

Bladder Cancer: Review Questions

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QUESTIONS

Choose the single best answer for each question.

1. All of the following regarding the epidemiology of bladder cancer in the United States are true EXCEPT

- (A) Bladder cancer is the most common malignancy affecting the urinary tract
- (B) Non-Hispanic whites are at highest risk
- (C) Smoking is the most important risk factor
- (D) There is no gender preference
- (E) Transitional cell carcinoma (TCC) is the most common type

2. A 60-year-old man with newly diagnosed high-grade superficial TCC of the bladder presents for a second opinion. One week ago, the patient underwent transurethral resection of the bladder tumor (TURBT) with multiple random biopsies, which revealed superficial TCC associated with several areas of carcinoma in situ, invasion into lamina propria but not into the muscle, and vascular invasion. He was told by another physician that his only option is a radical cystectomy. He would like to preserve his bladder but is worried about the possible spread of the cancer. What should be recommended to this patient?

- (A) Combined chemoradiotherapy
- (B) Radical cystectomy
- (C) Repeat TURBT and close surveillance
- (D) Repeat TURBT followed by intravesical bacillus Calmette-Guérin (BCG) therapy

3. A 75-year-old man presents to his oncologist 2 weeks after undergoing a cystoscopy and TURBT. Pathology revealed a muscle-invasive TCC. The patient has diabetes mellitus and hypertension, which have been well controlled with diet and lisinopril, respectively. He does not take any other medications. Physical examination is unremarkable. An echocardiogram performed 6 months ago revealed an ejection fraction of 65% and no significant wall motion or valve abnormalities. Computed tomography (CT) of the chest, abdomen, and pelvis revealed no evidence of metastatic disease. What is the next step in this patient's management?

- (A) Chemotherapy with gemcitabine and cisplatin (GC) alone
- (B) Neoadjuvant chemotherapy with methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC), followed by radical cystoprostatectomy and lymphadenectomy
- (C) Radiotherapy to the bladder and pelvic lymph nodes
- (D) Radical cystoprostatectomy and lymphadenectomy

4. A 61-year-old woman presents to the emergency department with a 3-day history of abdominal pain. The patient has no significant past medical history and takes no medications. She appears ill and is in acute distress. The patient is tachycardic with a normal temperature and blood pressure. The abdomen is mildly distended, with normal bowel sounds and a palpable mass in the suprapubic region that is tender to palpation. The remainder of the physical examination is unremarkable. CT scan of the abdomen and pelvis reveals an abnormal bladder with a large area of enhancement, wall thickening, and cystic changes; a small amount of fluid seen

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anterior to the bladder; and pathologically enlarged lymph nodes in the inguinal region bilaterally. The patient undergoes abdominal surgery, which reveals a 12-cm necrotic mass involving the bladder, uterus, fallopian tubes, ovaries, and vagina, which extends to the anterior pelvic wall. The surgeon describes spillage of tumor cells into the abdominal/pelvic cavity. Pathologic testing reveals a high-grade TCC with lymphovascular and perineural invasion with extension into the other organs. Two lymph nodes were resected and are found to be free of metastatic carcinoma. Four weeks later, the patient presents to discuss further therapy. Other than experiencing some abdominal discomfort, she has been doing well. CT scan of the chest, abdomen, and pelvis reveal no evidence of metastatic disease. What is the next step in the management of this patient?

- (A) Adjuvant chemotherapy
- (B) Close follow-up without further therapy
- (C) Concurrent chemoradiotherapy
- (D) Positron emission tomography (PET) scan to rule out metastatic disease

5. A 49-year-old man presents with intermittent suprapubic pain and hematuria of 2 weeks' duration. Past medical history includes hepatitis C, cocaine use, and gonorrhea treated 10 years ago. He takes no medications. Physical examination is unremarkable except for suprapubic tenderness to palpation. A complete blood count and comprehensive metabolic profile are normal. Urinalysis reveals 10 to 12 red blood cells and no leukocytes. Cystoscopy shows a large heterogeneous mass in the left posterior portion of the bladder. Biopsy of the mass reveals a poorly differentiated small cell carcinoma infiltrating into the muscle, and 1 random biopsy demonstrates TCC with no invasion into the lamina propria. CT of the chest, abdomen, and pelvis shows a fungating mass in the bladder with involvement into the extravesical fat and multiple pathologically enlarged lymph nodes scattered throughout the pelvis but no evidence of distant metastatic disease. What is the next step in the management of this patient?

