Non Muscle Invasive Bladder Cancer Management

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Non-Muscle-Invasive Bladder Cancer

- Malignant urothelial tumors that have not invaded the detrusor muscle
- Formerly known as Superficial Bladder tumors
- Stage Ta, Tis (carcinoma in situ) and T1

Ta	Noninvasive papillary carcinoma
Tis	Carcinoma in situ: “flat tumor”
T1	Tumor invades the lamina propria, but not beyond

Non-Muscle-Invasive Bladder Cancer

- NMIBC- 70% to 80% of all Bladder cancers
  - Ta- 70%
  - T1- 20%
  - CIS- 10%
- 15% to 20% progress to stage T2 disease or greater
- 50% to 70% develop recurrence following initial therapy
- <5 % develop metastasis without progression to invasive disease

Risk Stratification- American Urological Association

LOW RISK	INTERMEDIATE RISK	HIGH RISK
Solitary	Solitary low-grade tumor >3 cm	High-grade T1
Size <3 cm	Multifocal low-grade tumors	Any recurrent high-grade Ta
Low grade Ta	Low-grade tumor recurring within 1 yr	High-grade Ta >3 cm or Multifocal
	Solitary high-grade Ta tumors(High risk – EUA system)	Any CIS
	Low grade T1 tumor (High risk –EUA system)	Any BCG failure in a high-grade pt
		Lymphovascular invasion
		Any high-grade prostatic urethral involvement

Recurrence & Progression

Risk Category	Recurrence rate	Risk of Progression at 1 year
Low	15%	0.2%
Intermediate	38%	5%
High	61%	17%

Risk factors for Progression

- Grade- most important
- Stage
- Number, size of tumor
- Presence of carcinoma *in situ* (cis)- also for invasion, metastasis
- Recurrence rate
- Age at diagnosis

Management Options

- Endoscopic Surgical Management
- Perioperative Intravesical Therapy
- Adjuvant Intravesical therapy
- Refractory/Recurrent disease

Risk Stratification Based Initial management

- **Low risk-** no adjuvant systemic treatment, single dose of intravesical chemotherapy after TUR

- **Intermediate risk-** intravesical therapy following TURBT of all visible tumor (Options - BCG or intravesical chemotherapy)

- **High risk –** (T1 tumors , high-grade Ta tumors with an incomplete / suspected incomplete initial TURBT)

  - restaging TURBT 4-6 weeks after the initial cystoscopy/TURBT ,determine whether radical cystectomy may be indicated.

  - If not undergoing cystectomy, a course of intravesical therapy (agent of choice - BCG.)

Endoscopic Surgical Management

- TURBT
- Fluorescence Cystoscopy and Narrow Band Imaging
- Laser Therapy
- Office-Based Endoscopic Management

Transurethral Resection of Bladder Tumor (TURBT)

- Initial treatment for visible lesions
  - Remove all visible tumor
  - Pathologic examination to determine stage and grade

Complete TURBT

- The quality of the TURBT is of primary importance.
- resection of all visible bladder tumor with adequate depth to include muscularis propria.
- Biopsy of focal areas of suspected carcinoma in situ (CIS), and abnormal areas in the prostatic urethra and bladder neck
- EUA- should also be performed , presence of induration or a palpable mass suggests muscle invasive disease

Complications of TURBT

- **Common & immediate**- minor bleeding and irritative symptoms
- **Major**- uncontrolled hematuria and clinical bladder perforation (<5%)
- Perforation :
  - Majority: extraperitoneal
  - Resection at dome : intraperitoneal
- Incidence of perforation can be reduced by:
  - Avoiding overdistention of bladder
  - Anesthetic paralysis during resection of significant lateral wall lesions

Repeat TURBT- Indications

1. Complete tumor removal is not possible:
   - Excessive tumor volume (>3cm/ multifocal)
   - Medical instability requiring premature cessation
   - Risk of perforation
2. No muscle in original specimen for high grade disease
3. High grade T1 tumors (30% under-staged, even after complete initial TURBT)

