Management of Non-muscle-invasive Bladder Cancer

Bimal Bhindi, Ronald Kool, Girish S. Kulkarni, D. Robert Siemens, Armen G. Aprikian, Rodney H. Breau, Fadi Brimo, Adrian Fairey, Christopher French, Nawar Hanna, Jonathan I. Izawa, Louis Lacombe, Victor McPherson,Ricardo A. Rendon, Bobby Shayegan, Alan I. So, Alexandre R. Zlotta, Peter C. Black, Wassim Kassouf

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Overview

44 guideline statements on:

- Risk factors
- Symptoms and diagnosis
- Prognostic factors & risk stratification
- TURBT
- Intravesical therapy (chemotherapy, BCG)
  - Treatment adjustments if BCG shortage
  - BCG-unresponsive disease
- Timely cystectomy
- Followup recommendations

2021 guideline

LOW-RISK

Single
Ta low-grade
<3 cm
First occurrence
(50%)

HIGH-RISK

Multiple, recurrent, or >3 cm TaHG
Any T1
CIS

(15%)

Modified CUA risk stratification system

Intermediate	*Patients without CIS who are not included in the other risk categories:* 1. Recurrent, multifocal, and/or large (>3 cm) LG Ta – Consider sub-stratification: a) Low-intermediate-risk: 0 factors* – consider treating as low-risk patients b) Intermediate-risk: 1–2 factors c) High-intermediate-risk: ≥3 factors – consider treating as high-risk patients *Multiple tumors, >3 cm, time to recurrence (<1 year), and frequency of recurrence (>1/year) 2. Primary, solitary, and small (<3 cm) HG Ta – Consider treating as high-risk patients

Modified CUA risk stratification system

High	Any: 1. T1[§] 2. Recurrent, or multiple, or ≥3 cm HG Ta 3. Presence of CIS (primary or concomitant) [§]Very high-risk: HG T1 with any of the following: a) Multiple and ≥3 cm b) Presence of concurrent CIS (in the bladder or prostatic urethra) c) Presence of LVI d) Variant histology (e.g., micropapillary, plasmacytoid, sarcomatoid, neuroendocrine)

Prognostic factors for recurrence and progression

- Aggressive histological variants such as micropapillary, plasmacytoid, and sarcomatoid, are associated with increased risk of under-staging and progression *(LE 3)*
- Pathological review, preferably by a dedicated uro-pathologist, should be considered in settings where variant histology is suspected or atypical tumors are seen during TURBT (e.g., sessile mass) *(LE 3; weak recommendation)*

TUR quality

- Initial TURBT aims for complete tumor resection with sampling of the underlying detrusor muscle as the first step of curative intent treatment of NMIBC *(LE 2; strong recommendation)*
- When available, blue light cystoscopy (BLC) *(LE 1; weak recommendation)* can increase tumor detection at first TURBT and reduce recurrence risk
- A restaging TURBT should be performed in patients with T1 *NMIBC (LE 2; strong recommendation)*

Office fulguration of small superficial tumors

- Fulguration under local anesthesia might be considered for small (<5 mm) papillary tumors and negative cytology in patients with a prior history of papillary urothelial neoplasm of low malignant potential or LG Ta NMIBC (*LE 3; weak recommendation)*

TURBT recommendations

- Patients presenting with a positive urine cytology, but normal-appearing bladder at WLC and normal upper urinary tract imaging are at higher risk of harboring occult CIS and should undergo random bladder biopsies (or use of BLC with directed biopsies) *(LE 2; strong recommendation)*
- Biopsies or transurethral resection of the prostatic urethra should be included with random bladder biopsies *(LE 3; strong recommendation)*

TURBT recommendations cont'd

- Patients with CIS restricted to the prostatic urethral mucosa can be managed conservatively with transurethral resection of the prostate (TURP) plus intravesical BCG *(LE 3; weak recommendation)*
- In patients with HG T1 or CIS extending into the prostatic ducts, RC should be considered *(LE 3; weak recommendation)*
  - TURP followed by intravesical BCG is an alternative option. In this instance, close followup with repeat prostatic urethral biopsies after induction BCG should be considered *(LE 3; weak recommendation)*

Low-risk NMIBC
(LG, solitary, Ta <3 cm)

