Bladder Cancer Treatment

Treatment - Health professionals

General Information About Bladder Cancer

Incidence and Mortality

Estimated new cases and deaths from bladder cancer in the United States in 2012:[1]

- New cases: 73,510.
- Deaths: 14,880.

Prognosis

Approximately 70% to 80% of patients with newly diagnosed bladder cancer will present with superficial bladder tumors (i.e., stage Ta, Tis, or T1). Those who do present with superficial, noninvasive bladder cancer can often be cured, and those with deeply invasive disease can sometimes be cured by surgery, radiation therapy, or a combination of modalities that include chemotherapy. Studies have demonstrated that some patients with distant metastases have achieved long-term complete response following treatment with combination chemotherapy regimens. There are clinical trials suitable for patients with all stages of bladder cancer; whenever possible, patients should be included in clinical trials designed to improve on standard therapy.

The major prognostic factors in carcinoma of the bladder are the depth of invasion into the bladder wall and the degree of differentiation of the tumor. Most superficial tumors are well differentiated. Patients in whom superficial tumors are less differentiated, large, multiple, or associated with carcinoma *in situ* (Tis) in other areas of the bladder mucosa are at greatest risk for recurrence and the development of invasive cancer. Such patients may be considered to have the entire urothelial surface at risk for the development of cancer. Tis may exist for variable durations.

Adverse prognostic features associated with a greater risk of disease progression include the presence of multiple aneuploid cell lines, nuclear p53 overexpression, and expression of the Lewis-x blood group antigen.[2, 3, 4, 5] Patients with Tis who have a complete response to bacillus Calmette-Guérin have approximately a 20% risk of disease progression at 5 years; patients with incomplete response have approximately a 95% risk of disease progression.[2] Several treatment methods (i.e., transurethral surgery, intravesical medications, and cystectomy) have been used in the management of patients with superficial tumors, and each method can be associated with 5-year survival in 55% to 80% of patients treated.[2, 3, 6]

Invasive tumors that are confined to the bladder muscle on pathologic staging after radical cystectomy are associated with approximately a 75% 5-year progression-free survival rate. Patients with more deeply invasive tumors, which are also usually less well differentiated, and those with lymphovascular invasion experience 5-year survival rates of 30% to 50% following radical cystectomy.[7] When the patient presents with locally extensive tumor that invades pelvic viscera or with metastases to lymph nodes or distant sites, 5-year survival is uncommon, but considerable symptomatic palliation can still be achieved.[8]

Expression of the tumor suppressor gene *p53* also has been associated with an adverse prognosis for patients with invasive bladder cancer. A retrospective study of 243 patients treated by radical cystectomy found that the presence of nuclear p53

was an independent predictor for recurrence among patients with stage T1, T2, or T3 tumors.[9] Another retrospective study showed p53 expression to be of prognostic value when considered with stage or labeling index.[10]

Related Summaries

Other PDQ summaries containing information related to bladder cancer include the following:

- Bladder and Other Urothelial Cancers Screening
- Unusual Cancers of Childhood (bladder cancer in children)

References:

1. American Cancer Society.: Cancer Facts and Figures 2012. Atlanta, Ga: American Cancer Society, 2012. Available online. Last accessed May 25, 2012.

2. Hudson MA, Herr HW: Carcinoma in situ of the bladder. J Urol 153 (3 Pt 1): 564-72, 1995.

3. Torti FM, Lum BL: The biology and treatment of superficial bladder cancer. J Clin Oncol 2 (5): 505-31, 1984.

4. Lacombe L, Dalbagni G, Zhang ZF, et al.: Overexpression of p53 protein in a high-risk population of patients with superficial bladder cancer before and after bacillus Calmette-Guérin therapy: correlation to clinical outcome. J Clin Oncol 14 (10): 2646-52, 1996.

5. Stein JP, Grossfeld GD, Ginsberg DA, et al.: Prognostic markers in bladder cancer: a contemporary review of the literature. J Urol 160 (3 Pt 1): 645-59, 1998.

6. Witjes JA, Caris CT, Mungan NA, et al.: Results of a randomized phase III trial of sequential intravesical therapy with mitomycin C and bacillus Calmette-Guerin versus mitomycin C alone in patients with superficial bladder cancer. J Urol 160 (5): 1668-71; discussion 1671-2, 1998.

7. Quek ML, Stein JP, Nichols PW, et al.: Prognostic significance of lymphovascular invasion of bladder cancer treated with radical cystectomy. J Urol 174 (1): 103-6, 2005.

8. Thrasher JB, Crawford ED: Current management of invasive and metastatic transitional cell carcinoma of the bladder. J Urol 149 (5): 957-72, 1993.

9. Esrig D, Elmajian D, Groshen S, et al.: Accumulation of nuclear p53 and tumor progression in bladder cancer. N Engl J Med 331 (19): 1259-64, 1994.

10. Lipponen PK: Over-expression of p53 nuclear oncoprotein in transitional-cell bladder cancer and its prognostic value. Int J Cancer 53 (3): 365-70, 1993.

Cellular Classification of Bladder Cancer

More than 90% of bladder carcinomas are transitional cell carcinomas derived from the uroepithelium. About 6% to 8% are squamous cell carcinomas, and 2% are adenocarcinomas.[1] Adenocarcinomas may be either of urachal origin or of nonurachal origin; the latter type is generally thought to arise from metaplasia of chronically irritated transitional epithelium.[2] Pathologic grade, which is based on cellular atypia, nuclear abnormalities, and the number of mitotic figures is of great prognostic importance.

References:

1. Mostofi FK, Davis CJ, Sesterhenn IA: Pathology of tumors of the urinary tract. In: Skinner DG, Lieskovsky G, eds.: Diagnosis and Management of Genitourinary Cancer. Philadelphia, Pa: WB Saunders, 1988, pp 83-117.

