Guidelines

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

Mubarak Al-mansour, Ahmad Saadeddin[1], Sultan Alkhateeb[2], Ashraf Abusamra[3], Danny Rabah[4,5], Mohammed Alotaibi[6], Esam Murshid[7], Abdullah Alsharm[8], Imran Ahmad[9], Khalid Alghamdi[10],Shouki Bazarbashi[11]

Princess Noura Oncology Center, [3]Section of Urology, Department of Surgery, King Khaled Hospital, King Abdulaziz Medical City-Jeddah, [9]Department of Oncology, King Faisal Specialist Hospital and Research Center, Jeddah, [1]Department of Oncology, [2]Department of Surgery, Division of Urology, King Abdulaziz Medical City, [4]Department of Surgery, Division of Urology, King Khalid University Hospital, College of Medicine, [5]Princess Al-Johora Al-Ibrahim Centre for Cancer Research (Uro-Oncology Research Chair), King Saud University, Riyadh, Kingdom of Saudi Arabia, [6]Department of Urology, [11]Section of Medical Oncology, King Faisal Specialist Hospital and Research Center, Departments of Oncology, [7]Prince Sultan Military Medical City, [8]King Fahad Medical City, [10]Division of Urology, Security Forces Hospital, Riyadh, Kingdom of Saudi Arabia

**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

**Address for correspondence:**
Prof. Danny Rabah, Department of Surgery, Division of Urology, King Khalid University Hospital, College of Medicine, Princess Al-Johora Al-Ibrahim Centre for Cancer Research (Uro-Oncology Research Chair), King Saud University, Riyadh, Kingdom of Saudi Arabia. E-mail: drabah@ksu.edu.sa
**Received:** 15.04.2014, **Accepted:** 15.04.2014

## MANUSCRIPT

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]

| Access this article online | |
|---|---|
| Quick Response Code: | Website: www.urologyannals.com |
| | DOI: 10.4103/0974-7796.140941 |

1. Staging:[2]
   Appendix I.
2. 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
   3.1.1. 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.
3.1.3.1.3. 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)
3.1.3.1.4.1. Incomplete initial resection.
3.1.3.1.4.2. 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. T1 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
4.1.1. 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-1).
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 1 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 1 year[14-16].(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 recommended.[17, 18]
4.1.3.3. Multiple high-grade Ta - T1:
4.1.3.3.1. It is recommended to repeat TURBT at 2-4 weeks, after initial resection.
4.1.3.3.2. Intravesical BCG induction plus maintenance for 1-3 years[15] (EL-1).
4.1.3.3.3. Immediate radical cystectomy can be considered for the highest risk patients (T1 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).

5.1.2. 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.

5.1.4. 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:

5.1.6.1. 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/m$^2$ at day 1 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 ± 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

6.1. Patients with normal renal function and fit for chemotherapy (PS 0-2), are treated with combination cisplatin and gemcitabine for a maximum of six cycles (EL-1).[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-1),[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 | | |
| 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 propia (inner half) | | |
| pT2b | Tumor invades deep muscularis propia (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 | | |
| Regional lymph nodes (N)* | | | |
| NX | Lymph nodes cannot be assessed | | |
| N0 | No lymph node metastasis | | |
| N1 | Single regional lymph node metastasis in the true pelvic (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 | No | 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 |

