

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

Mubarak Al-mansour, Ahmad Saadeddin¹, Sultan Alkhateeb², Ashraf Abusamra³, Danny Rabah^{4,5}, Mohammed Alotaibi⁶, Esam Murshid⁷, Abdullah Alsharm⁸, Imran Ahmad⁹, Khalid Alghamdi¹⁰, Shouki Bazarbashi¹¹

Princess Noura Oncology Center, ³Section of Urology, Department of Surgery, King Khaled Hospital, King Abdulaziz Medical City-Jeddah,

⁹Department of Oncology, King Faisal Specialist Hospital and Research Center, Jeddah, ¹Department of Oncology, ²Department of Surgery, Division of Urology, King Abdulaziz Medical City, ⁴Department of Surgery, Division of Urology, King Khalid University Hospital, College of Medicine, ⁵Princess Al-Johora Al-Ibrahim Centre for Cancer Research (Uro-Oncology Research Chair), King Saud University, Riyadh, Kingdom of Saudi Arabia, ⁶Department of Urology, ¹¹Section of Medical Oncology, King Faisal Specialist Hospital and Research Center, Departments of Oncology, ⁷Prince Sultan Military Medical City, ⁸King Fahad Medical City, ¹⁰Division 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 presented. They are categorized according to 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 on muscle 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-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 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-I).
 - 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-I).
 - 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

- 275

- 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		
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, Chéchele-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, Bouffoux 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 RJ, 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, Böhle 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? AGETUG 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.