2. Wilson TG, Pritchett TR, Lieskovsky G, et al.: Primary adenocarcinoma of bladder. Urology 38 (3): 223-6, 1991.

Stage Information for Bladder Cancer

Note: This Stage Information section has been updated to include information from the seventh edition (2010) of the

American Joint Committee on Cancer's *AJCC Cancer Staging Manual*. The PDQ Adult Treatment Editorial Board, which is responsible for maintaining this summary, is currently reviewing the new staging categories to determine whether additional changes need to be made to other parts of the summary. Any necessary changes will be made as soon as possible.

The clinical staging of carcinoma of the bladder is determined by the depth of invasion of the bladder wall by the tumor. This determination requires a cystoscopic examination that includes a biopsy, and examination under anesthesia to assess the size and mobility of palpable masses, the degree of induration of the bladder wall, and the presence of extravesical extension or invasion of adjacent organs. Clinical staging, even when computed tomographic and/or magnetic resonance imaging scans and other imaging modalities are used, often underestimates the extent of tumor, particularly in cancers that are less differentiated and more deeply invasive.[1, 2, 3]

Definitions of TNM

The American Joint Committee on Cancer has designated staging by TNM classification to define bladder cancer.[4]

Table 1. Primary Tumor (T)[a]

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.

[a]*Reprinted with permission from AJCC: Urinary bladder. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 497–505.*

Table 2. Regional Lymph Nodes (N)[a,b]

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 metastases in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node).
N3	Lymph node metastases to the common iliac lymph nodes.

[a]*Reprinted with permission from AJCC: Urinary bladder. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 497–505.*

[b]*Regional lymph nodes include both primary and secondary drainage regions. All other nodes above the aortic bifurcation are considered distant lymph nodes.*

Table 3. Distant Metastasis (M)[a]

M0	No distant metastasis.
M1	Distant metastasis.

[a]*Reprinted with permission from AJCC: Urinary bladder. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 497–505.*

Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 497–505.

Table 4. Anatomic Stage/Prognostic Groups[a]

Stage	T	N	M
0a	Ta	N0	M0
0is	Tis	N0	M0
I	T1	N0	M0
II	T2a	N0	M0
	T2b	N0	M0
III	T3a	N0	M0
	T3b	N0	M0
	T4a	N0	M0
IV	T4b	N0	M0
	Any T	N1–3	M0
	Any T	Any N	M1

[a]*Reprinted with permission from AJCC: Urinary bladder. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 497–505.*

An older, less frequently used staging system was derived by comparing clinical estimates of stage with the pathologic stage of radical cystectomy specimens.[2, 3] To better ensure uniform staging and reporting of clinical results, the use of the modern TNM classification described above is recommended.

References:

1. Consensus conference. Magnetic resonance imaging. JAMA 259 (14): 2132-8, 1988.
2. Marshall VF: The relationship of the preoperative estimate to the pathologic demonstration of the extent of vesical neoplasms. J Urol 68(4): 714-723, 1952.
3. Skinner DG: Current state of classification and staging of bladder cancer. Cancer Res 37 (8 Pt 2): 2838-42, 1977.
4. Urinary bladder. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 497-505.

Treatment Option Overview

Prolonged survival in most patients with superficial cancers is achieved by transurethral resection (TUR) with or without intravesical chemotherapy. Cure is not possible for the majority of patients with deeply invasive tumors and for most patients with regional or distant metastases. In North America, the standard treatment of patients with invasive bladder cancers is radical cystectomy and urinary diversion. Other treatment approaches include TUR and segmental resection with or without radiation therapy, combined chemotherapy-radiation therapy, or either followed by salvage cystectomy, when needed, for local failure.

Many newly diagnosed bladder cancer patients are candidates for participation in a clinical trial. Clinical trials include studies of chemoprevention of superficial disease, adjuvant chemotherapy for advanced local or regional disease, preservation of bladder function with chemotherapy-radiation therapy, and development of more effective systemic therapy and methods of palliation for metastatic tumors.[1, 2, 3, 4, 5, 6]

Reconstructive techniques that fashion low-pressure storage reservoirs from the reconfigured small and large bowel eliminate the need for external drainage devices and, in some male patients, allow voiding per urethra. These techniques are designed to improve the quality of life for patients who require cystectomy.[7]

References:

1. Thrasher JB, Crawford ED: Current management of invasive and metastatic transitional cell carcinoma of the bladder. J Urol 149 (5): 957-72, 1993.

2. Housset M, Maulard C, Chretien Y, et al.: Combined radiation and chemotherapy for invasive transitional-cell carcinoma of the bladder: a prospective study. J Clin Oncol 11 (11): 2150-7, 1993.

3. Kachnic LA, Kaufman DS, Heney NM, et al.: Bladder preservation by combined modality therapy for invasive bladder cancer. J Clin Oncol 15 (3): 1022-9, 1997.

4. Lamm DL, Riggs DR, Shriver JS, et al.: Megadose vitamins in bladder cancer: a double-blind clinical trial. J Urol 151 (1): 21-6, 1994.

5. Raghavan D, Huben R: Management of bladder cancer. Curr Probl Cancer 19 (1): 1-64, 1995 Jan-Feb.

6. Sauer R, Birkenhake S, Kühn R, et al.: Efficacy of radiochemotherapy with platin derivatives compared to radiotherapy alone in organ-sparing treatment of bladder cancer. Int J Radiat Oncol Biol Phys 40 (1): 121-7, 1998.

7. Hautmann RE, Miller K, Steiner U, et al.: The ileal neobladder: 6 years of experience with more than 200 patients. J Urol 150 (1): 40-5, 1993.