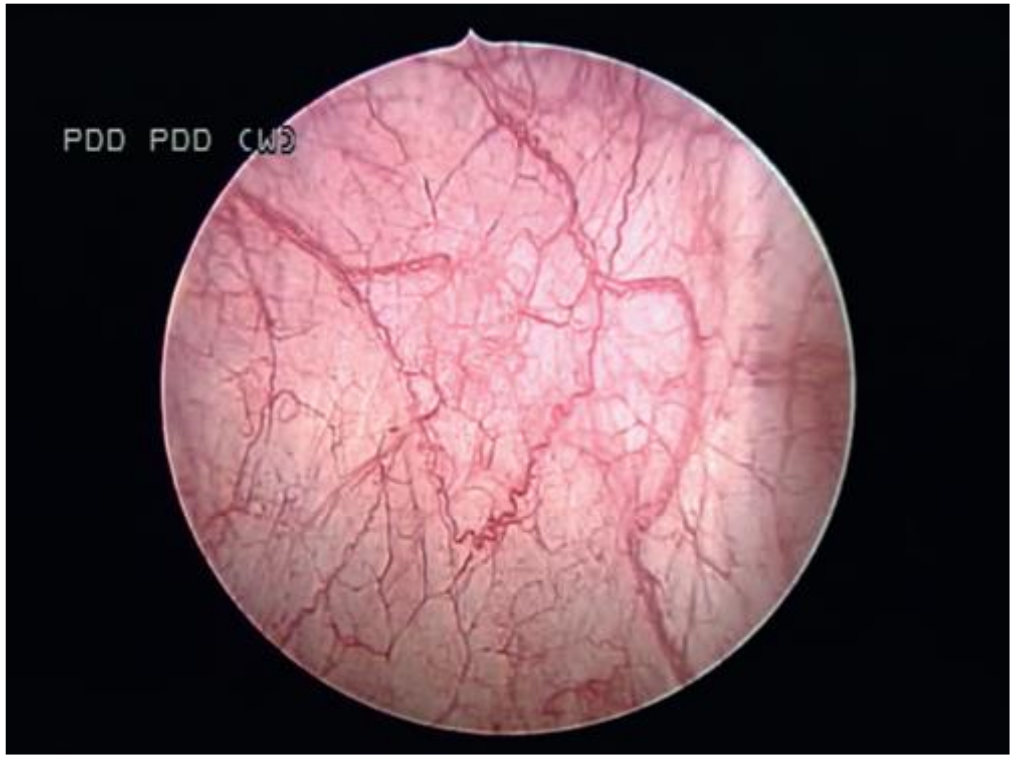
Repeat TURBT

- Timing- within 6 weeks after the initial resection(No consensus)
- Re-TURBT
  - Reduces risk of recurrence
  - Improves progression free survival
  - Increases efficacy of BCG in preventing progression

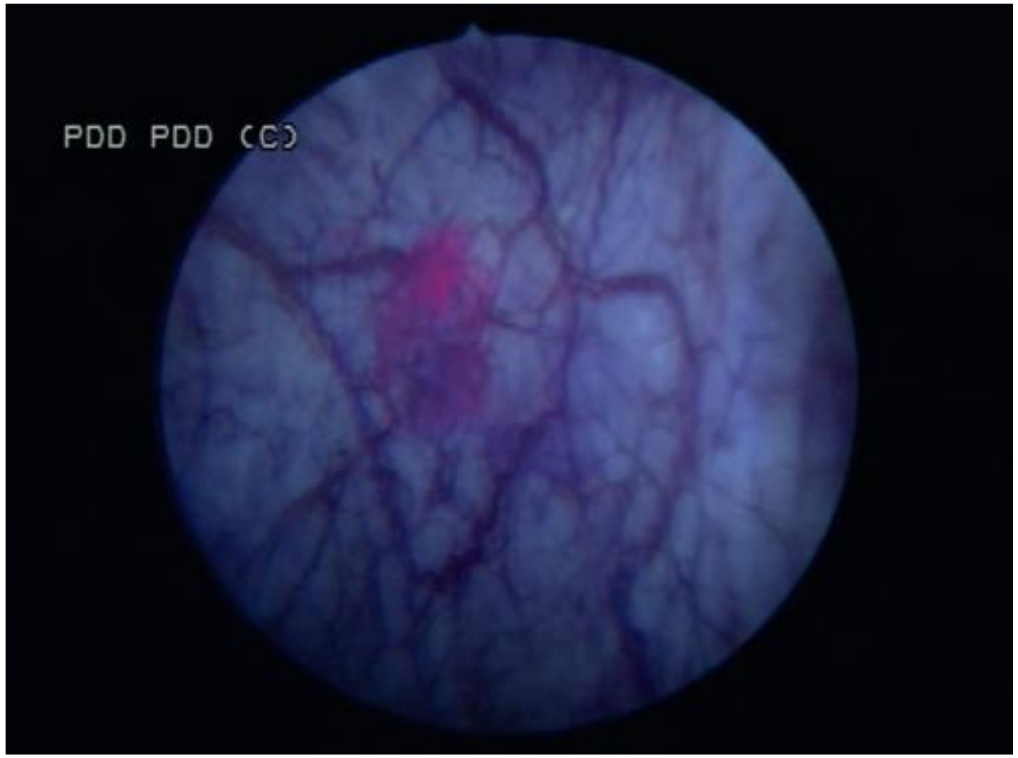
The effect of restaging transurethral resection on recurrence and progression rates in patients with nonmuscle invasive bladder cancer Sfakianos JP, Kim PH, Hakimi AA, Herr HW J Urol. 2014 Feb;191(2):341-5

Fluorescence Cystoscopy and Narrow Band Imaging

- Small papillary tumors & 1/3rd CIS overlooked on cystoscopy are identified
- Intravesical instillation - heaxaminolevulinate (HAL) or 5-aminolevulinic acid (ALA) → accumulate in neoplastic tissue → emit red fluorescence under blue light.
- **Narrow band imaging (NBI) -** improve visibility of blood vessels
- NBI light is composed of two specific wavelengths that are absorbed by hemoglobin;
  - 415-nm light - superficial mucosal layer
  - 540-nm light –deep layers