- (A) Chemotherapy with cisplatin and etoposide
- (B) Chemotherapy with MVAC
- (C) PET scan
- (D) Radical cystoprostatectomy with lymph node dissection
- (E) Radiotherapy

ANSWERS AND EXPLANATIONS

1. (D) There is no gender preference. In the United

States, the male to female incidence of bladder cancer is almost 4:1.¹ The male predominance appears to be related to the greater prevalence of smoking and exposure to occupational carcinogens in men. Bladder cancer is the most common malignancy affecting the urinary system, with approximately 67,000 new cases of bladder cancer and 13,750 deaths from the disease each year in the United States. Non-Hispanic white men are at highest risk for developing bladder cancer, followed by African Americans and Latinos, Asians, and American Indians.² A possible explanation for these disparities is variations in acetylator phenotypes in different racial/ethnic groups. More than 90% of bladder carcinomas are TCCs derived from the uroepithelium; approximately 6% to 8% are squamous cell carcinomas, 2% are adenocarcinomas, and 1% are small cell carcinoma.³ Although the relative risk of developing bladder cancer is higher in patients exposed to occupational toxins as compared with those who smoke, smoking is more prevalent, making it the single most important risk factor for the development of urothelial tumors.¹

2. (D) Repeat TURBT followed by intravesical BCG therapy. Although this patient has superficial bladder cancer, he also has high-risk features, including associated high-grade carcinoma in situ and vascular invasion, which increases his chance of relapse after TURBT alone.⁴ When administered with TURBT, intravesical therapy has been shown to increase 10-year progression-free survival and disease-specific survival by 25%, with a 5-year survival rate similar to that achieved with immediate radical cystectomy; these results support use of TURBT and BCG rather than cystectomy as initial therapy for these patients.^{5,6} TURBT alone has been reported to be sufficient for carefully selected patients without high-risk features and in the absence of a palpable mass or hydronephrosis. Radiotherapy does not reduce or delay progression or death from superficial bladder cancer.⁷

3. (B) Neoadjuvant chemotherapy with MVAC, followed by radical cystoprostatectomy and lymphadenectomy. Two intergroup trials and a meta-analysis have shifted the treatment for muscle-invasive bladder TCC towards the use of neoadjuvant chemotherapy, with between 13% and 24% reduction in mortality.⁸⁻¹⁰ Compared with local treatment alone, neoadjuvant cisplatin-based chemotherapy was associated with a 14% relative decrease in the risk of death and a 5% absolute survival benefit at 5 years.

Many oncologists substitute standard-dose MVAC for 12 weeks (3 cycles) in muscle-invasive TCC of the urothelium with either GC for 12 weeks or high-dose MVAC with granulocyte-colony stimulating factor for 4 cycles (8 weeks). This recommendation is based on the results of 2 randomized controlled studies performed in patients with metastatic disease, which showed that GC and high-dose MVAC are equally effective but less toxic than standard-dose MVAC.^{11,12}

4. (A) Adjuvant chemotherapy. Adjuvant chemotherapy with CISCA (cisplatin, cyclophosphamide, doxorubicin), MVAC, or MVEC (methotrexate, vinblastine, cisplatin, epirubicin) has been shown to improve the outcome of patients with TCC of the bladder, although the number of patients enrolled in these studies was small, and the methodology has been called into question.^{13,14} In addition, the benefits of neoadjuvant chemotherapy have been well documented.⁸⁻¹⁰ Therefore, most genitourinary oncologists recommend adjuvant therapy in patients with a poor prognosis who have not undergone chemotherapy prior to surgery. PET is not indicated for staging of bladder cancer.

