

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

Sultan Alkhateeb, Mubarak Al-Mansour<sup>1</sup>, Mohammed Alotaibi<sup>2</sup>, Ahmad Saadeddin<sup>3</sup>, Ashraf Abusamra<sup>4</sup>, Danny Rabah<sup>5</sup>, Esam Murshid<sup>6</sup>, Abdullah Alsharm<sup>7</sup>, Imran Ahmad<sup>8</sup>, Hussain Kushi<sup>9</sup>, Abdullah Alghamdi<sup>10</sup>, Khalid Alghamdi<sup>11</sup>, Shouki Bazarbashi<sup>12</sup>

Department of Surgery, Division of Urology, King Abdulaziz Medical City, King Saud Bin Abdulaziz University for Health Sciences, Departments of <sup>2</sup>Urology and <sup>8</sup>Oncology, King Faisal Specialist Hospital and Research Center, <sup>3</sup>Department of Oncology, King Abdulaziz Medical City, <sup>5</sup>Department of Surgery, College of Medicine and Uro-Oncology Research Chair, King Saud University, <sup>6</sup>Department of Oncology, Oncology Center, Prince Sultan Medical Military City, <sup>7</sup>Department of Medical Oncology, Comprehensive Cancer Center, King Fahad Medical City, <sup>10</sup>Department of Urology, Prince Sultan Medical Military Center, <sup>11</sup>Department of Surgery, Division of Urology, Security Forces Hospital, <sup>12</sup>Department of Oncology, Section of Medical Oncology, Oncology Center, King Faisal Specialist Hospital and Research Center, Riyadh, <sup>1</sup>Department of Oncology, King Abdulaziz Medical City, King Saud Bin Abdulaziz University for Health Sciences, <sup>4</sup>Department of Surgery, Urology Section, King Khalid Hospital, King Abdulaziz Medical City, Ministry of National Guard Health Affairs, <sup>9</sup>Department of Radiation Oncology, Princess Norah Oncology Center, King Abdulaziz Medical City, Jeddah, Saudi Arabia

## Abstract

This is an update to the previously published Saudi guidelines for the evaluation, medical, and 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 7<sup>th</sup> edition. The guidelines are presented with supporting evidence level, they are 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 policy makers in the management of patients diagnosed with urothelial cell carcinoma of the urinary bladder.

**Key Words:** Guidelines, management, Saudi Oncology Society, Saudi Urological Association, urothelial carcinoma

### Address for correspondence:

Dr. Sultan Alkhateeb, Department of Surgery, Division of Urology, King Abdulaziz Medical City, King Saud Bin Abdulaziz University for Health Sciences, P.O. Box: 22490 (1446), Riyadh 11426, Saudi Arabia. E-mail: alkhateeb@nghi.med.sa

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## INTRODUCTION

According to the cancer incidence report in Saudi Arabia for the year 2010, there were 243 new cases of urinary bladder cancer accounting for 2.4% of all newly diagnosed cases of cancer. It ranked the 8<sup>th</sup> and 20<sup>th</sup> most common cancer in males and females, respectively. It affected 193 (78.4%) males and 50 (20.6%) females with a male to female ratio of 385:100. The overall age-standardized incidence rate was 2.3/100,000, in males it was 3.6/100,000 and in females it was 1/100,000. The median age at diagnosis was 63 among males (range 11–101 years) and 64 among females (range 28–97 years).<sup>[1]</sup>

## STAGING

The staging is shown in Appendix I.<sup>[2]</sup>

## GRADING

The World Health Organization grading of urinary tumors 2004<sup>[3]</sup> will be used as follow:

- Urothelial papilloma
- Papillary urothelial neoplasm of low malignant potential
- Low-grade papillary urothelial carcinoma
- High-grade papillary urothelial carcinoma.

## PATHOLOGY REPORTING OF BLADDER TUMOR SPECIMEN MUST AT LEAST INCLUDE THE FOLLOWING INFORMATION

- The histological tumor type
- The presence or absence of lamina propria and muscularis propria
- The depth of invasion, i.e., pathological T-stage referred to in section 1
- The presence or absence of carcinoma *in situ* (CIS)
- The grade of tumor as referred to in section 2
- Any urothelial carcinoma a variant.<sup>[4]</sup>

## EVALUATION OF BLADDER TUMOR

Evaluation should include history and physical examination, urine cytology, and diagnostic cystoscopy

- If the findings of the diagnostic cystoscopy are suggestive of noninvasive
  - Transurethral resection of bladder tumor (TURBT)
  - Single-dose intravesical chemotherapy (mitomycin or doxorubicin) should be considered within 24 h from TURBT to reduce the rate of local recurrence<sup>[5]</sup>
  - Imaging of the upper tract (ultrasound, computed tomography [CT], or magnetic resonance imaging [MRI] urogram) if not already done.

