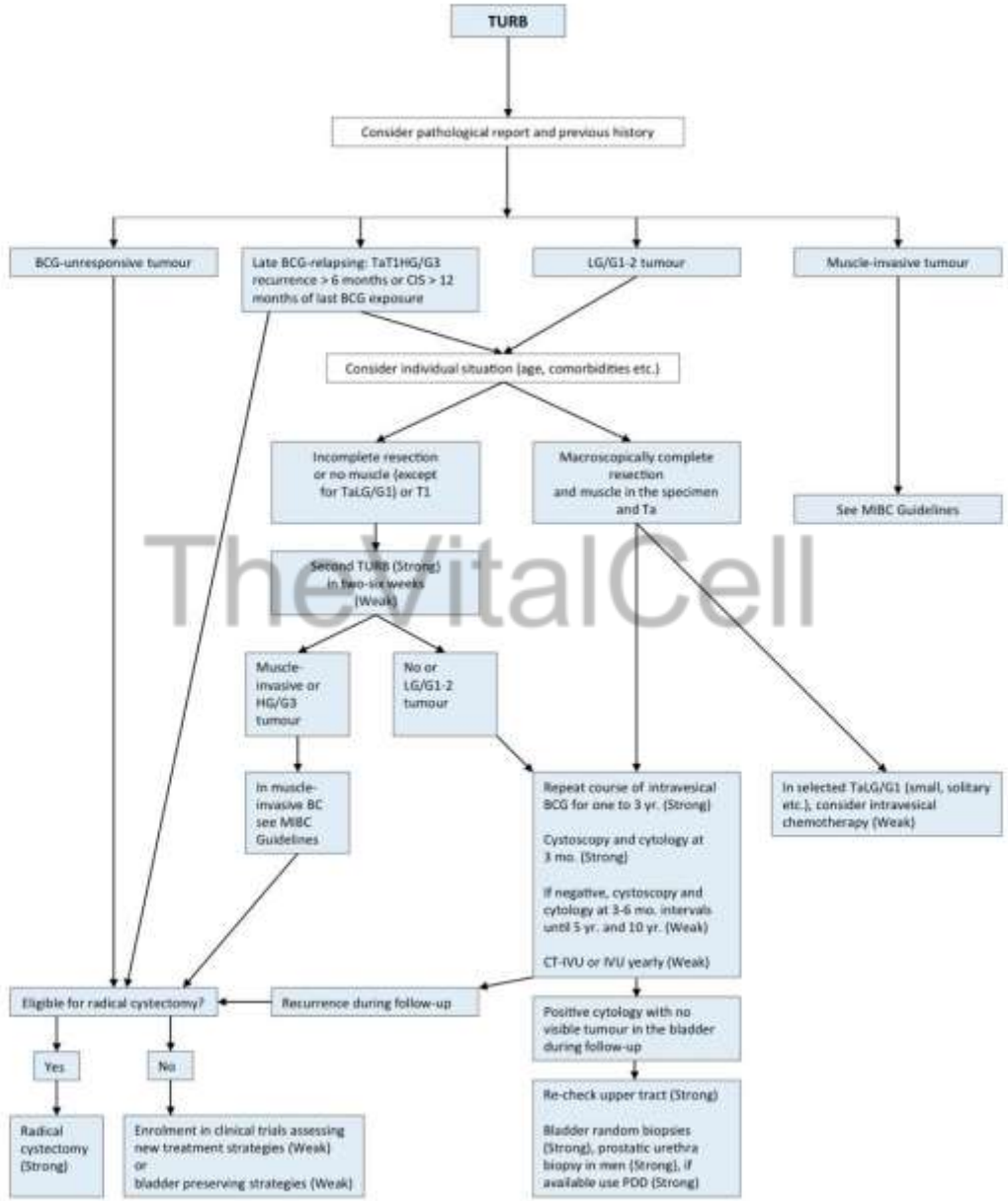


Summary



Summary

Figure 7.2: Treatment strategy in recurrence during or after intravesical BCG



BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; HG = high-grade; IVU = intravenous urography; LG = low-grade; PDD = photodynamic diagnosis; TURB = transurethral resection of the bladder.