White light microscopy reveals normal-appearing mucosa



Blue light microscopy reveals accumulation of hexaminolevulinate in the same area proven subsequently to contain a small focus of carcinoma in situ

Fluorescence Cystoscopy and Narrow Band Imaging

- Appears more effective than white light endoscopy for the detection of multifocal tumors and CIS, may improve outcomes of TURBT
- A meta-analysis (n-2906 ,14 randomized trials)- fluorescent cystoscopy improved tumor detection and decreased risk of subsequent recurrences
- Disadvantages-
  - slightly higher false positive rate (mainly due to inflammation and scarring),
  - requirement for a special lens system,
  - the need to instill the photosensitizer one hour prior to cystoscopy,
  - potentially higher costs.

Perioperative Intravesical Therapy

- Tumor cell implantation immediately after resection- early recurrences
- Initial tumors- most commonly found on the floor and lower sidewalls of the bladder
- Recurrences- near the dome as a result of flotation
- Intravesical chemotherapy kill such cells before implantation
- Single Instillation for low- Intermediate risk

Perioperative Intravesical Therapy

- Drugs: Mitomycin C (MMC) and Gemcitabine
- Other agents used- Epirubicin, Pirarubicin
- Single dose within 24 hours (preferable 6 hrs)
  - ➢ Decreases 5 yr recurrence rate by 35%
- MC complication- local irritative symptoms
- Contraindications: Perforation, drug allergy
- BCG not administered immediately after TUR - risk of bacterial sepsis and death is high

Immediate Intravesical Chemotherapy

Study	No of pts	Intervention	End point	Result
Systematic review EUA, 2015 Sylvester et al.	2278 (Ta, T1)	• TURB alone • TURB f/b single instillation	• Risk of recurrence • 5 yr recurrence rate • Time to progrsn	• 35% reduction • 14% difference • No difference
PRT, Netherlands 2017 Bosscheiter et al	2243 (all)	• Immediate MMC • Delayed MMC	• 3 yr recurrence risk • Time to recurrence • Adverse event	• Signf less in immed arm (27% vs 36%) • Signf less in immed arm • No diff.
SWOG S0337, New York May 2018 Messing et al.	406 (Low grade)	• Gemcitabine • Placebo	• 4 year recurrence rate	• Signf decreased in Gem arm (35% vs 47%)

Adjuvant Intravesical Therapy

- Patients at significant risk for developing progressive or recurrent disease following TURBT:
  - Multifocal CIS/tumor
  - CIS associated with Ta or T1 tumors
  - Grade 3
  - Tumors rapidly recurring following initial TURBT

Immunotherapy

1) Bacille Calmette-Guérin (BCG)

- Attenuated mycobacterium developed as a vaccine for tuberculosis
- Antitumor activity in many malignancies including bladder
- **Morales**- described original regimen of percutaneous dose
- **Brosman**- Intravesical regimen
- Strains: Connaught, Tokyo, TICE, Danish 1331

BCG- Mechanism of Action

Directly binds to fibronectin within the bladder wall

↓

Stimulation of cell-based immunologic response and an antiangiogenic state

↓

Cytokine induction by upregulation of IFN-γ, IL-2, and IL-12 (T Helper 1)

↓

Activation of cell-mediated cytotoxic mechanisms

Pre Installation

- 2 - 6 weeks after tumor resection, allows re-epithelialization, minimizing intravasation of live bacteria
- Urinalysis- confirm absence of infection or significant bleeding
- Traumatic catheterization- delay for around 1 week
- Fluid, diuretic, and caffeine restriction
  - Limits dilution of the agent by urine
  - Adequate retention of the agent for 2 hours.

Preparation of agent

- 1 vial of BCG is suspended in 50 mL preservative free saline (0.9% Sodium Chloride Injection)
- Used within 2 hours of reconstitution.
- Aseptic technique.
- Precautions - gloves or double gloves, mask, face shield, and non-permeable gown
- Reconstituted via syringe/reconstitution supplies provided with BCG.
- Avoid exposing BCG to direct sunlight.

Administration

- Urethral catherization to drain bladder, abort if traumatic
- Recon. BCG instilled per gravity flow or by gentle injection.
- Patient remains in suspension for 2 hours
- Patient turn from side to side to bathe the entire urothelium (no evidence)
- Void in seated position to avoid splashing
- Disinfect with bleach

BCG Schedule

- **Induction BCG** - weekly for six weeks for patients with intermediate- and high-risk disease, generally starting two to six weeks after .
- **Maintenance therapy** – Maintenance BCG is given weekly for three weeks at months 3, 6, 12, 18, 24, 30, and 36 for patients with high-risk disease.
  - For patients with intermediate-risk disease, maintenance therapy is continued for only one year.
- Dose reduction during maintenance therapy and/or the use of a fluoroquinolone given 8 and 20 hours after BCG dosing may improve the rates of treatment completion.