- If the findings of the diagnostic cystoscopy are suggestive of invasive, or high-grade disease
  - Consider imaging (CT scan or MRI) of the abdomen and pelvis before TURBT (EL3)<sup>[6,7]</sup>
  - Examination under anesthesia and TURBT.

## MANAGEMENT OF NONMUSCLE INVASIVE UROTHELIAL BLADDER CARCINOMA

Repeat TURBT within 2–4 weeks is indicated if incomplete resection, high-grade, pathological T1, or there is no muscle in specimen.<sup>[8–10]</sup>

### Risk stratification for nonmuscle invasive urothelial bladder carcinoma

This depends on the following factors: Tumor stage, grade, presence of CIS, number of tumors, tumor size, and prior recurrence rate.<sup>[11]</sup>

- Low-risk nonmuscle invasive bladder cancer (NMIBC) (solitary small volume, low-grade Ta)
- Intermediate risk NMIBC (multifocal and/or large volume low-grade Ta, recurrence at 3 months)
- High-risk NMIBC (high-grade Ta, all T1, CIS).

### Low-risk

Surveillance cystoscopy (3–6 months) intervals [Appendix 2].

### Intermediate-risk

- Adjuvant intravesical (6-week induction) bacillus Calmette–Guerin (BCG) (preferred) or mitomycin<sup>[12]</sup>
- Surveillance cystoscopy and cytology (3–6 months) intervals
- Upper tract imaging every 2 years or as indicated.

### High-risk including carcinoma *in situ*

- Adjuvant intravesical BCG [6-week induction followed by maintenance see Appendix 3]<sup>[13,14]</sup>
- Close surveillance cystoscopy, cytology, and upper tract imaging
- Consider early cystectomy in selected patients.<sup>[15]</sup>

### Recurrence of nonmuscle invasive disease

- TURBT
- Adjuvant intravesical therapy if not given before or as a second induction<sup>[16]</sup>
- If two induction of adjuvant intravesical therapy was given before, then consider changing the intravesical therapy
- Consider early cystectomy in recurrent CIS, T1, and high-grade disease with prior treatment with no more than two induction of intravesical therapy.<sup>[17,18]</sup>

### Positive urine cytology without gross evidence of disease

- Multiple biopsies of the bladder and prostatic urethra<sup>[19–21]</sup>
- Selective cytology of the upper tract

- Upper tract imaging (CT or MRI urogram, or retrograde pyelogram)
- Ureteroscopy if suspicion of upper tract tumor.

### MANAGEMENT OF MUSCLE INVASIVE UROTHELIAL BLADDER CARCINOMA

Staging should include complete blood count, renal function and serum electrolytes, liver function test including alkaline phosphatase, imaging of the chest, abdomen, and pelvis (CT or MRI), bone scan if elevated alkaline phosphatase or symptoms of bone pain.<sup>[22]</sup>

#### Clinical T2–T4a disease with negative lymph nodes

- Neoadjuvant cisplatin-based combination chemotherapy<sup>[23-25]</sup>
  - Considered in clinical T2
  - Strongly recommended in clinical T3.
- Radical cystectomy with extended lymphadenectomy (open, laparoscopic, or Robotic) is considered the standard treatment<sup>[26]</sup>
- Bilateral pelvic lymphadenectomy should be performed and include at a minimum common, internal and external iliac, and obturator nodes
- Bladder preservation with tri-modality combination of maximum TURBT followed concurrent chemoradiation with early radical cystectomy in failure is an alternative to upfront radical cystectomy<sup>[26-31]</sup> in selected patients with solitary disease, no CIS, no hydronephrosis, normal renal function, and adequate bladder capacity<sup>[32]</sup>
- In patient undergoing bladder preservation, early evaluation is recommended after 45 Gy, if there is residual/recurrent tumor than consider cystectomy and if there is the complete response then complete radiotherapy to 60–65 Gy total dose<sup>[33]</sup>
- Patients who are not candidate for radical treatment, consider TURBT and/or palliative radiotherapy
- After surgery with positive lymph nodes or pathological T3 or T4 disease, consider adjuvant cisplatin-based combination chemotherapy if no neoadjuvant was given.<sup>[34]</sup>

