Review Article

Saudi Oncology Society and Saudi Urology Association combined clinical management guidelines for urothelial cell carcinoma of the urinary bladder 2017

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Abstract

This is an update to the previously published Saudi guidelines for the evaluation and medical/surgical management of patients diagnosed with urothelial cell carcinoma of the urinary bladder. It is categorized according to the stage of the disease using the tumor node metastasis staging system, 7th edition. The guidelines are presented with their accompanying supporting evidence level, which is based on comprehensive literature review, several internationally recognized guidelines, and the collective expertise of the guidelines committee members (authors) who were selected by the Saudi Oncology Society and Saudi Urological Association. Considerations to the local availability of drugs, technology, and expertise have been regarded. These guidelines should serve as a roadmap for the urologists, oncologists, general physicians, support groups, and health-care policymakers in the management of patients diagnosed with urothelial cell carcinoma of the urinary bladder.

Keywords: Carcinoma, Guidelines, management, Saudi Oncology Society, Saudi Urological Association, urothelial

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Received: 18.11.2017, **Accepted:** 18.12.2017

Access this article online

Quick Response Code:

Website: www.urologyannals.com

DOI: 10.4103/UA.UA_176_17

How to cite this article: Alharbi H, Alkhateeb S, Murshid E, Alotaibi M, Abusamra A, Rabah D, *et al*. Saudi Oncology Society and Saudi Urology Association combined clinical management guidelines for urothelial cell carcinoma of the urinary bladder 2017. Urol Ann 2018;10:133-7.

INTRODUCTION

According to the cancer incidence report in Saudi Arabia for the year 2013, there were 280 new cases of urinary bladder cancer, accounting for 4.3% and 0.8% of all newly diagnosed cases of cancer in men and women, respectively. Urinary bladder cancer is ranked the 8th most common cancer in males and the 20th most common in females. Of the 280 cases, 227 affected males (81%) and 53 affected females (19%). The overall age-standardized incidence rate was 3.8/100,000, in males and 1/100,000 in females. The median age at diagnosis was 63 years among males and 64 years among females.[1]

STAGING

The American Joint Committee on Cancer tumor, nodes, metastases staging definitions for bladder cancer should be used[2] [Tables 1 and 2].

TUMOR GRADING

The 2016 World Health Organization Classification of Tumors of the Urinary System[3] will be used as follows:[4]

1. Noninvasive urothelial lesions
    i. Urothelial carcinoma *in situ*
    ii. Papillary urothelial carcinoma, low grade
    iii. Papillary urothelial carcinoma, high grade
    iv. Papillary urothelial neoplasm of low malignant potential.
2. Urothelial papilloma
3. Inverted urothelial papilloma
4. Urothelial proliferation of uncertain malignant potential (hyperplasia)
5. Urothelial dysplasia
6. Invasive urothelial tumor.

PATHOLOGY REPORTING

Surgical pathology reporting must include the following:

1. The histological tumor type
2. The presence or absence of lamina propria and muscularis propria
3. The depth of invasion (i.e., pathological T stage) referred to in Section 1
4. The presence or absence of carcinoma *in situ* (CIS)
5. The grade of tumor as referred to in Section 2
6. Any urothelial carcinoma variant.[5]

EVALUATION OF THE BLADDER TUMOR

The initial evaluation should include history and physical examination, complete blood count, renal function, urine cytology, and bladder ultrasonography. Initial diagnostic cystoscopy should be done with transurethral bladder tumor resection (TURBT) to achieve complete resection if possible.[6] Imaging of the upper tract should be done by ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) urogram. If the cystoscopy findings confirm the invasive disease, do CT or MRI of abdomen and pelvis, as well as chest imaging.[7,8]