Stage 0 Bladder Cancer

Note: Some citations in the text of this section are followed by a level of evidence. The PDQ editorial boards use a formal ranking system to help the reader judge the strength of evidence linked to the reported results of a therapeutic strategy. (Refer to the PDQ summary on Levels of Evidence for more information.)

Stage 0 bladder cancer is defined by the following TNM classifications:

- Ta, N0, M0
- Tis, N0, M0

Patients with stage 0 bladder tumors can be cured by a variety of treatments, even though the tendency for new tumor formation is high. In a series of patients with Ta or T1 tumors, who were followed for a minimum of 20 years or until death, the risk of bladder cancer recurrence following initial resection was 80%.[1] Patients at greatest risk of recurrent disease are those whose tumors are large, poorly differentiated, multiple, or associated with nuclear p53 overexpression. In addition, patients with carcinoma *in situ* (Tis) or dysplasia of grossly uninvolved bladder epithelium are at greater risk of recurrence and progression.[1, 2, 3]

Transurethral resection (TUR) and fulguration are the most common and conservative forms of management. Careful surveillance of subsequent bladder tumor progression is important. One retrospective series addressed the value of performing a second TUR within 2 to 6 weeks of the first.[4][Level of evidence: 3iiDiv] A second TUR performed on 38 patients with Tis or Ta disease found that nine patients (24%) had lamina propria invasion (T1) and three patients (8%) had muscle invasion (T2). Such information may change the definitive management options in these individuals.

Patients who require more aggressive forms of treatment are those with extensive multifocal recurrent disease and/or other unfavorable prognostic features. Segmental cystectomy is applicable to only a small minority of patients because of the tendency of bladder carcinoma to involve multiple regions of the bladder mucosa and to occur in areas that cannot be segmentally resected.

Intravesical therapy with thiotepa, mitomycin, doxorubicin, or bacillus Calmette-Guérin (BCG) is most often used in patients with multiple tumors or recurrent tumors or as a prophylactic measure in high-risk patients after TUR. Administration of intravesical BCG plus subcutaneous BCG following TUR was compared with TUR alone in patients with Ta and T1 lesions. Treatment with BCG delayed progression to muscle-invasive and/or metastatic disease, improved bladder preservation, and decreased the risk of death from bladder cancer.[5, 6]

A randomized study of patients with superficial bladder cancer also reported a decrease in tumor recurrence in patients given intravesical and percutaneous BCG compared with controls.[7] Two nonconsecutive 6-week treatment courses with BCG may be necessary to obtain optimal response.[8] Patients with a T1 tumor at the 3-month evaluation after a 6-week course of BCG and patients with Tis that persists after a second 6-week BCG course have a high likelihood of developing muscle-invasive disease and should be considered for cystectomy.[8, 9, 10]

Another randomized study that compared intravesical and subcutaneous BCG with intravesical doxorubicin showed better response rates and freedom from recurrence with the BCG regimen for recurrent papillary tumors as well as for Tis.[11] A randomized trial from the Swedish-Norwegian Bladder Cancer Group compared 2 years of intravesical treatment with mitomycin C versus BCG. No difference was observed in tumor progression or overall survival (OS) between the two arms at

mitomycin C versus BCG. No difference was observed in tumor progression or overall survival (OS) between the two arms at 5 years.[12][Level of evidence: 1iiDii] Although BCG may not prolong OS for Tis disease, it appears to afford complete response rates of about 70%, thereby decreasing the need for salvage cystectomy.[13]

Studies show that intravesical BCG delays tumor recurrence and tumor progression.[6, 14] Preliminary results from a prospective randomized trial suggest that maintenance BCG, when given to patients who are disease-free after a 6-week induction course, improves survival.[15] One study that compared mitomycin with interferon-α-2b showed an improved outcome with mitomycin, even though interferon was better tolerated.[16]

Standard treatment options:

1. TUR with fulguration.[17]
2. TUR with fulguration followed by intravesical BCG. BCG is the treatment of choice for Tis.[5, 7, 9, 13, 14]
3. TUR with fulguration followed by intravesical chemotherapy.[2, 11, 17]
4. Segmental cystectomy (rarely indicated).[17]
5. Radical cystectomy in selected patients with extensive or refractory superficial tumor.[17, 18]

Treatment options under clinical evaluation:

1. Photodynamic therapy after intravenous hematoporphyrin derivative appears capable of completely eradicating tumors in 50% of the treated patients who were in a small study with minimal follow-up.[19] Further evaluation of this technique is needed.
2. Intravesical interferon-alpha-2a has shown activity against papillary tumors and Tis both as primary treatment and as secondary treatment after failure of other intravesical agents.[20]
3. Use of chemoprevention agents after treatment to prevent recurrence.[21]

References:

1. Holmäng S, Hedelin H, Anderström C, et al.: The relationship among multiple recurrences, progression and prognosis of patients with stages Ta and T1 transitional cell cancer of the bladder followed for at least 20 years. J Urol 153 (6): 1823-6; discussion 1826-7, 1995.

2. Igawa M, Urakami S, Shirakawa H, et al.: Intravesical instillation of epirubicin: effect on tumour recurrence in patients with dysplastic epithelium after transurethral resection of superficial bladder tumour. Br J Urol 77 (3): 358-62, 1996.

3. Lacombe L, Dalbagni G, Zhang ZF, et al.: Overexpression of p53 protein in a high-risk population of patients with superficial bladder cancer before and after bacillus Calmette-Guérin therapy: correlation to clinical outcome. J Clin Oncol 14 (10): 2646-52, 1996.

4. Herr HW: The value of a second transurethral resection in evaluating patients with bladder tumors. J Urol 162 (1): 74-6, 1999.

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 13 (6): 1404-8, 1995.

