Saudi oncology society and Saudi urology association combined clinical management guidelines for urothelial urinary bladder cancer

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Abstract In this report, updated guidelines for the evaluation, medical, and surgical management of transitional cell carcinoma of the urinary bladder are resented. They are categorized according the stage of the disease using the TNM staging system 7th edition. The recommendations are presented with supporting level of evidence.

Key Words: Guidelines, management, Saudi, urothelial urinary bladder cancer

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Bladder cancer ranked 13 among the most common cancer diagnosis in Saudi Arabia, affecting 3.6/100,000 men and 1/100,000 women. In 2010, there were an estimated 243 new cases of bladder cancer accounting for 2.5% of all newly diagnosed cases. It affected 193 (78.4%) males and 50 (21.6%) females with a male:female ratio of 385:100. The most common histological subtypes is transitional cell carcinoma (82%) followed by squamous cell carcinoma $(4\%).^{[1]}$

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1. Staging:^[2]

Appendix I.

- Grading: The World Health Organization grading of urinary tumors 2004^[3] will be used as follow:
 - 2.1. Urothelial papilloma.
 - 2.2. Papillary urothelial neoplasm of low malignant potential.
 - 2.3. Low-grade papillary urothelial carcinoma.
 - 2.4. High-grade papillary urothelial carcinoma.
- 3. Initial evaluation and risk stratification of bladder tumors
 - 3.I.I. Complete history and physical examination.
 - 3.1.2. Urine cytology.
 - 3.1.3. Cystoscopy, which should include:
 - 3.1.3.1. Transurethral resection of bladder tumors (TURBT): The following should be observed
 - 3.1.3.1.1. The goal of TURBT is to define the stage and grade of tumor (diagnostic) and to resect all grossly visible tumors (therapeutic).

- 3.1.3.1.2. Deep resection is important to assess the depth of tumor invasion to the muscle.
- 3.I.3.I.3. Random bladder and prostatic urethral biopsies are indicated only in patients with positive urine cytology with normal appearing bladder.^[4-6] Evidence Level -3 (EL-3).
- 3.1.3.1.4. Second TURBT is recommended to be done within 2-4 weeks from initial resection in the following conditions:^[7-9] (EL-2)

3.I.3.I.4.I. Incomplete initial resection.

- 3.I.3.I.4.2. No muscle tissue in the initial resection specimen.
- 3.1.3.1.4.3. High-grade onmuscle invasive bladder tumor.
- 3.1.3.1.4.4. TI bladder tumor.
- 3.1.4. Blood count and chemistry profile including alkaline phosphatase for muscle invasive bladder tumors.
- 3.1.5. Imaging:
 - 3.1.5.1. Imaging of upper urinary tract (computed tomography [CT] or intravenous urogram [IVU]) is indicated if a patient has tumors located in the trigon, multifocal or high-risk tumors (see item 3.2.3)^[10,11] (EL-3).
 - 3.1.5.2. CT abdominal/pelvis or magnetic resonance imaging and chest X-ray or CT chest are indicated for staging of muscle invasive bladder tumor.
 - 3.1.5.3. Bone scan is only indicated if a patient is symptomatic or if elevated alkaline phosphatase.

The risk stratification for nonmuscle invasive bladder cancer (NMIBC) depends on the following factors: Tumor stage, grade, presence of carcinoma *in situ* (CIS), number of tumors, tumor size, and prior recurrence rate:^[12]

- 3.1.6. Low-risk NMIBC (low-grade Ta with tumor size <3 cm).
- 3.1.7. Intermediate risk NMIBC (low-grade Ta with either multifocal disease or with tumor size >3 cm or recurrence at 3 months).
- 3.1.8. High-risk NMIBC (high-grade Ta, all T1, CIS).
- 3.1.9. Utilization of nomograms and risk calculators is encouraged for more objective risk assessment.^[12]
- 4. Management of NMIBC
 - 4.1. Intravesical therapy