Table 1: Tumor, node, and metastasis staging for urothelial bladder carcinoma

Primary tumor (T)	Regional lymph nodes (N)*	Distant metastasis (M)
TX: Primary tumor cannot be assessed	NX: Regional lymph node (s) cannot be assessed	M0: No distant metastasis
T0: No evidence of primary tumor	N0: No regional lymph node metastasis	M1: Distant metastasis or positive peritoneal cytology cytology
Ta: Noninvasive papillary carcinoma	N1: Single regional lymph node metastasis in the true pelvis**	
T_{is}: Carcinoma *in situ*: "Flat tumor"	N2: Multiple regional lymph node metastases in the true pelvis**	
T1: Tumor invades subepithelial connective tissue	N3: Lymph node metastasis to the common iliac lymph node	
T2: Tumor invades muscularis propria pT2a: Tumor invades superficial muscularis propria (inner half) pT2b: Tumor invades deep muscularis propria (outer half)		
T3: Tumor invades perivesical tissue pT3a: Microscopically pT3b: Macroscopically (extravesical mass)		
T4a: Tumor invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall T4a: Tumor invades prostatic stroma, uterus, vagina T4b: Tumor invades pelvic wall, abdominal wall		

*Lymph nodes: Regional lymph nodes include both primary and secondary drainage regions. All other nodes above the aortic bifurcation are consider distant lymph nodes, **Lymph nodes of the true pelvis: hypogastric, obturator, external iliac, or presacral

MANAGEMENT OF NONMUSCLE INVASIVE UROTHELIAL BLADDER CARCINOMA

1. If the findings of the diagnostic cystoscopy are suggestive of a noninvasive bladder tumor
   i. Conduct TURBT to achieve complete resection, if possible
   ii. Repeat TURBT within 2–4 weeks, indicated if the resection was incomplete, the disease is high-grade Ta or T1, or if no muscle examination was performed
   iii. Administer a single postoperative instillation of intravesical chemotherapy (e.g., mitomycin C or epirubicin/doxorubicin) within 24 h of TURBT, unless perforation is suspected[9-11]
   iv. Provide further treatment according to risk stratification.
2. Risk stratification for nonmuscle invasive urothelial bladder carcinoma
   i. Risk depends on the following factors: T stage, the presence of CIS, grade, recurrence rate, number of tumors, and tumor size[12] [Table 3][13]
   ii. Low-risk, nonmuscle, invasive bladder cancer (NMIBC) (solitary small volume, low-grade Ta)
   iii. Intermediate risk NMIBC (multifocal and/or large volume low-grade Ta, recurrence at 3 months)
   iv. High-risk NMIBC (high-grade Ta, all T1, CIS).
3. Management of low-risk NMIBC– Surveillance cystoscopy (3–6 months) intervals [Table 4]
4. Management of intermediate risk NMIBC:
   i. Intravesical bacillus Calmette–Guerin (BCG) or mitomycin induction (weekly for 6 weeks)[14]
   ii. Surveillance cystoscopy and cytology
   iii. Upper tract imaging every 2 years or as indicated.
5. Management of high-risk nonmuscle, invasive bladder cancer, including carcinoma *in situ*
   i. Intravesical BCG or mitomycin induction (weekly for 6 weeks) and maintenance therapy (3 weekly injections) at 3, 6, 12, 18, 24, 30, and 36 months from induction[15,16]
   ii. Close surveillance cystoscopy, cytology, and upper tract imaging
   iii. Consider early cystectomy in selected patients.
6. Recurrence of nonmuscle invasive disease
   i. TURBT
   ii. Adjuvant intravesical therapy if not given before or as a second induction[17]
   iii. If two inductions of adjuvant intravesical therapy were given before, then consider changing the intravesical therapy
   iv. Consider early cystectomy in recurrent CIS, T1, and high-grade disease with prior treatment with no >2 inductions of intravesical therapy.[18,19]
7. Positive urine cytology without gross evidence of disease
   i. Multiple biopsies of the bladder and prostatic urethra[20-22]
   ii. Selective cytology of the upper tract
   iii. Upper tract imaging (CT, MRI, or retrograde pyelogram)
   iv. Ureteroscopy if suspicion of upper tract tumor.

Table 2: Urothelial bladder carcinoma anatomical stages and prognostic groups

Stage grouping	T stage	N stage	M stage
Stage 0a	Ta	N0	M0
Stage 0_{is}	T_{is}	N0	M0
Stage I	T1	N0	M0
Stage II	T2a	N0	M0
	T2b	N0	M0
Stage III	T3a	N0	M0
	T3b	N0	M0
Stage IV	T4a	N0	M0
	T4b	N0	M0
	Any T	N1–N3	M0
	Any T	Any N	M1