6. Lamm DL, Griffith JG: Intravesical therapy: does it affect the natural history of superficial bladder cancer? Semin Urol 10 (1): 39-44, 1992.

7. Sarosdy MF, Lamm DL: Long-term results of intravesical bacillus Calmette-Guerin therapy for superficial bladder cancer. J Urol 142 (3): 719-22, 1989.

8. Coplen DE, Marcus MD, Myers JA, et al.: Long-term followup of patients treated with 1 or 2, 6-week courses of intravesical bacillus Calmette-Guerin: analysis of possible predictors of response free of tumor. J Urol 144 (3): 652-7, 1990.

9. Catalona WJ, Hudson MA, Gillen DP, et al.: Risks and benefits of repeated courses of intravesical bacillus Calmette-Guerin therapy for superficial bladder cancer. J Urol 137 (2): 220-4, 1987.

10. Herr HW: Progression of stage T1 bladder tumors after intravesical bacillus Calmette-Guerin. J Urol 145 (1): 40-3; discussion 43-4, 1991.

11. Lamm DL, Blumenstein BA, Crawford ED, et al.: A randomized trial of intravesical doxorubicin and immunotherapy with bacille Calmette-Guérin for transitional-cell carcinoma of the bladder. N Engl J Med 325 (17): 1205-9, 1991.

12. Malmström PU, Wijkström H, Lundholm C, et al.: 5-year followup of a randomized prospective study comparing mitomycin C and bacillus Calmette-Guerin in patients with superficial bladder carcinoma. Swedish-Norwegian Bladder Cancer Study Group. J Urol 161 (4): 1124-7, 1999.

13. De Jager R, Guinan P, Lamm D, et al.: Long-term complete remission in bladder carcinoma in situ with intravesical TICE bacillus Calmette Guerin. Overview analysis of six phase II clinical trials. Urology 38 (6): 507-13, 1991.

14. Herr HW, Wartinger DD, Fair WR, et al.: Bacillus Calmette-Guerin therapy for superficial bladder cancer: a 10-year followup. J Urol 147 (4): 1020-3, 1992.

15. Lamm DL, Crawford ED, Blumenstein B, et al.: Maintenance BCG immunotherapy of superficial bladder cancer: a randomized prospective Southwest Oncology Group study. [Abstract] Proceedings of the American Society of Clinical Oncology 11: A-627, 203, 1992.

16. Boccardo F, Cannata D, Rubagotti A, et al.: Prophylaxis of superficial bladder cancer with mitomycin or interferon alfa-2b: results of a multicentric Italian study. J Clin Oncol 12 (1): 7-13, 1994.

17. Soloway MS: The management of superficial bladder cancer. In: Javadpour N, ed.: Principles and Management of Urologic Cancer. 2nd ed. Baltimore, Md: Williams and Wilkins, 1983, pp 446-467.

18. Amling CL, Thrasher JB, Frazier HA, et al.: Radical cystectomy for stages Ta, Tis and T1 transitional cell carcinoma of the bladder. J Urol 151 (1): 31-5; discussion 35-6, 1994.

19. Prout GR Jr, Lin CW, Benson R Jr, et al.: Photodynamic therapy with hematoporphyrin derivative in the treatment of superficial transitional-cell carcinoma of the bladder. N Engl J Med 317 (20): 1251-5, 1987.

20. Torti FM, Shortliffe LD, Williams RD, et al.: Alpha-interferon in superficial bladder cancer: a Northern California Oncology Group Study. J Clin Oncol 6 (3): 476-83, 1988.

21. Lamm DL, Riggs DR, Shriver JS, et al.: Megadose vitamins in bladder cancer: a double-blind clinical trial. J Urol 151 (1): 21-6, 1994.

Stage I Bladder Cancer

Note: Some citations in the text of this section are followed by a level of evidence. The PDQ editorial boards use a formal ranking system to help the reader judge the strength of evidence linked to the reported results of a therapeutic strategy. (Refer to the PDQ summary on Levels of Evidence for more information.)

Stage I bladder cancer is defined by the following TNM classification:

- T1, N0, M0

Patients with stage I bladder tumors can be cured by a variety of treatments, even though the tendency for new tumor formation is high. In a series of patients with Ta or T1 tumors who were followed for a minimum of 20 years or until death, the risk of bladder recurrence following initial resection was 80%.[1] Patients at greatest risk of recurrent disease are those whose tumors are large, poorly differentiated, multiple, or associated with nuclear p53 overexpression.[2] In addition, patients with carcinoma *in situ* (Tis) or dysplasia of grossly uninvolved bladder epithelium are at greater risk of recurrence and progression.[1, 3, 4]

Transurethral resection (TUR) and fulguration are the most common and conservative forms of management. Careful surveillance of subsequent bladder tumor progression is important. One retrospective series addressed the value of performing a second TUR within 2 to 6 weeks of the first.[5][Level of evidence: 3iiDiv] A second TUR performed on 58 patients with T1 disease found that 14 patients (24%) had residual (T1) disease and 16 patients (28%) had muscle invasion (T2). Such information may change the definitive management options in these individuals.

Patients who require more aggressive forms of treatment are those with extensive multifocal recurrent disease and/or other unfavorable prognostic features. Segmental cystectomy is applicable to only a small minority of patients because of the tendency of bladder carcinoma to involve multiple regions of the bladder mucosa and to occur in areas that cannot be segmentally resected.