## REFERENCES

1. Saudi Cancer Registry Annual Report, 2010. Available from: http://www.scr.org.sa. Accessed 17 May 2014.
2. Sobin DH, Wittekind Ch. TNM Classification of Malignant Tumours. 6th ed. New York: Wiley-Liss; 2002. p. 199-202.
3. Eble JN, Sauter G, Epstein J, Sesterhenn I, editors. WHO Classification of Tumors of the Urinary System and Male Genital Organs. Lyon: IARCC Press; 2004. p. 29-34.
4. Mungan MU, Canda AE, Tuzel E, Yorukoglu K, Kirkali Z. Risk factors for mucosal prostatic urethral involvement in superficial transitional cell carcinoma of the bladder. Eur Urol 2005;48:760-3.
5. Kirkali Z, Chan T, Manoharan M, Algaba F, Busch C, Cheng L, *et al*. Bladder cancer: Epidemiology, staging and grading, and diagnosis. Urology 2005;66:4-34.
6. Matzkin H, Soloway MS, Hardeman S. Transitional cell carcinoma of the prostate. J Urol 1991;146:1207-12.
7. Grimm MO, Steinhoff C, Simon X, Spiegelhalder P, Ackermann R, Vogeli TA. Effect of routine repeat transurethral resection for superficial bladder cancer: A long-term observational study. J Urol 2003;170:433-7.
8. Divrik RT, Yildirim U, Zorlu F, Ozen H. The effect of repeat transurethral resection on recurrence and progression rates in patients with T1 tumors of the bladder who received intravesical mitomycin: A prospective, randomized clinical trial. J Urol 2006;175:1641-4.
9. Jahnson S, Wiklund F, Duchek M, Mestad O, Rintala E, Hellsten S, *et al*. Results of second-look resection after primary resection of T1 tumour of the urinary bladder. Scand J Urol Nephrol 2005;39:206-10.
10. Palou J, Rodríguez-Rubio F, Huguet J, Segarra J, Ribal MJ, Alcaraz A, *et al*. Multivariate analysis of clinical parameters of synchronous primary superficial bladder cancer and upper urinary tract tumor. J Urol 2005;174:859-61.
11. Millán-Rodríguez F, Chéchile-Toniolo G, Salvador-Bayarri J, Huguet-Pérez J, Vicente-Rodríguez J. Upper urinary tract tumors after primary superficial bladder tumors: Prognostic factors and risk groups. J Urol 2000;164:1183-7.
12. Sylvester RJ, van der Meijden AP, Oosterlinck W, Witjes JA, Bouffioux C, Denis L, *et al*. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: A combined analysis of 2596 patients from seven EORTC trials. Eur Urol 2006;49:466-5.
13. Sylvester RJ, Oosterlinck W, van der Meijden AP. A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: A meta-analysis of published results of randomized clinical trials. J Urol 2004;171:2186-90, quiz 2435.
14. Brausi M. Approaches to the management of non-muscle invasive bladder cancer (NMIBC): A review of current guidelines and best practice recommendations from the International bladder cancer group (IBCG). European Urology 2008;7:615-17.
15. Oddens J, Brausi M, Sylvester R, Bono A, van de Beek C, van Andel G, *et al*. Final results of an EORTC-GU cancers group randomized study of maintenance bacillus Calmette-Guérin in intermediate- and high-risk Ta, T1 papillary carcinoma of the urinary bladder: One-third dose versus full dose and 1 year versus 3 years of maintenance. Eur Urol 2013;63:462-72.
16. Sylvester RJ1, van der MEIJDEN AP, Lamm DL, Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: A meta-analysis of the published results of randomized clinical trials. J Urol. 2002;168:1964-70.
17. Böhle A, Bock PR. Intravesical bacille Calmette-Guérin versus mitomycin C in superficial bladder cancer: Formal meta-analysis of comparative studies on tumor progression. Urology 2004;63:682-6.
18. Van der Meijden AP, Sylvester R, Oosterlinck W, Solsona E, Boehle A, Lobel B, *et al*. EAU guidelines on the diagnosis and treatment of urothelial carcinoma *in situ*. Eur Urol 2005;48:363-71.
19. Babjuk M, Oosterlinck W, Sylvester R, Kaasinen E, Böhle A, Palou-Redorta J, *et al*. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder. Eur Urol 2008;54:303-14.
20. Nieder AM, Brausi M, Lamm D, O'Donnell M, Tomita K, Woo H, *et al*.

Management of stage T1 tumors of the bladder: International Consensus Panel. Urology 2005;66:108-25.
21. Persad R, Lammb D, Brausi M, Soloway M, Palou J, Bo¨hle A, *et al*. Current approaches to the management of non-muscle invasive bladder cancer: Comparison of current guidelines and recommendations. Eur Urol Suppl 2008;7:637-50.
22. Winquist E, Kirchner TS, Segal R, Chin J, Lukka H, Genitourinary cancer disease site group, cancer care ontario program in evidence-based care practice guidelines initiative. Neoadjuvant chemotherapy for transitional cell carcinoma of the bladder: A systematic review and meta-analysis. J Urol 2004;171:561-9.
23. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: Update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. Eur Urol 2005;48:202-5.
24. Advanced Bladder Cancer Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: A systematic review and meta-analysis. Lancet 2003;361:1927-34.
25. Ruggeri EM, Giannarelli D, Bria E, Carlini P, Felici A, Nelli F, *et al*. Adjuvant chemotherapy in muscle-invasive bladder carcinoma: A pooled analysis from phase III studies. Cancer 2006;106:783-8.
26. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: Bladder cancer including upper tract tumors and urothelial carcinoma of the prostate. Version 1; 2010.
27. von der Maase H, Sengelov L, Roberts JT, Ricci S, Dogliotti L, Oliver T, *et al*. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol 2005;23:4602-8.
28. De Santis M, Bellmunt J, Mead G, Kerst JM, Leahy M, Maroto P, *et al*. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer "unfit" for cisplatin-based chemotherapy: Phase II - results of EORTC study 30986. J Clin Oncol 2009;27:5634-9.
29. Bellmunt J, Théodore C, Demkov T, Komyakov B, Sengelov L, Daugaard G, *et al*. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. J Clin Oncol 2009;27:4454-61.
30. Joly F1, Houédé N, Noal S, Chevreau C, Priou F, Chinet-Charrot P, *et al*. Do patients with advanced urothelial carcinoma benefit from weekly paclitaxel chemotherapy? A GETUG phase II study. Clin Genitourin Cancer 2009;7:E28-33.

**How to cite this article:** Al-mansour M, Saadeddin A, Alkhateeb S, Abusamra A, Rabah D, Alotaibi M, *et al*. Saudi oncology society and Saudi urology association combined clinical management guidelines for urothelial urinary bladder cancer. Urol Ann 2014;6:273-7.

**Source of Support:** Nil, **Conflict of Interest:** None.