Table 3: Risk stratification for nonmuscle invasive urothelial bladder carcinoma

Low risk	Intermediate risk	High risk
LG solitary Ta ≤3 cm	Recurrence within 1 year, LG Ta	HG T1
PUNLMP	Solitary LG Ta >3 cm	Any recurrent, HG Ta
	LG Ta, multifocal	HG Ta, >3 cm (or multifocal)
	HG Ta, ≤3 cm	Any CIS
	LG T1	Any BCG failure in HG patient
		Any variant histology
		Any LVI
		Any HG prostatic urethral involvement

LG: Low-grade, PUNLMP: Papillary urothelial neoplasm of low malignant potential, HG: High-grade, CIS: Carcinoma *in situ*, LVI: Lymphovascular invasion, BCG: Bacillus Calmette–Guerin

MANAGEMENT OF MUSCLE-INVASIVE UROTHELIAL BLADDER CARCINOMA

Staging should include complete blood count; renal function; serum electrolytes; liver function test, including alkaline phosphatase; imaging of the chest, abdomen, and pelvis (CT or MRI); and a bone scan if elevated alkaline phosphatase or symptoms of bone pain are present.[23]

1. Clinical T2–T4a disease with negative lymph nodes
   i. Neoadjuvant cisplatin-based combination chemotherapy:[24-26]
      - Considered in clinical T2
      - Strongly recommended in clinical T3.
   ii. Radical cystectomy with extended

Table 4: Suggested follow-up schedule for nonmuscle invasive disease

	3 months	6 months	9 months	12 months
Years 1 and 2	Cystoscopy Urine cytology	Cystoscopy Urine cytology	Cystoscopy Urine cytology	Cystoscopy Urine cytology Upper tract imaging
Years 3, 4, and 5	Cystoscopy Urine cytology		Cystoscopy Urine cytology Annual upper tract imaging	

Consider prolonging the intervals and omitting upper tract imaging after the first year for low-risk disease

lymphadenectomy (open, laparoscopic, or robotic) is considered the standard treatment[27]

iii. Bilateral pelvic lymphadenectomy should be performed and include, at a minimum, the common, internal and external iliac, and obturator nodes

iv. Bladder preservation with trimodality combination of complete resection of the bladder tumor TURBT, followed by concurrent chemoradiation with early radical cystectomy in failure, are alternatives to upfront radical cystectomy[27-32] in selected patients with solitary disease, no CIS, no hydronephrosis, normal renal function, and adequate bladder capacity[33]

v. In patients undergoing bladder preservation, early evaluation by cystoscopy with or without biopsy is recommended after 40–45 Gy for the whole bladder and regional nodes. If there is residual/recurrent tumor, then consider cystectomy. If there is complete response, then complete radiotherapy to 60–65 Gy total dose in conventional fractionation; altered fractionation regimens, such as 50–52.5 Gy in 20 fractions, may also be considered[34]

vi. For patients who are not candidates for radical treatment, consider TURBT and/or palliative radiotherapy

vii. If no neoadjuvant chemotherapy is given, consider adjuvant cisplatin-based chemotherapy following pathological criteria (pT3–4, positive nodes).[35]

2. Clinical T4b or positive locoregional lymph node disease
   i. Cisplatin-based combination chemotherapy or chemoradiation
   ii. Reevaluate the response during the treatment with imaging and/or TURBT
   iii. If chemoradiation was used:
      - Observation for patients who achieved complete response.
      - If partial response, consider cystectomy.
   iv. If cisplatin-based combination chemotherapy was used:
      - In responding patients, consider cystectomy or chemoradiation
      - In nonresponding patients, consider chemoradiation.
3. Metastatic disease
   i. Chemotherapy is the mainstay of treatment
   ii. Patients with normal renal function and fit for chemotherapy (performance status [PS] 0–2) are treated with combination cisplatin and gemcitabine for a maximum of six cycles[36]
   iii. Patients with decreased renal function and/or unfit (PS 3) are treated with combination of carboplatin and gemcitabine[37] or single-agent gemcitabine, carboplatin, or atezolizumab[38]
   iv. There is no standard, second-line therapy; patients who relapse or progress on the first-line may be given atezolizumab,[38] vinflunine, or taxanes as second-line chemotherapy
   v. Patients who present with local recurrence may benefit from palliative radiation therapy.

Financial support and sponsorship

Funding was provided by the Saudi Oncology Society for this work.

Conflicts of interest

There are no conflicts of interest.

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