Intravesical therapy with thiotepa, mitomycin, doxorubicin, or bacillus Calmette Guérin (BCG) is most often used in patients with multiple tumors or recurrent tumors or as a prophylactic measure in high-risk patients after TUR. Administration of

with multiple tumors or recurrent tumors or as a prophylactic measure in high-risk patients after TUR. Administration of intravesical BCG combined with subcutaneous BCG following TUR was compared with TUR alone in patients with Ta and T1 lesions. Treatment with BCG delayed progression to muscle-invasive and/or metastatic disease, improved bladder preservation, and decreased the risk of death from bladder cancer.[6, 7]

A randomized study of patients with superficial bladder cancer also reported a decrease in tumor recurrence in patients given intravesical and percutaneous BCG compared with controls.[8] Two nonconsecutive 6-week courses with BCG may be necessary to obtain optimal response.[9] Patients with a T1 tumor at the 3-month evaluation after a 6-week course of BCG and patients with Tis that persists after a second 6-week BCG course have a high likelihood of developing muscle-invasive disease and should be considered for cystectomy.[9, 10, 11] A randomized study that compared intravesical and subcutaneous BCG to intravesical doxorubicin showed better response rates and freedom from recurrence with the BCG regimen for recurrent papillary tumors as well as for Tis.[12] Preliminary results of one study have shown a possible survival benefit with maintenance BCG after a 6-week induction course.[13] Another study that compared alternating mitomycin and BCG with BCG alone, both given for 24 months, found that the efficacy was equal, but that the side effects of the combined regimen were slightly less.[14][Level of evidence: 1iiDiii] A similar trial comparing sequential mitomycin and BCG to mitomycin alone also found no major differences in toxic effects or efficacy.[15][Level of evidence: 1iiDiii] A randomized trial from the Swedish-Norwegian Bladder Cancer Group compared 2 years of intravesical treatment with mitomycin C versus BCG for patients at high risk for recurrence or progression. At 5 years, a significant improvement was noted in disease-free survival with BCG ($P = .04$); however, no difference was observed in tumor progression or overall survival between the two arms.[16]

Standard treatment options:

1. TUR with fulguration.[17, 18]
2. TUR with fulguration followed by intravesical BCG.[6, 8, 10, 11, 14]
3. TUR with fulguration followed by intravesical chemotherapy.[3, 14]
4. Segmental cystectomy (rarely indicated).[17]
5. Radical cystectomy in selected patients with extensive or refractory superficial tumor.[19]
6. Interstitial implantation of radioisotopes with or without external-beam radiation therapy.[20, 21]

Treatment options under clinical evaluation:

1. Use of chemoprevention agents after treatment to prevent recurrence.[22]
2. Intravesical therapies.

References:

1. Holmäng S, Hedelin H, Anderström C, et al.: The relationship among multiple recurrences, progression and prognosis of patients with stages Ta and T1 transitional cell cancer of the bladder followed for at least 20 years. J Urol 153 (6): 1823-6; discussion 1826-7, 1995.

2. Smits G, Schaafsma E, Kiemeney L, et al.: Microstaging of pT1 transitional cell carcinoma of the bladder: identification of subgroups with distinct risks of progression. Urology 52 (6): 1009-13; discussion 1013-4, 1998.

3. Igawa M, Urakami S, Shirakawa H, et al.: Intravesical instillation of epirubicin: effect on tumour recurrence in patients with dysplastic epithelium after transurethral resection of superficial bladder tumour. Br J Urol 77 (3): 358-62, 1996.

4. Lacombe L, Dalbagni G, Zhang ZF, et al.: Overexpression of p53 protein in a high-risk population of patients with superficial bladder cancer before and after bacillus Calmette-Guérin therapy: correlation to clinical outcome. J Clin Oncol 14 (10): 2646-52, 1996.

5. Herr HW: The value of a second transurethral resection in evaluating patients with bladder tumors. J Urol 162 (1): 74-6, 1999.

6. 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 13 (6): 1404-8, 1995.

7. Lamm DL, Griffith JG: Intravesical therapy: does it affect the natural history of superficial bladder cancer? Semin Urol 10 (1): 39-44, 1992.

8. Sarosdy MF, Lamm DL: Long-term results of intravesical bacillus Calmette-Guerin therapy for superficial bladder cancer. J Urol 142 (3): 719-22, 1989.

9. Coplen DE, Marcus MD, Myers JA, et al.: Long-term followup of patients treated with 1 or 2, 6-week courses of intravesical bacillus Calmette-Guerin: analysis of possible predictors of response free of tumor. J Urol 144 (3): 652-7, 1990.

10. Catalona WJ, Hudson MA, Gillen DP, et al.: Risks and benefits of repeated courses of intravesical bacillus Calmette-Guerin therapy for superficial bladder cancer. J Urol 137 (2): 220-4, 1987.

11. Herr HW: Progression of stage T1 bladder tumors after intravesical bacillus Calmette-Guerin. J Urol 145 (1): 40-3; discussion 43-4, 1991.

12. Lamm DL, Blumenstein BA, Crawford ED, et al.: A randomized trial of intravesical doxorubicin and immunotherapy with bacille Calmette-Guérin for transitional-cell carcinoma of the bladder. N Engl J Med 325 (17): 1205-9, 1991.

13. Lamm DL, Crawford ED, Blumenstein B, et al.: Maintenance BCG immunotherapy of superficial bladder cancer: a randomized prospective Southwest Oncology Group study. [Abstract] Proceedings of the American Society of Clinical Oncology 11: A-627, 203, 1992.

14. Rintala E, Jauhiainen K, Kaasinen E, et al.: Alternating mitomycin C and bacillus Calmette-Guerin instillation prophylaxis for recurrent papillary (stages Ta to T1) superficial bladder cancer. Finnbladder Group. J Urol 156 (1): 56-9; discussion 59-60, 1996.

15. Witjes JA, Caris CT, Mungan NA, et al.: Results of a randomized phase III trial of sequential intravesical therapy with mitomycin C and bacillus Calmette-Guerin versus mitomycin C alone in patients with superficial bladder cancer. J Urol 160 (5): 1668-71; discussion 1671-2, 1998.