#### Clinical T4b or positive locoregional lymph node disease

- Cisplatin-based combination chemotherapy or chemoradiation
- Reevaluate the response during the treatment with imaging and/or TURBT
- If chemoradiation was used:
  - Observation for patients who achieved complete response

- If partial response consider cystectomy.
- If cisplatin-based combination chemotherapy was used:
  - In responding patients, consider cystectomy or chemoradiation
  - In nonresponding patients, consider chemoradiation.

#### Metastatic disease

- Chemotherapy is the mainstay of treatment
- Patients with normal renal function and fit for chemotherapy (PS 0–2) are treated with combination cisplatin and gemcitabine for a maximum of 6 cycles<sup>[35]</sup>
- Patients with decreased renal function and/or unfit (PS 3) are treated with combination of Carboplatin and gemcitabine or single agent gemcitabine or carboplatin<sup>[36]</sup>
- Patient who relapse or progress on the above regimens may be given vinflunine or taxanes as second-line chemotherapy
- Patients who present with local recurrence may benefit from palliative radiation therapy
- Consider clinical trials.

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**APPENDIX**

**Appendix 1: Tumor, node, metastasis staging**

| Primary tumor (T) |   |
|-------------------|---|
| TX                | Primary tumor cannot be assessed  |
| T0                | No evidence of primary tumor  |
| Ta                | Noninvasive papillary carcinoma   |
| Tis               | Carcinoma in situ: "flat tumor"   |
| T1                | Tumor invades subepithelial connective tissue   |
| 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)   |
| T4                | 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 considered distant lymph node

| Regional lymph nodes (N)* |   |
|---------------------------|---|
| NX                        | Lymph nodes cannot be assessed  |
| N0                        | No lymph node metastasis  |
| N1                        | Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)              |
| N2                        | Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node metastasis) |
| N3                        | Lymph node metastasis to the common iliac lymph nodes   |

| Distant metastasis (M) |                       |
|------------------------|-----------------------|
| M0                     | No distant metastasis |
| M1                     | Distant metastasis    |

| Anatomic stage/prognostic groups |       |       |    |
|----------------------------------|-------|-------|----|
| Stage 0a                         | Ta    | N0    | M0 |
| Stage 0is                        | Tis   | N0    | M0 |
| Stage I                          | T1    | N0    | M0 |
| Stage II                         | T2a   | N0    | M0 |
|                                  | T2b   | N0    | M0 |
| Stage III                        | T3a   | N0    | M0 |
|                                  | T3b   | N0    | M0 |
|                                  | T4a   | N0    | M0 |
| Stage IV                         | T4b   | N0    | M0 |
|                                  | Any T | N1-3  | M0 |
|                                  | Any T | Any N | M1 |

**Appendix 2: Suggested follow up schedule for nonmuscle invasive disease**

|              | 3 months                     | 6 months                     | 9 months   | 12 months   |
|--------------|------------------------------|------------------------------|--|---|
| Year 1 and 2 | Cystoscopy<br>Urine cytology | Cystoscopy<br>Urine cytology | Cystoscopy<br>Urine cytology                               | Cystoscopy<br>Urine cytology<br>Upper tract imaging |
| Year 3, 4, 5 | Cystoscopy<br>Urine cytology |                              | Cystoscopy<br>Urine cytology<br>Annual upper tract imaging |   |

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

**Appendix 3: Induction and maintenance schedule for adjuvant intravesical BCG treatment in nonmuscle invasive disease, 12 months for intermediate-risk, and 36 months for high-risk disease**

| Type of adjuvant intravesical therapy | Details of therapy adjuvant intravesical therapy  |
|---------------------------------------|---|
| Induction dose                        | 6 doses intravesical BCG, once every week   |
| Maintenance                           | 3 doses intravesical BCG, once every week at 3, 6, 12, 18, 24, 30, and 36 months from induction |

Hold treatment if traumatic catheterization, or persistent gross hematuria, or documented urinary tract infection, or severe local symptoms or fever suggesting BCG sepsis and treat patients accordingly. BCG: Bacillus Calmette-Guerin