5. (A) Chemotherapy with cisplatin and etoposide. There is no consensus on the standard treatment approach for small cell carcinoma of the bladder due to the rarity of the disease and lack of prospective clinical trials. Patients are treated similarly to small cell malignancies from other primary sites (eg, lung). Although there have been some long-term survival observations of superficial small cell bladder cancer treated with transurethral resection and intravesical bCG, surgery alone is not recommended for more advanced stages. In a retrospective analysis of 64 cases of small cell carcinoma of the bladder, investigators found no survival difference between patients who had cystectomy and those who did not.¹⁵ In a retrospective review, 5-year disease-free survival was 36% for patients treated with surgery alone and 78% for patients treated with chemotherapy followed by surgery. There was a higher complete pathologic re-

sponse for patients receiving cisplatin and etoposide versus MVAC chemotherapy.¹⁶ PET scan has not yet been proven to add further information on bladder cancer staging or restaging; thus, it cannot be recommended at this time.

REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2007. *CA Cancer J Clin* 2007;57:43-66.
2. Howe HL, Wu X, Ries LA, et al. Annual report to the nation on the status of cancer, 1975-2003, featuring cancer among U.S. Hispanic/Latino populations. *Cancer* 2006;107:1711-42.
3. Mostofi FK, Davis CJ, Sesterhenn IA. Pathology of tumors of the urinary tract. In: Skinner DG, Lieskovsky G, editors. *Diagnosis and management of genitourinary cancer*. Philadelphia: WB Saunders; 1988:83-117.
4. Herr HW. Tumor progression and survival in patients with T1G3 bladder tumors: 15-year outcome. *Br J Urol* 1997;80:762-5.
5. Herr HW, Schwalb DM, Zhang ZF, et al. Intravesical bacillus Calmette-Guérin therapy prevents tumor progression and death from superficial bladder cancer: ten-year follow-up of a prospective randomized trial. *J Clin Oncol* 1995; 13:1404-8.
6. Brake M, Loertzer H, Horsch R, Keller H. Long-term results of intravesical bacillus Calmette-Guérin therapy for stage T1 superficial bladder cancer. *Urology* 2000;55:673-8.
7. Harland SJ; UK NCRI Bladder Clinical Studies Group. A randomised trial of radical radiotherapy in pT1G3 NXM0 bladder cancer (MRC BS06) [abstract]. *J Clin Oncol* 2005;23(16 Suppl):4505a.
8. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. International Collaboration of Trialists [published erratum appears in *Lancet* 1999; 354:1650]. *Lancet* 1999;354:533-40.
9. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer [published erratum appears in *N Engl J Med* 2003;349:1880]. *N Engl J Med* 2003;349:859-66.
10. Advanced Bladder Cancer Overview Collaboration. Neoadjuvant chemotherapy for invasive bladder cancer. *Cochrane Database Syst Rev* 2005;(2): CD005246.
11. von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol* 2000;18:3068-77.
12. Sternberg CN, de Mulder P, Schornagel JH, et al; EORTC Genito-Urinary Cancer Group. Seven-year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumors. *Eur J Cancer* 2006;42:50-4.
13. Skinner DG, Daniels JR, Russell CA, et al. The role of adjuvant chemotherapy following cystectomy for invasive bladder cancer: a prospective comparative trial. *J Urol* 1991;145:459-64.
14. Stöckle M, Meyenburg W, Wellek S, et al. Advanced bladder cancer (stages pT3b, pT4a, pN1 and pN2): improved survival after radical cystectomy and 3 adjuvant cycles of chemotherapy. Results of a controlled prospective study. *J Urol* 1992;148:302-6.
15. Cheng L, Pan X, Yang XJ, et al. Small cell carcinoma of the urinary bladder: a clinicopathologic analysis of 64 patients. *Cancer* 2004;101:957-62.
16. Siefker-Radtke AO, Dinney CP, Abrahams NA, et al. Evidence supporting preoperative chemotherapy for small cell carcinoma of the bladder: a retrospective review of M.D. Anderson Cancer experience. *J Urol* 2004;172:481-4.

ONCOLOGY

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