Management of non-muscle invasion bladder cancer (NMIBC)

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Incidence

- Bladder cancer is the second most common cancer of the GU tract.

- Bladder is the 8th most common cancer in Taiwanese male (the 5th common is prostate cancer). Cancer registry annual report, 2019, Taiwan

Risk

- Smoking is the most important risk factor (approximately 50%), because the aromatic amines and N-nitroso compounds induce DNA damage (double-stranded breaks).

Eur Urol 2016;70:458–66.

Cancer Res 2009;69:6857–64.

- Occupational exposure

Aluminium production
Rubber production industry Dye industry
Coal-tar pitch
Dry cleaning
Hairdressers and barbers
Printing
Textile manufacturing

Eur Urol 2018; 74: 784-795.

Histopathology

- Urothelial bladder cancer
  Papilloma (rare benign)
  Urothelial cell carcinoma (90%)

- Non-urothelial bladder cancer
  Adenocarcinoma including urachal Carcinoma (<2%)
  Am J Clin Exp Urol. 2015; 3(2): 51–63.
  Squamous cell carcinoma (2-5%) Arab J Urol. 2016 Sep; 14(3): 183–191.
  Small cell carcinoma (or neuroendocrine features) Orphanet J Rare Dis. 2011; 6: 75.
  Mixed Histology

Symptoms

- Intermittent gross or microscopic hematuria (85-90%)
- Lower urinary tract symptoms (frequency, urgency and dysuria)
- Flank pain if retroperitoneal metastasis or ureteral obstruction.

Signs

- Bimanual palpable mass : if large-volume or invasion tumor.
- Lymphedema : tumor metastasis induced occlusion of pelvic lymphadenopathy
- Hepatomegaly and supraclavicular lymphadenopathy : if tumor metastasis

Laboratory finding

- Uranalysis
- Urinary cytology
- Urinary biomarkers (limitations) : Nuclear matrix protein 22 (NMPs), Bladder tumor antigen (BTA). Urol Oncol. 2021 Jan;39(1):41-51.
- Two transcription factors : BLCA-1 and BLCA-4. J Urol, 174 (2005), pp. 64-68

Image

- Computer tomography urography (CTU)
- Magnetic resonance imaging urography (MRU) : if poor renal function or contrast allergy
- Bone scan : if suspected bone metastasis.

Definition of NMIBC

- Papillary tumours confined to the mucosa and invading the lamina propria : stage Ta and T1 (Union International Contre le Cancer 2017, 8th edition, TNM classification).

- Flat, high- grade tumours confined to the mucosa : CIS (Tis).

Eur Urol 81 (2022) 75–94

Primary assessment of NMIBC

- Cystoscopy is initially performed as an outpatient procedure (A flexible instrument results in better compliance compared to a rigid instrument, especially in men).

- PDD (Fluorescence cystoscopy) : using violet light after intravesical instillation of 5-aminolaevulinic acid or hexaminolaevulinic acid. PDD had higher sensitivity for detection of tumor lesions than white light endoscopy.

Int J Technol Assess Health Care, 27(2011), pp. 3-10

Treatment selection

- Counselling on smoking cessation if smoker.
- Transurethral resection of bladder tumors (TUR-Bt) : completely remove all visible lesions. BJU Int, 123 (2019), pp. 646-650
- The achieve good prognosis of TUR-Bt : Exophytic part of the tumor, the underlying bladder wall (presence of detrusor muscle) and the edges of the resection area or an en-bloc technique. Eur Urol, 78 (2020), pp. 546-569
- A second TURB (14–42 days after the initial resection) can increase recurrence-free survival for T1/high grade tumor. Int J Clin Oncol, 25 (2020), pp. 698-704

  BJU Int, 116 (2015), pp. 721-726

Risk groups of progression to muscle-invasive bladder cancer (MIBC)

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 unresponsivel Variant histologiesm Lymphovascular invasion Prostatic urethral invasion

J Urol 2016;196:1021

Intravesical chemotherapy

- A single, immediate, postoperative intravesical instillation of chemotherapy (mitomycin C, epirubicin, gemcitabine or pirarubicin) significantly reduces the recurrence rate compared to TURB alone.

Urol, 69 (2016), pp. 231-244

- Additional adjuvant intravesical chemotherapy instillations : in patients with intermediate-risk group (reduction of 13–14%).

J Urol, 155 (1996), pp. 1233-1238

Intravesical Bacillus Calmette-Guerin (BCG) immunotherapy

- BCG (empirical 6-weekly schedule) after TURB is superior to TUR-Bt alone or TURB-t + chemotherapy in preventing the recurrence of NMIBC.

  Eur Urol, 56 (2009), pp. 247-256

- In intermediate- and high-risk group : compared BCG with epirubicin and Interferon, epirubicin, or MMC and confirmed the superiority of BCG for prevention of tumor recurrence (reduction 32%).

  Eur Urol, 56 (2009), pp. 247-256

- In the risk of intermediate- and high risk group: maintenance BCG (3-weekly schedule) reduction the progression rate.

Intravesical Bacillus Calmette-Guerin (BCG) immunotherapy

- CIS cannot be cured by an endoscopic procedure alone, CIS must be treated using intravesical BCG instillations. J Urol, 174 (2005), pp. 86-91

Combination therapy

- Intravesical BCG + chemotherapy : Combination therapy is more effective in reducing recurrences but more toxic. It is no difference in progression free survival rate. Front Oncol, 9 (2019), p. 121

Treatment of failure of intravesical chemotherapy therapy

- Recurrence during or after intravesical chemotherapy : intravesical BCG instillations.

Treatment failure after intravesical BCG immunotherapy

- NMIBC may not respond at all (BCG-refractory) or may relapse after an initial response (BCG-relapsing).

- Radical cystectomy is the standard and preferred option.

Radical cystectomy (RC) for NMIBC

- Immediate RC for NMIBC with very high risk of disease progression.

  Eur Urol, 62 (2012), pp. 118-125

- Early RC is strongly recommended for patients with BCG-unresponsive tumors.

  J Urol, 177 (2007), pp. 1283-1286

Follow-up of patients with **Low risk** NMIBC

	Year						
	1	2	3	4	5	5-10	>10
Cystoscopy and urinary cytology	3,12 month	Annually				As clinically indicated	
Upper tract and abdominal pelvic imaging	Baseline imaging	As clinically indicated					

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Follow-up of patients with **Intermediate risk** NMIBC

	year						
	1	2	3	4	5	5-10	>10
Cystoscopy and urinary cytology	3, 6, 12 month	Every 6 month	Annually			As clinically indicated	
Upper tract and abdominal pelvic imaging	Baseline imaging	As clinically indicated					

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Follow-up of patients with **High risk** NMIBC

	Year						
	1	2	3	4	5	5-10	>10
Cystoscopy and urinary cytology	Every 3 month		Every 6 month			Annually	As clinically indicated
Upper tract imaging	Baseline imaging and at 12 month	Every 1–2 year					As clinically indicated

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Progression

- Most NMIBC can be managed with curative intent.
- The 5-year overall survival (OS) rate of NIMBC is approximately 90%. Histopathology.2019;74:112-134.
- Approximately 15% to 20% of NMIBCs (CIS or high-grade tumor) may progress to MIBC. *CA Cancer J Clin.* 2018;68:7-30

Thank for your attention