Duration and Dose of BCG maintenance therapy

Study	No. of pts	Intervention	Objective	Result
EORTC-GU Group EU 2012	1355	• 1/3rd vs Full dose • 1 yr Vs 3 Yr	• Non inferiority trial with null hypothesis of 10% decrease in disease free rate	• No diff in toxicity • Intermediate risk- FD for 1 yr • High risk- FD for 3 yr

Contraindications to BCG Therapy

Absolute

- Immunosuppressed and immunocompromised patients
- Immediately after transurethral resection (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

- 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

Spanish Urological Club for Oncological Treatment (CUETO)

Predicting Nonmuscle Invasive Bladder Cancer Recurrence and Progression in Patients Treated With Bacillus Calmette-Guerin: The CUETO Scoring Model

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Purpose: Bacillus Calmette-Guerin is the most effective therapy for nonmuscle invasive bladder cancer. Recently to calculate the risks of recurrence and progression based on data from 7 European Organisation for Research and Treatment of Cancer trials a scoring system was reported. However, in that series only 171 patients were treated with bacillus Calmette-Guerin. We developed a risk stratification model to provide accurate estimates of recurrence and progression probability after bacillus Calmette-Guerin.

Materials and Methods: Data were analyzed on 1,062 patients treated with bacillus Calmette-Guerin and included in 4 Spanish Urological Club for Oncological Treatment trials. Stepwise multivariate Cox models were used to determine the effect of prognostic factors. In each patient the weight of all factors was summed to a total score. Patients were then divided into groups, and cumulative recurrence and progression rates were calculated.

Results: A scoring system was calculated with a score of 0 to 16 for recurrence and 0 to 14 for progression. Patients were categorized into 4 groups by score, and recurrence and progression probabilities were calculated in each group. For recurrence the variables were gender, age, grade, tumor status, multiplicity and associated Tis. For progression the variables were age, grade, tumor status, T category, multiplicity and associated Tis. For recurrence calculated risks using Spanish Urological Club for Oncological Treatment tables were lower than those obtained with Sylvester tables. For progression probabilities were lower in our model only in patients with high risk tumors.

Conclusions: We propose a scoring model to stratify the risk of recurrence and progression in patients treated with bacillus Calmette-Guerin.

Key Words: urinary bladder, urinary bladder neoplasms, Mycobacterium bovis, risk, prognosis

Abbreviations and Acronyms

AIC = Akaike's information criterion

BCG = bacillus Calmette-Guerin

CUETO = Spanish Urological Club for Oncological Treatment

EORTC = European Organisation for Research and Treatment of Cancer

Submitted for publication February 20, 2009.
Study received Institutional review board approval.

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For another article on a related topic see page 2472.

BACILLUS Calmette-Guerin is currently the most effective intravesical therapy for nonmuscle invasive bladder cancer with a high and intermediate risk of recurrence and progression. Intravesical chemotherapy can decrease the

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TURBT Vs TURBT + BCG

Study	No. of pts	Intervention	End points	Results
PRT, MSKCC 1995 Herr et al	86	• TURB • TURB + BCG	• 10yr PFR • 10yr DSSR	• 61.9% vs 37% • 75% vs 55%
Systematic review 2001 Shelley et al	585	• TURB • TURB + BCG	• Recurrence at 1 yr	• 56% reduction (signf)
Meta-analysis 2006 (China) Han et al	4767	• TURB • TURB + BCG	• Recurrence	• Signf diff (40% vs 49.7%)

BCG Treatment of Carcinoma in Situ

- Approved by FDA for carcinoma in situ treatment
- Approximately 50% of patients experience a durable response for a median period of 4 years.
- Over a 10-year period, approximately 30% of patients remain free of tumor progression or recurrence,

BCG Toxicity & Management

GRADE 1: MODERATE SYMPTOMS <48 HOURS

- Mild or moderate irritative voiding symptoms, mild hematuria, fever <38.5°C.

Assessment

- Possible urine culture to rule out bacterial urinary tract infection.

Symptom Management

- Anticholinergics, topical antispasmodics, analgesics, NSAIDs

GRADE 2: SEVERE SYMPTOMS AND/OR >48 HOURS

- Severe irritative voiding symptoms, hematuria, or symptoms lasting >48 hr

Assessment

- Urine culture, chest radiograph, liver function tests.

Management

- Management of mycobacterial infections and complications.
- Dose reduction to one half to one third of dose when instillations resume.

Antimicrobial Agents

- Isoniazid and rifampin, 300 mg/day and 600 mg/day, orally until symptom resolution.
- Observe for rifampin drug-drug interactions (e.g., warfarin)

GRADE 3: SERIOUS COMPLICATIONS

HEMODYNAMIC CHANGES, PERSISTENT HIGH-GRADE FEVER)

Allergic Reactions (Joint Pain, Rash)

- Grade 1 and 2 maneuvers plus the following:
- Isoniazid, 300 mg/day, and rifampin, 600 mg/day, for 3-6 mo depending on response.