- 4.I.I. Low-risk tumors: A single immediate postoperative instillation of mitomycin C or doxorubicin within 24 h (preferably within 6 h) if no suspicion of bladder perforation should be considered.^[13] (EL-I).
- 4.1.2. Intermediate risk: It is recommended to give single immediate instillation of chemotherapy followed by induction and maintenance bacille Calmette-Guerin (BCG) for I year {Oddens, 2013 #66}^[14,15] (EL-2).
- 4.1.3. High-risk
 - 4.1.3.1. Referral to higher centers should be considered.
 - 4.1.3.2. CIS:

4.1.3.2.1. It is recommended to give induction intravesical BCG plus maintenance for at least I year^[1+16].(EL-1).
4.1.3.2.1.1. Assess response at 3 months, if no response; additional 6 weeks course of BCG, If no response on biopsy at 6 months radical cystectomy is recom

- 1 s recom mended.^[17, 18]
- 4.1.3.3. Multiple high-grade Ta TI: 4.1.3.3.1. It is recommended to repeat TURBT at
 - 2-4 weeks, after initial resection. 4.1.3.3.2. IntravesicalBCGinduction
 - plus maintenance for I-3 years^[15] (EL-I).
 - 4.1.3.3.3. Immediate radical cystectomy can be considered for the highest risk patients (TI high-grade with or without CIS)^[19] (EL-3).
- 4.2. Treatment of intravesical therapy failure:
 - 4.2.1. Definition of intravesical therapy failure:^[19] Defined as persistent or worsening of the disease on BCG treatment such as higher stage, grade, appearance of CIS, or muscle invasive disease at 3 or 6 months assessment.
 - 4.2.2. Management of intravesical therapy failure: 4.2.2.1. Patients with recurrence of NMIBC

following immediate intravesical chemotherapy may benefit from BCG treatment.

- 4.2.2.2. Patients with initial BCG therapy failure who experience recurrence of high-grade disease at 6 months should be offered cystectomy.^[20]
- 4.2.2.3. In case of failure before maintenance BCG has been completed, cystectomy should be considered if high-grade T1 or CIS is present. But for high-grade Ta recurrences, repeat resection, and induction intravesical therapy could be started^[21] (EL-3).
- 4.3. Follow-up:
 - 4.3.1. Low-risk: Cystoscopy and cytology at 3 and 6 months then every 6 months afterwards for 5 years (EL-3).
 - 4.3.2. High-risk: Cystoscopy and urinary cytology every 3 months for 2 years, then every 6 months for 3 years, then annual (EL-3).
 - 4.3.3. Intermediate risk: Similar to high-risk, however schedule can be adapted according to individual patient.^[19]
 - 4.3.4. Annual imaging of upper urinary tract with either CT scan or IVU in high-risk group.
- 5. Management of muscle invasive bladder cancer
 - 5.1. Radical cystectomy and urinary diversion:
 - 5.1.1. Radical cystectomy is the preferred curative treatment for localized bladder cancer (EL-3).
 - 5.I.2. Radical cystectomy includes removal of regional lymph nodes, the extent of which has not been sufficiently defined (EL-3).
 - 5.1.3. Laparoscopic and robotic radical cystectomy are optional.
 - 5.I.4. Orthotopic bladder or other continent urinary diversion options should be offered to male and female patients lacking any contra-indications.
 - 5.1.5. Neo-adjuvant cisplatin based chemotherapy improved overall survival by 5-7% at 5 years and this option should be offered to patients especially with locally advanced disease (T3, T4)^[22-24] (EL-1).
 - 5.1.6. Follow-up after radical cystectomy:
 - 5.I.6.I. Urine cytology, creatinine and electrolytes blood test every 3-9 months for 2 years and then as clinically indicated.^[25]
 - 5.1.6.2. CT chest, abdomen, and pelvis every 3-9 months for 2 years based on risk of recurrence and as clinically indicated.^[26]