16. Malmström PU, Wijkström H, Lundholm C, et al.: 5-year followup of a randomized prospective study comparing mitomycin C and bacillus Calmette-Guerin in patients with superficial bladder carcinoma. Swedish-Norwegian Bladder Cancer Study Group. J Urol 161 (4): 1124-7, 1999.

17. Soloway MS: The management of superficial bladder cancer. In: Javadpour N, ed.: Principles and Management of Urologic Cancer. 2nd ed. Baltimore, Md: Williams and Wilkins, 1983, pp 446-467.

18. Herr HW, Reuter VE: Evaluation of new resectoscope loop for transurethral resection of bladder tumors. J Urol 159 (6): 2067-8, 1998.

19. Amling CL, Thrasher JB, Frazier HA, et al.: Radical cystectomy for stages Ta, Tis and T1 transitional cell carcinoma of the bladder. J Urol 151 (1): 31-5; discussion 35-6, 1994.

20. Goffinet DR, Schneider MJ, Glatstein EJ, et al.: Bladder cancer: results of radiation therapy in 384 patients. Radiology 117 (1): 149-53, 1975.

21. van der Werf-Messing B, Hop WC: Carcinoma of the urinary bladder (category T1NxM0) treated either by radium implant or by transurethral resection only. Int J Radiat Oncol Biol Phys 7 (3): 299-303, 1981.

22. Lamm DL, Riggs DR, Shriver JS, et al.: Megadose vitamins in bladder cancer: a double-blind clinical trial. J Urol 151 (1): 21-6, 1994.

Stage II Bladder Cancer

Note: Some citations in the text of this section are followed by a level of evidence. The PDQ editorial boards use a formal ranking system to help the reader judge the strength of evidence linked to the reported results of a therapeutic strategy. (Refer to the PDQ summary on Levels of Evidence for more information.)

Stage II bladder cancer is defined by the following TNM classifications:

- T2a, N0, M0
- T2b, N0, M0

Stage II bladder cancer may be controlled in some patients by transurethral resection (TUR), but often more aggressive forms of treatment are dictated by recurrent tumor or by the large size, multiple foci, or undifferentiated grade of the neoplasm. Segmental cystectomy is appropriate only in very selected patients.

Radical cystectomy is considered standard treatment. Radical cystectomy includes removal of the bladder, perivesical tissues, prostate, and seminal vesicles in men and the uterus, tubes, ovaries, anterior vaginal wall, and urethra in women and may or may not be accompanied by pelvic lymph node dissection.[1] Studies suggest that radical cystectomy with preservation of sexual function can be performed in some men and that new forms of urinary diversion can obviate the need for an external urinary appliance.[2, 3, 4, 5] In a retrospective analysis from a single institution, elderly patients (≥70 years) in good general health were found to have similar clinical and functional results following radical cystectomy when compared with younger patients.[6]

After radical cystectomy, however, an approximate 50% risk of recurrence still exists for patients with muscle-invasive disease. The addition of preoperative radiation therapy to radical cystectomy did not result in any survival advantage when compared with radical cystectomy alone in a prospective, randomized trial.[7] Because the disease commonly recurs with distant metastases, systemic chemotherapy administered before or after cystectomy has been evaluated as a means of improving outcome. Administration of chemotherapy before cystectomy (i.e., neoadjuvant) may be preferable to postoperative treatment because tumor downstaging from chemotherapy may enhance resectability, occult metastatic disease may be treated as early as possible, and chemotherapy may be better tolerated. A randomized study conducted by the Southwest Oncology Group compared three cycles of neoadjuvant cisplatin, methotrexate, vinblastine, and doxorubicin (MVAC) administered prior to cystectomy with cystectomy alone in 317 patients with stage T2 to stage T4a bladder cancer and showed that 5-year survival was 57% in the group receiving neoadjuvant chemotherapy and 43% in the group treated with cystectomy alone, which is a difference of borderline statistical significance ($P = .06$ by stratified log-rank test).[8] No deaths or postoperative complications were associated with neoadjuvant chemotherapy. In addition, 38% of patients who received neoadjuvant chemotherapy had a pathologic complete response at the time of surgery, and 85% of those achieving a pathologic complete response were alive at 5 years.[8][Level of evidence: 1iiA]

A larger, randomized study, conducted by the Medical Research Council and the European Organization for Research and Treatment of Cancer, evaluated three cycles of neoadjuvant cisplatin, vinblastine, and methotrexate (CMV) administered prior to cystectomy or radiation therapy in 976 patients with stage T2 grade 3, stage T3, or stage T4a disease. Although this study demonstrated an improvement in 3-year survival from 50% in patients who received no neoadjuvant chemotherapy to 55.5% in those who had, this difference was not statistically significant ($P = .075$) because the study had been originally powered to detect a 10% absolute difference in survival.[9][Level of evidence: 1iiA] A meta-analysis of 10 randomized trials of neoadjuvant chemotherapy, including updated data for 2,688 individual patients, showed that platinum-based combination chemotherapy was associated with a significant 13% relative reduction in the risk of death and resulted in an improvement in 5-year survival from 45% to 50% ($P = .016$). Neoadjuvant single-agent cisplatin was not associated with any such survival benefit in the meta-analysis.[10] Based on these findings, it is reasonable to offer neoadjuvant platinum-based combination chemotherapy prior to cystectomy in patients with muscle-invasive bladder cancer. The two regimens that have been most extensively studied and show the strongest evidence of benefit in this setting are MVAC and CMV. There is no data from clinical trials demonstrating equivalent effectiveness with newer regimens such as gemcitabine and cisplatin or high-dose MVAC.