Solid Organ Involvement (Epididymis, Liver, Lung, Kidney, Bone, Prostate)

- Isoniazid, 300 mg/day; rifampin, 600 mg/day; ethambutol, 15 mg/ kg/day single daily dose for 3-6 mo.

Immunotherapy- Interferon

- Glycoproteins with multiple antitumor activities:
  - Inhibition of nucleotide synthesis
  - Upregulation of tumor antigens
  - Antiangiogenic properties
  - Stimulation of cytokine release with enhanced T- and B-cell activation, enhanced NK cell activity.
- More expensive and less effective than BCG or intravesical chemotherapy in eradicating residual disease, preventing recurrence of papillary disease, and treating CIS

Intravesical Chemotherapy

- Used for immediate and high risk patients
- BCG contraindication
- Refractory/recurrent setting previously treated with BCG
- Drugs: Mitomycin C, Doxorubicin, Epirubicin, Gemcitabine, Thiotepa, Taxanes

Mitomycin C

- Alkylating agent- inhibits DNA synthesis.
- single intravesical administration following resection of low-risk non-muscle invasive bladder cancer.
- Adjuvant- given as multiple treatments following TURBT.
- Instilled weekly for 6-8 weeks, dose range: 20-60 mg.
- Electromotive intravesical MMC improve drug delivery into bladder tissue with reported reduction in recurrence rates with MMC from 58% to 31%,
- Relapse-free survival also improved with chemotherapy plus hyperthermia compared with BCG
- Common side effects are skin desquamation and rash.

Doxorubicin and its Derivatives

- Anthracycline antibiotic- bind to DNA base pairs → inhibit topoisomerase II & protein synthesis.
- The principal side effect of intravesical doxorubicin is chemical cystitis, which can occur in up to half of patients.
- Others- Epirubicin, Valrubicin

Thiotepa

- Only chemotherapeutic agent approved by the FDA specifically for the intravesical treatment of papillary bladder cancer.
- Non cell cycle specific alkylating agent
- Significantly decrease tumor recurrence by upto 41%
- Hematopoietic toxicity common

Long-term fate of 90 patients with superficial bladder cancer randomly assigned to receive or not to receive thiotepa.
Prout GR Jr, Koontz WW Jr, Coombs LJ, Hawkins IR, Friedell GH Urol. 1983;130(4):677.

Novel Agents

- **Gemcitabine :** reduction of recurrence of 39% - 70% in heavily pretreated BCG-refractory patients
- **Taxanes** have been formulated into an active intravesical treatment, but current published data are limited to preclinical studies

BCG Versus Chemotherapy

Study	No. of pts	Intervention	End point	Result
Meta analysis Shelley et al (2003)	1901	• BCG • Mitomycin C	• Tumor recurrence • Disease free survival	• Signf less in BCG (31% diff) • No signf diff
Meta analysis Bohle et al (2004)	2410	• BCG • MMC	• Tumor Progression	• Signf diff seen in BCG over MMC when maintenance BCG given
EORTC 30906 (2005) Reijke et al	168 (CIS)	• BCG • Epirubicin	• CR • Time to recurrence • CIS recurrence rate	• No difference (56% vs 65%) • Low for BCG (1.4 vs 5.4yr) • High in Epirubicin (45% vs 16%)
EORTC 30911 (2009) Sylvester et al	957	• Epirubicin • BCG • BCG + Isoniazid	• Time to recurrence • Progression • Distant metastases • Overall survival • Disease-specific survival	• Significant difference favouring BCG group for all end points except distant metastasis

AGENT	PERIOPERATIVE USE	RISK GROUP	CYSTITIS (%)	OTHER TOXICITY	DROPOUT (%)	CONCENTRATION AND DOSE
Doxorubicin (Adriamycin)	Yes	Low to intermediate	20-40	Fever, allergy, contracted bladder, 5%	2-16	50 mg/50 mL
Epirubicin	Yes	Low to intermediate	10-30	Contracted bladder rare	3-6	50 mg/50 mL
Thiotepa	Yes	Low to intermediate	10-30	Myelosuppression 8%-19%	2-11	30 mg/30 mL
Mitomycin	Yes	Low to intermediate	30-40	Rash 8%-19%, contracted bladder 5%	2-14	40 mg/20-40 mL
BCG	No	Intermediate to high	60-80	Serious infection, 5%	5-10	1 vial/50 mL
Interferon	No	Salvage	<5	Flulike symptoms 20%	Rare	50-100 MU/50 mL
Gemcitabine	Yes	Salvage	Mild	Occasional nausea	<10	1-2 g/50-100 mL