- 5.2. Radiation therapy should be offered for patients with localized disease not fit for surgery and chemotherapy (EL-3).
- 5.3. Bladder Sparing treatment: Multimodality treatment should be considered as an option for the selected group of patients and well-informed compliant patients (EL-3):
 - 5.3.1. Patients selected for bladder sparing treatment should have the following:
 - 5.3.1.1. Clinically T2-T3 tumor.
 - 5.3.1.2. No hydronephrosis.
 - 5.3.1.3. Normal renal function.
 - 5.3.1.4. No multifocal disease or CIS.
 - 5.3.1.5. Functional bladder.
 - 5.3.1.6. Urothelial histology.
 - 5.3.1.7. No prostatic urethral involvement.
 - 5.3.2. Multimodality therapy should consist of:
 - 5.3.2.1. Aggressive and visibly complete TURBT.
 - 5.3.2.2. Concurrent cisplatin at 70-100 mg/m² at day I and 22 of radiation therapy.
 - 5.3.2.3. Cystoscopy with biopsy must be done either mid-way through the treatment or 2-3 months after completion of chemoradiotherapy course. Patients with positive biopsy should undergo radical cystectomy.
 - 5.3.2.4. The total dose of radiotherapy is biologically equivalent to 64-66 Gy.
 - 5.3.3. Follow-up should include cystoscopy every 3 months for 2 years, then every 6 months for the next 3 years then annual.
 - 5.3.4. Superficial recurrent disease should be treated locally (TURBT \pm BCG) (EL-3).
- 5.4. Adjuvant chemotherapy:
 - 5.4.1. Adjuvant chemotherapy could be considered using cisplatin and gemcitabine regimen in patients with:^[25]
 - 5.4.1.1. Normal renal function.
 - 5.4.1.2. Performance status (PS) 0-2.
 - 5.4.1.3. Pathological stage T3, T4 or node positive disease.
 - 5.4.1.4. Patients should not have received neo-adjuvant chemotherapy.
 - 5.4.1.5. Urothelial histology.
- 6. Advanced, Metastatic and recurrent disease: Platinum-based chemotherapy is the standard
 - 6.I. Patients with normal renal function and fit for chemotherapy (PS 0-2), are treated with combination cisplatin and gencitabine for a maximum of six cycles (EL-I).^[27]

- 6.2. Patients with decreased renal function and/or unfit (PS 3) are treated with a combination of carboplatin and gemcitabine or single agent gemcitabine (EL-2).^[28]
- 6.3. Options of second-line chemotherapy include single agent vinflunine (EL-I),^[29] and taxanes (LE-2).^[30]
- 6.4. Patients who present with local recurrence may benefit from palliative radiation therapy.

APPENDIX

Appendix I: TNM staging

Primary tumor (T)					
TX		Primary tumor cannot be assessed			
ТО	No evidence of primary tumor				
Та	Noninvasive papillary carcinoma				
Tis	Carcinoma in situ: "flat tumor"				
T1	Tumor inv	ades subepithel	ial		
	connective	e tissue			
T2	Tumor inv	ades muscularis	propria		
pT2a	Tumor inva	ades superficial			
	musculari	s propia (inner h	alf)		
pT2b		ades deep musc			
	propia (outer half) Tumor invades perivesical tissue				
Т3					
рТЗа	Microscopically				
pT3b	Macroscopically (extravesical				
P100	mass)				
T4	,	ades any of the			
	following: Prostatic stroma,				
	seminal vesicles, uterus, vagina,				
		, abdominal wal			
T4a		ades prostatic s			
14a	uterus, va		cronia,		
T4b					
		Tumor invades pelvic wall, abdominal wall			
Regional lymph nodes (N)*	abuomina	wan			
NX					
NO	Lymph nodes cannot be assessed				
N1	No lymph node metastasis Single regional lymph node				
IN I	0 0		e		
		s in the true			
		ogastric, obtura			
		ac, or presacral			
N2	lymph nod	,			
	Multiple regional lymph				
		istasis in the tru			
		ogastric, obtura			
		ac, or presacral	lymph		
	node meta	,			
N3		de metastasis to			
	common i	iac lymph node	S		
Distant metastasis (M)					
MO	No distant metastasis				
M1	Distant metastasis				
Anatomic stage/					
prognostic groups					
Stage 0a	Ta	NO	MO		
Stage Ois	Tis	No	MO		
Stage I	T1	NO	MO		
Stage II	T2a	NO	MO		
	T2b	NO	MO		
Stage III	T3a	NO	MO		
	T3b	NO	MO		
	T4a	NO	MO		
Stage IV	T4b	NO	MO		
	Any T	N 1-3	MO		
	Any T Any T	Any N	M 1		

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