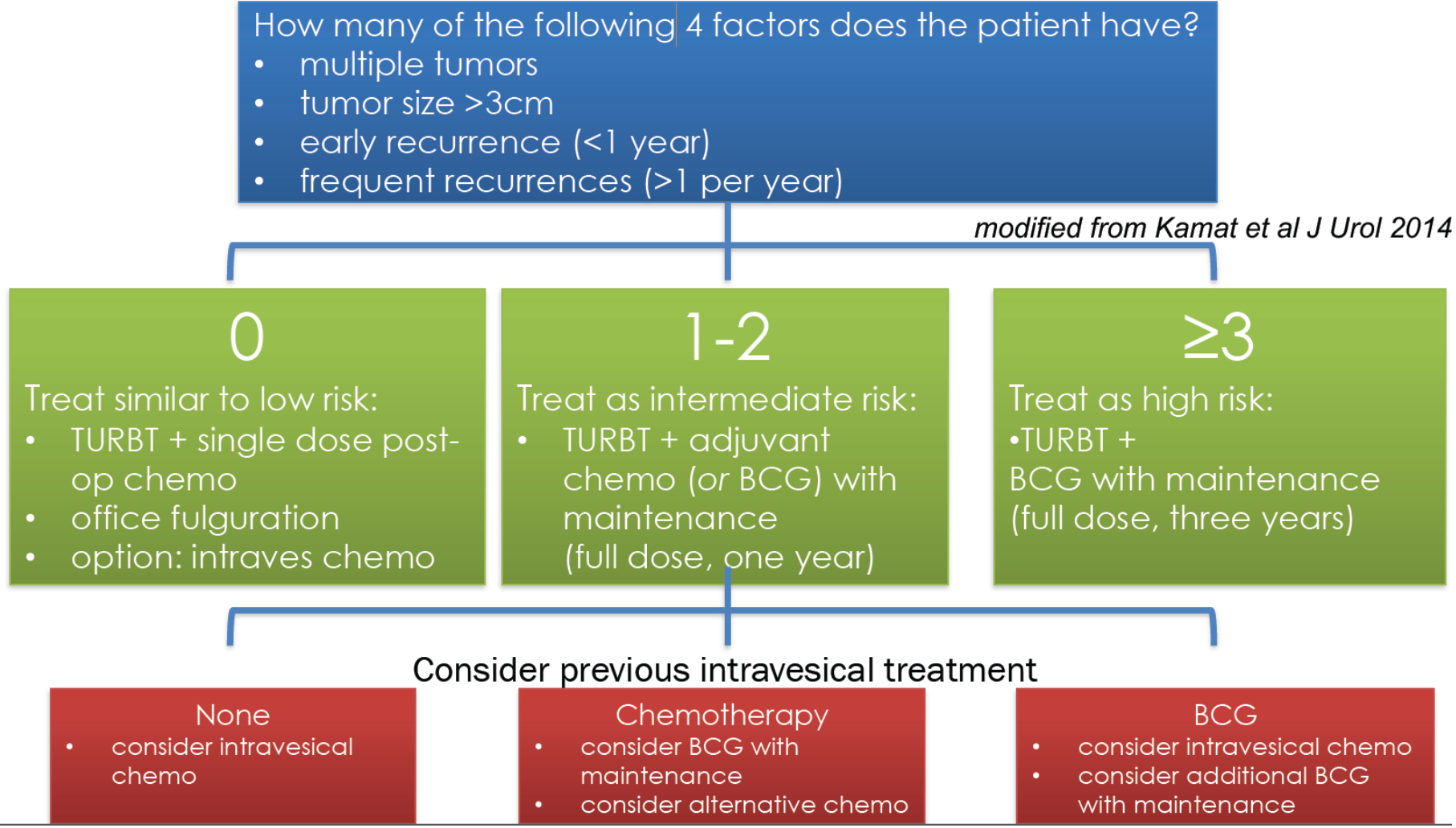
- Administration of single perioperative instillation of intravesical chemotherapy within 24 hours of TURBT
- No subsequent induction (adjuvant) intravesical
- therapy
- Surveillance cysto at 3–4 months
  - If negative ⟹ cysto 6–9 months later, then annually for 5 years
  - No need cytology, no need further upper tract imaging

Single postoperative instillation of chemotherapy (SIC)