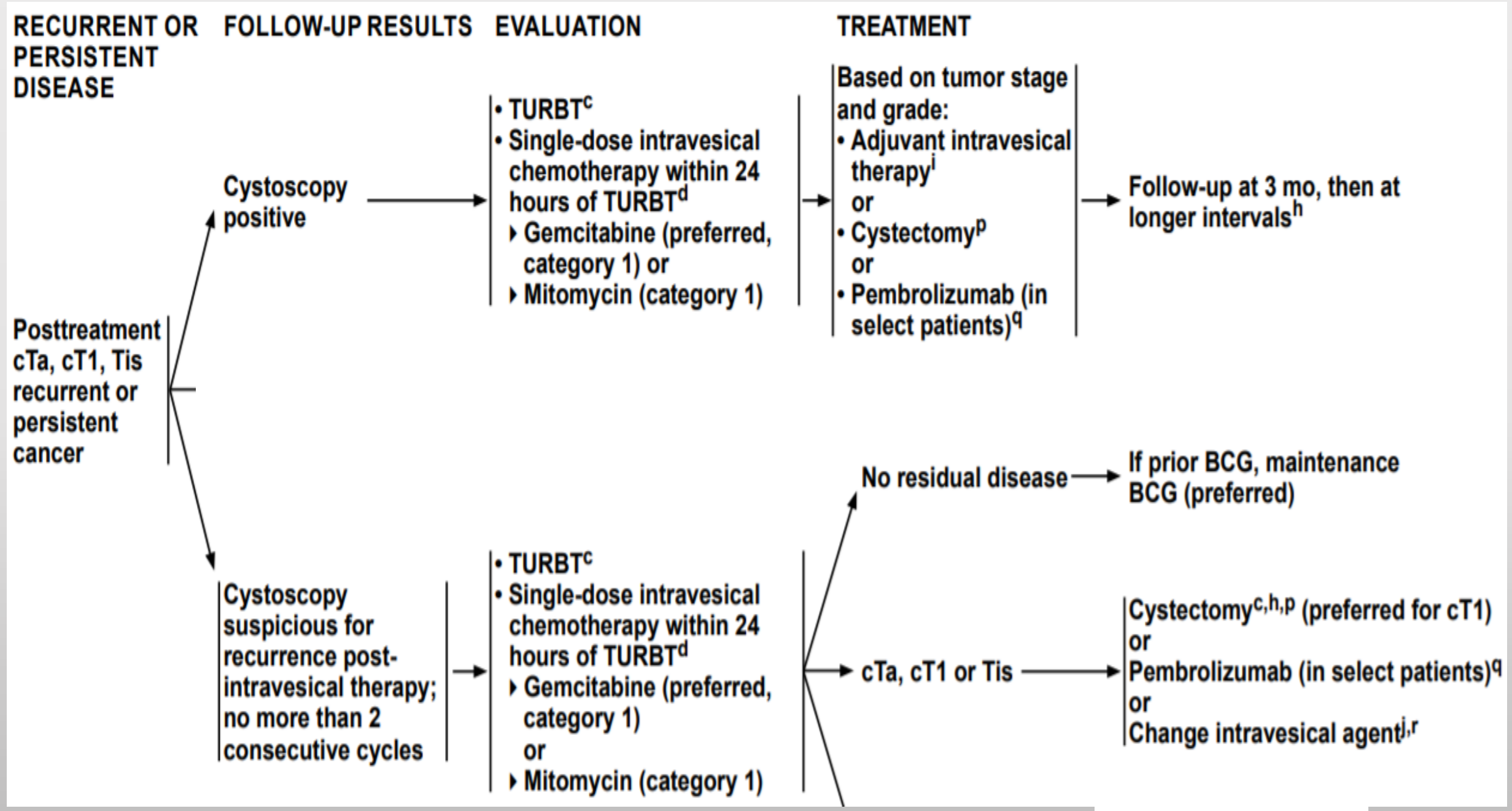
Refractory/Recurrent Disease

Refractory/Recurrent Disease

- Persistent disease after BCG therapy can be categorized:

1. **BCG refractory** (nonimproving or worsening disease despite BCG),
2. **BCG resistant** (recurrence or persistence of lesser degree, stage, or grade after an initial course, which then resolves with further BCG)
3. **BCG relapsing** (recurrence after initial resolution with BCG)

- BCG-refractory patients - high-risk group and should be strongly considered for immediate cystectomy.
- Declaring failure may take up to 6 months because the response rate for patients with high-grade bladder cancer treated with BCG increases from 57% to 80%, 3 to 6 months after therapy


RECURRENT OR PERSISTENT DISEASE
FOLLOW-UP RESULTS
EVALUATION
TREATMENT
Posttreatment cTa, cT1, Tis recurrent or persistent cancer
Cystoscopy positive
• TURBT[c]
• Single-dose intravesical chemotherapy within 24 hours of TURBT[d]
▸ Gemcitabine (preferred, category 1) or
▸ Mitomycin (category 1)
Based on tumor stage and grade:
• Adjuvant intravesical therapy[i]
or
• Cystectomy[p]
or
• Pembrolizumab (in select patients)[q]
Follow-up at 3 mo, then at longer intervals[h]
Cystoscopy suspicious for recurrence post-intravesical therapy; no more than 2 consecutive cycles
• TURBT[c]
• Single-dose intravesical chemotherapy within 24 hours of TURBT[d]
▸ Gemcitabine (preferred, category 1)
or
▸ Mitomycin (category 1)
No residual disease
If prior BCG, maintenance BCG (preferred)
cTa, cT1 or Tis
Cystectomy[c,h,p] (preferred for cT1)
or
Pembrolizumab (in select patients)[q]
or
Change intravesical agent[i,r]