In patients who are not willing or able to undergo radical cystectomy, definitive radiation therapy is an option that yields a 5-year survival of approximately 30%.[11, 12, 13] Approximately 50% of patients have dysuria and urinary frequency during treatment, which resolves several weeks after treatment, and 15% report acute toxic effects of the bowel. In addition, compared with patients treated with radical cystectomy, those treated with definitive radiation therapy report less sexual dysfunction.[14] Randomized trials, conducted from the 1950s through the 1980s, of definitive radiation therapy (with salvage cystectomy only for incomplete response or failure) versus preoperative radiation therapy followed by cystectomy have found similar or worse survival in patients who received definitive radiation therapy.[15, 16, 17]

Systemic chemotherapy has been incorporated with definitive radiation therapy to develop a more effective bladder-sparing approach for patients with locally advanced disease. The utility of this multimodality approach was confirmed in a prospective, randomized comparison of radiation therapy and chemoradiation therapy, which reported an improved rate of local control when cisplatin was given in conjunction with radiation therapy, even though there was no improvement in the rate of distant metastases or overall survival (OS).[18][Level of evidence: 1iiA] In some nonrandomized studies, 50% or more of the patients who had bladder-preserving therapy (i.e., initial TUR of as much tumor as possible followed by concurrent chemoradiation therapy) were alive at 5 years, and 75% of those survivors had an intact bladder.[19, 20, 21] In a phase III study (RTOG-8903), the Radiation Therapy Oncology Group evaluated the potential benefit of adding two cycles of neoadjuvant methotrexate, cisplatin, and vinblastine prior to concurrent cisplatin and radiation therapy, but neoadjuvant chemotherapy was associated with increased hematologic toxic effects and yielded no improvement in response rate, freedom from distant metastases, or OS when compared with chemoradiation therapy alone.[22] Because no randomized trials have directly compared the bladder-preserving chemoradiation therapy approach with radical cystectomy, it is not clear if the former is as effective as the latter. Choice of treatment should be guided by a patient's overall medical condition and by consideration of the adverse effects of therapy.

Treatment options:

1. Radical cystectomy with or without pelvic lymph node dissection.[23]

2. Neoadjuvant platinum-based combination chemotherapy followed by radical cystectomy.[8]
3. External-beam radiation therapy (EBRT) with or without concurrent chemotherapy .[11, 12, 13, 18, 19, 20, 21]
4. Interstitial implantation of radioisotopes before or after EBRT.[24, 25]
5. TUR with fulguration (in selected patients).
6. Segmental cystectomy (in selected patients).[23]

References:

1. Olsson CA: Management of invasive carcinoma of the bladder. In: deKernion JB, Paulson DF, eds.: Genitourinary Cancer Management. Philadelphia, Pa: Lea and Febiger, 1987, pp 59-94.

2. Brendler CB, Steinberg GD, Marshall FF, et al.: Local recurrence and survival following nerve-sparing radical cystoprostatectomy. J Urol 144 (5): 1137-40; discussion 1140-1, 1990.

3. Skinner DG, Boyd SD, Lieskovsky G: Clinical experience with the Kock continent ileal reservoir for urinary diversion. J Urol 132 (6): 1101-7, 1984.

4. Fowler JE: Continent urinary reservoirs and bladder substitutes in the adult: part I. Monographs in Urology 8(2): 1987.

5. Fowler JE: Continent urinary reservoirs and bladder substitutes in the adult: part II. Monographs in Urology 8(3): 1987.

6. Figueroa AJ, Stein JP, Dickinson M, et al.: Radical cystectomy for elderly patients with bladder carcinoma: an updated experience with 404 patients. Cancer 83 (1): 141-7, 1998.

7. Smith JA, Crawford ED, Blumenstein B, et al.: A randomized prospective trial of pre-operative irradiation plus radical cystectomy versus surgery alone for transitional cell carcinoma of the bladder: a Southwest Oncology Group study. [Abstract] J Urol 139(4, Part 2): 266A, 1988.

8. Grossman HB, Natale RB, Tangen CM, et al.: Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 349 (9): 859-66, 2003.

9. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. International collaboration of trialists. Lancet 354 (9178): 533-40, 1999.

10. Advanced Bladder Cancer Meta-analysis Collaboration.: Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. Lancet 361 (9373): 1927-34, 2003.

11. Gospodarowicz MK, Hawkins NV, Rawlings GA, et al.: Radical radiotherapy for muscle invasive transitional cell carcinoma of the bladder: failure analysis. J Urol 142 (6): 1448-53; discussion 1453-4, 1989.

12. Yu WS, Sagerman RH, Chung CT, et al.: Bladder carcinoma. Experience with radical and preoperative radiotherapy in 421 patients. Cancer 56 (6): 1293-9, 1985.

13. Jahnson S, Pedersen J, Westman G: Bladder carcinoma--a 20-year review of radical irradiation therapy. Radiother Oncol 22 (2): 111-7, 1991.

14. Henningsohn L, Wijkström H, Dickman PW, et al.: Distressful symptoms after radical radiotherapy for urinary bladder cancer. Radiother Oncol 62 (2): 215-25, 2002.

15. Miller LS: Bladder cancer: superiority of preoperative irradiation and cystectomy in clinical stages B2 and C. Cancer 39 (2 Suppl): 973-80, 1977.

16. Horwich A, Pendlebury S, Dearnaley DP, et al.: Organ conservation in bladder cancer. Eur J Cancer 31 (Suppl 6): S208-9, 1995.

17. Sell A, Jakobsen A, Nerstrøm B, et al.: Treatment of advanced bladder cancer category T2 T3 and T4a. A randomized multicenter study of preoperative irradiation and cystectomy versus radical irradiation and early salvage cystectomy for residual tumor. DAVECA protocol 8201. Danish Vesical Cancer Group. Scand J Urol Nephrol Suppl 138: 193-201, 1991.