- SIC should be offered to all patients with presumed low-risk NMIBC at TURBT and administered within 24 hours after endoscopic resection *(LE 1; strong recommendation)*
- SIC is recommended for intermediate-risk NMIBC and patients with ≤1 recurrence/year and EORTC recurrence score <5 *(LE 1; strong recommendation)*. SIC should be discussed even when further adjuvant intravesical chemotherapy is planned *(LE 2; weak recommendation)*
- SIC should not be administered after extensive resection or when bladder perforation is suspected *(LE 3; strong recommendation)*

Intermediate-risk NMIBC
(Multifocal or recurrent TaLG)

- Administration of single perioperative instillation of intravesical chemotherapy within 24 hours of TURBT
- Consider 6-week induction course intravesical intravesical chemotherapy (or BCG)
- 1-year maintenance therapy


How many of the following 4 factors does the patient have?
• multiple tumors
• tumor size >3cm
• early recurrence (<1 year)
• frequent recurrences (>1 per year)
modified from Kamat et al J Urol 2014
0
Treat similar to low risk:
• TURBT + single dose post-op chemo
• office fulguration
• option: intraves chemo
1-2
Treat as intermediate risk:
• TURBT + adjuvant chemo (or BCG) with maintenance (full dose, one year)
≥3
Treat as high risk:
•TURBT + BCG with maintenance (full dose, three years)
Consider previous intravesical treatment
None
• consider intravesical chemo
Chemotherapy
• consider BCG with maintenance
• consider alternative chemo
BCG
• consider intravesical chemo
• consider additional BCG with maintenance

High-risk NMIBC
(TaHG, T1, CIS)*

- Patients with newly-diagnosed CIS, HG Ta, or HG T1 tumors should received a six-week course of induction BCG
- In high-risk patients who completely respond to induction BCG, clinicians should continue with 3 years of maintenance BCG

High-risk NMIBC cont'd

- Surveillance cysto at 3–4 months
  - If negative ⟹ cysto + cytology q 3–4 months x 2 years, q 6 months x 2 years, then annually
- Consider upper tract evaluation in first year then every 2 yrs
  - Risk of upper tract tumors up to 10% in HG T1 patients with long-term followup

Merits of timely cystectomy

- Upfront RC should be offered to patients with HG T1 disease with additional adverse tumor pathological features *(LE 3; strong recommendation)*:
  - Variant histology (e.g., micropapillary, plasmacytoid, sarcomatoid)
  - Extensive invasion of the lamina propria or invasion into or beyond the muscularis mucosa (T1b/c)
  - Presence of LVI, concomitant CIS in the bladder or prostatic urethra
  - Multiple and large (≥3 cm) tumors or persistent HG T1 upon restaging TURBT

BCG-unresponsive NMIBC

- RC with pelvic lymph node dissection is the standard of care for BCG-unresponsive bladder cancer in surgically fit patients *(LE 3; strong recommendation)*
- For patients with BCG-unresponsive CIS or HG Ta, a second-line bladder-preserving therapy can be considered before RC *(LE 3; weak recommendation)*

BCG-unresponsive NMIBC cont'd

- Promising efficacy has been reported with intravenous pembrolizumab, intravesical oportuzumab monatox, nadofaragene firadenovec, and BCG plus N-803. These should be considered as potential options in patients with BCG unresponsive CIS who are unfit for or refuse to undergo RC *(LE 2; weak recommendation)*
- Alternative options such as sequential intravesical gemcitabine/docetaxel (induction plus maintenance) or single-agent chemotherapy may be considered for patients with BCG-unresponsive disease who are unfit for or refuse to undergo RC *(LE 3; weak recommendation)*

Summary

- Optimizing first-line therapy will ensure salvage is only given for true failures
  - Proper staging
  - High-quality TURBT and re-TUR if T1
  - Maintenance intravesical therapy
- Fluorescent cystoscopy improves resection and decrease early recurrence
  - Also in setting of normal cysto with +ve cytology

Summary cont'd

- For intermediate-risk NMIBC
  - Induction plus one year of maintenance with intravesical chemotherapy (or BCG)
  - Consider substratification
- For high-risk NMIBC
  - BCG induction with 3-year maintenance
- Discuss merits of early cystectomy in patients with T1HG and adverse features

Additional considerations

- Smoking cessation
- Don’t forget about upper tract and prostatic urethra in patients with frequent recurrences

Summary cont'd

- **Radical cystectomy is recommended for BCG-unresponsive disease**
- Other options:
  - PDL1 inhibition
  - Other promising salvage intravesical therapy (oportuzumab monatox, nadofaragene firadenovec, BCG+ N-803)