Refractory/Recurrent Disease

- Initial treatment chemotherapy → BCG course
- Patients failed BCG →second course of BCG gives a 30% to 50% response.
- Patients who cannot tolerate BCG may be considered for salvage chemotherapy, but the risk of failure and progression is high.
- Pembrolizumab- Phase II KEYNOTE 057 study
  - 75% CR > 6 months FU
  - 53% CR >9 months FU

Alternative options for Refractory Disease

Photodynamic therapy (PDT)

- Administration of photosensitizing agent such as porfimer sodium (Photofrin) systemically intravesically.
- 2-3 days after the substance has cleared from the normal tissue (for Photofrin), patient is given an intravesical treatment with red laser light (630 nm) for 12 to 20 minutes.
- Intravesical intralipid allows for more uniform distribution of laser light
- After excitation by light, the photosensitizer reacts with molecular oxygen to form free radicals and reactive singlet oxygen, which are cytotoxic.

Refractory/Recurrent -PDT

- Response rate in CIS patients from combined series is 66%, with a duration of 37 to 84 months.
- PDT has been limited by significant side effects such as bladder contracture or irritability (50%) and dermal sensitivity (19%)

Jocham D, Beer M, Baumgartner R, et al. Long-term experience with integral photodynamic therapy of TIS bladder carcinoma. Ciba Found Symp 1989;146:198–205

Laser Therapy

- Minimally invasive ablation of tumors - 2.5 cm
- Optimal candidate- patient with recurrent, low-grade lesions whose biology is already known.
- Neodymium : yttrium-aluminum-garnet (Nd : YAG) laser
- **Most significant complication-** forward scatter of laser energy to adjacent structures → perforation of a hollow, viscous organ (overlying bowel)
  - Most commonly occurs with Nd : YAG laser (deeper tissue penetration) than with holmium (Ho):YAG and potassium titanyl phosphate (KTP) lasers

Laser Therapy

- Under direct visualization and discontinue once tissue appears white (protein denaturation)
- Advantage : negligible bleeding
- Disadvantage : More expensive; no tissue available for pathologic inspection

Office-Based Endoscopic Management

- Small, low-grade recurrences (typically <0.5 mL, but up to 1 cm diameter) - diathermy or laser ablation.
- Instillation of 1% to 2% lidocaine - mucosal analgesia.

Role of Cystectomy

- Patient with extensive bladder involvement who cannot be rendered visually disease-free after TURBT, even after multiple attempts.
- Disease complicated by symptoms related to the bladder pathology (severe urinary frequency, hemorrhage) that cannot be adequately managed medically.
- Pure squamous cell or adenocarcinoma histology.
- Patients at high risk for progression to muscle invasive disease:
  - Recurrence of high-risk disease within six months after initial TURBT and intravesical BCG therapy
  - Large or multifocal T1 lesions
  - Persistent high-grade T1 disease on repeat TURBT
  - T1 tumor with lymphovascular invasion or variant histology, such as micropapillary, sarcomatoid or neuroendocrine/small cell, features

Role of Radiation therapy

- Restricted to individuals who refuse cystectomy after the failure of intravesical therapy or who are unsuitable for major surgery.
- There is no significant advantage of RT in terms of progression free survival and overall survival

A Randomized Trial of Radical Radiotherapy for the Management of pT1G3 NXM0 Transitional Cell Carcinoma of the Bladder. S. J. Harland

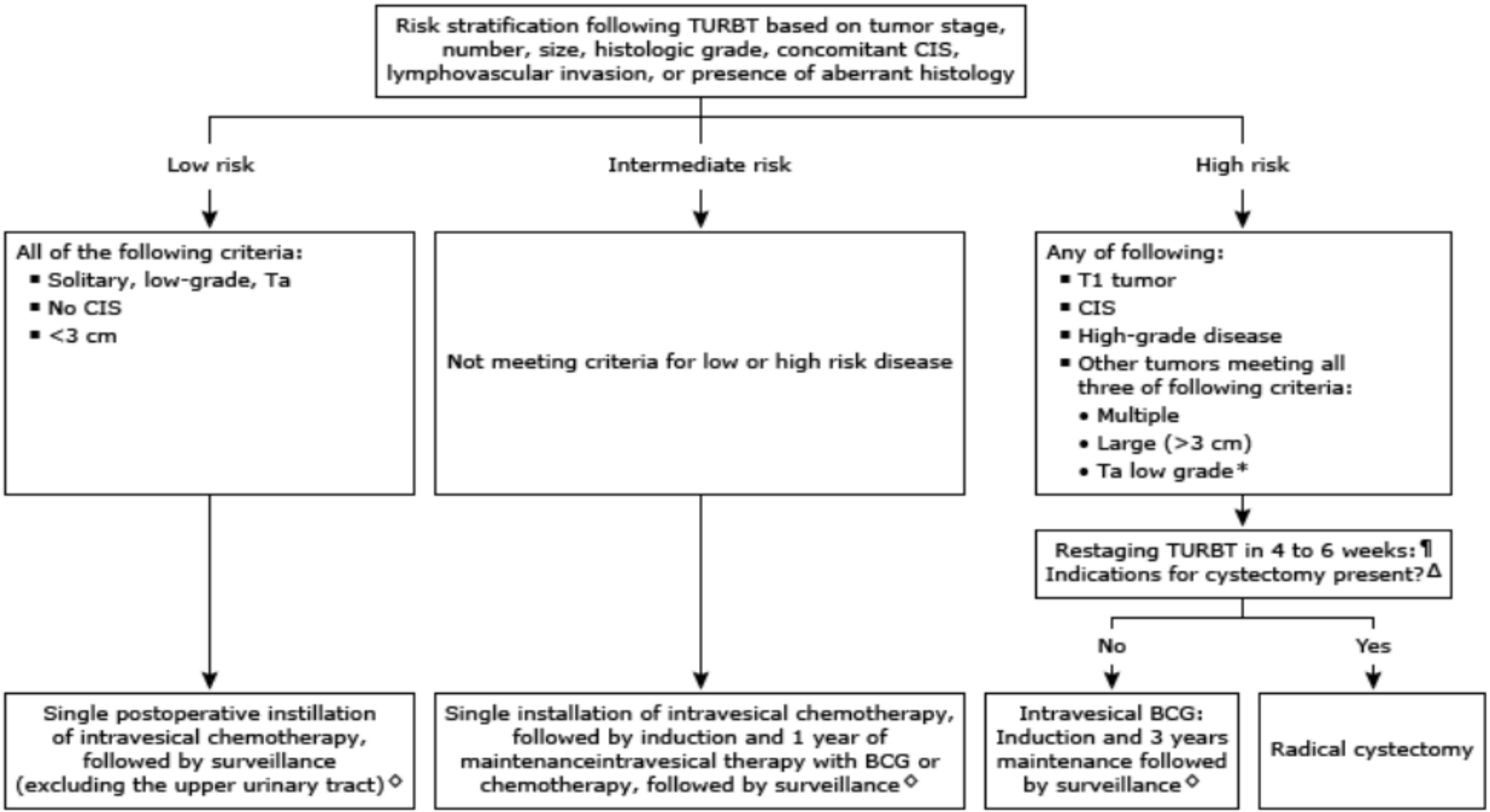
Surveillance

Post-treatment evaluation

- Repeat cystoscopy -approximately 6 weeks after completing the induction cycle with BCG (three months after the start of treatment).
- Urine cytology should be done routinely
- Persistent CIS following an induction course of BCG should not be considered treatment failure.
- Instead, one round of maintenance therapy (or repeat induction therapy) should be administered prior to determining treatment failure.

RISK	TUMOR STATUS	CYSTOSCOPY SCHEDULE	UPPER TRACT IMAGING
Low	Solitary Ta low grade	3 mo after initial resection Annually beginning 9 mo after initial surveillance if no recurrence Consider cessation at 5 or more yr Consider cytology or tumor markers	Not necessary unless hematuria present
Intermediate	Multiple Ta low grade Large tumor Recurrence at 3 mo	Every 3 mo for 1-2 yr Semiannually or annually after 2 yr Consider cytology or tumor markers Restart clock with each recurrence	Consider imaging, especially for recurrence Imaging for hematuria
High	Any high grade (including CIS)	Every 3 mo for 2 yr Semiannually for 2 yr Annually for lifetime Cytology at same schedule Consider tumor markers Restart clock with each recurrence	Imaging annually for 2 yr, then consider lengthening interval

SUMMARY


Risk stratification following TURBT based on tumor stage, number, size, histologic grade, concomitant CIS, lymphovascular invasion, or presence of aberrant histology
Low risk
Intermediate risk
High risk
All of the following criteria:
Solitary, low-grade, Ta
No CIS
<3 cm
Not meeting criteria for low or high risk disease
Any of following:
T1 tumor
CIS
High-grade disease
Other tumors meeting all three of following criteria:
Multiple
Large (>3 cm)
Ta low grade*
Restaging TURBT in 4 to 6 weeks: ¶ Indications for cystectomy present? Δ
No
Yes
Single postoperative instillation of intravesical chemotherapy, followed by surveillance (excluding the upper urinary tract) ◇
Single installation of intravesical chemotherapy, followed by induction and 1 year of maintenanceintravesical therapy with BCG or chemotherapy, followed by surveillance ◇
Intravesical BCG: Induction and 3 years maintenance followed by surveillance ◇
Radical cystectomy

THANK YOU