18. Coppin CM, Gospodarowicz MK, James K, et al.: Improved local control of invasive bladder cancer by concurrent cisplatin and preoperative or definitive radiation. The National Cancer Institute of Canada Clinical Trials Group. J Clin

Oncol 14 (11): 2901-7, 1996.

19. Kachnic LA, Kaufman DS, Heney NM, et al.: Bladder preservation by combined modality therapy for invasive bladder cancer. J Clin Oncol 15 (3): 1022-9, 1997.

20. Housset M, Maulard C, Chretien Y, et al.: Combined radiation and chemotherapy for invasive transitional-cell carcinoma of the bladder: a prospective study. J Clin Oncol 11 (11): 2150-7, 1993.

21. Rödel C, Grabenbauer GG, Kühn R, et al.: Combined-modality treatment and selective organ preservation in invasive bladder cancer: long-term results. J Clin Oncol 20 (14): 3061-71, 2002.

22. Shipley WU, Winter KA, Kaufman DS, et al.: Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with selective bladder preservation by combined radiation therapy and chemotherapy: initial results of Radiation Therapy Oncology Group 89-03. J Clin Oncol 16 (11): 3576-83, 1998.

23. Richie JP: Surgery for invasive bladder cancer. Hematol Oncol Clin North Am 6 (1): 129-45, 1992.

24. van der Werf-Messing BH, van Putten WL: Carcinoma of the urinary bladder category T2,3NXM0 treated by 40 Gy external irradiation followed by cesium137 implant at reduced dose (50%). Int J Radiat Oncol Biol Phys 16 (2): 369-71, 1989.

25. Pos F, Horenblas S, Dom P, et al.: Organ preservation in invasive bladder cancer: brachytherapy, an alternative to cystectomy and combined modality treatment? Int J Radiat Oncol Biol Phys 61 (3): 678-86, 2005.

Stage III Bladder Cancer

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Stage III bladder cancer is defined by the following TNM classifications:

- T3a, N0, M0
- T3b, N0, M0
- T4a, N0, M0

A few highly selected patients with stage III bladder cancer may be suitable for segmental cystectomy or interstitial radiation therapy.

For most patients, radical cystectomy is considered standard treatment. Radical cystectomy includes removal of the bladder, perivesical tissues, prostate, and seminal vesicles in men and the uterus, tubes, ovaries, anterior vaginal wall, and urethra in women and may or may not be accompanied by pelvic lymph node dissection.[1] Studies such as the RTOG-8512 trial suggest that radical cystectomy with preservation of sexual function can be performed in some men, and new forms of urinary diversion can obviate the need for an external urinary appliance.[2, 3, 4, 5] In a retrospective analysis from a single institution (RTOG-8903), elderly patients (≥70 years) in good general health were found to have similar clinical and functional results following radical cystectomy when compared with younger patients.[6]

After radical cystectomy, however, an approximate 50% risk of recurrence still exists for patients with muscle-invasive disease. The addition of preoperative radiation therapy to radical cystectomy did not result in any survival advantage when compared with radical cystectomy alone in a prospective, randomized trial.[7] Because the disease commonly recurs with distant metastases, systemic chemotherapy administered before or after cystectomy has been evaluated as a means of improving outcome. Administration of chemotherapy before cystectomy (i.e., neoadjuvant) may be preferable to postoperative treatment since tumor downstaging from chemotherapy may enhance resectability, occult metastatic disease may be treated as early as possible, and chemotherapy may be better tolerated. A randomized study conducted by the Southwest Oncology Group compared three cycles of neoadjuvant cisplatin, methotrexate, vinblastine, and doxorubicin administered prior to cystectomy with cystectomy alone in 317 patients with stage T2 to stage T4a bladder cancer, and showed that 5-year survival was 57% in the group receiving neoadjuvant chemotherapy and 43% in the group treated with cystectomy alone, which is a difference of borderline statistical significance ($P = .06$ by stratified log-rank test).[8] No deaths or postoperative complications were associated with neoadjuvant chemotherapy. In addition, 38% of patients who received neoadjuvant chemotherapy had a pathologic complete response at the time of surgery, and 85% of those achieving a pathologic complete response were alive at 5 years.[8][Level of evidence: 1iiA]

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A larger, randomized study, conducted by the Medical Research Council and the European Organization for Research and Treatment of Cancer, evaluated three cycles of neoadjuvant cisplatin, vinblastine, and methotrexate administered prior to cystectomy or radiation therapy in 976 patients with stage T2 grade 3, stage T3, or stage T4a disease. Although this study demonstrated an improvement in 3-year survival from 50% in patients who received no neoadjuvant chemotherapy to 55.5% in those who had, this difference was not statistically significant ($P = .075$) because the study had been originally powered to detect a 10% absolute difference in survival.[9][Level of evidence: 1iiA] A meta-analysis of 10 randomized trials of neoadjuvant chemotherapy, including updated data for 2,688 individual patients, showed that platinum-based combination chemotherapy was associated with a significant 13% relative reduction in the risk of death and resulted in an improvement in 5-year survival from 45% to 50% ($P = .016$). Neoadjuvant single-agent cisplatin was not associated with any such survival benefit in the meta-analysis.[10] Based on these findings, it is reasonable to offer neoadjuvant platinum-based combination chemotherapy prior to cystectomy in patients with muscle-invasive bladder cancer. The two regimens that have been most extensively studied and show the strongest evidence of benefit in this setting are MVAC and CMV. There is no data from clinical trials demonstrating equivalent effectiveness with newer regimens such as gemcitabine and cisplatin or high-dose MVAC.

In an effort to reduce the toxic effects of platinum-based regimens given in the perioperative setting, a German multicenter study randomized 327 patients with pathologic T3a-T4a and/or N+ disease after radical cystectomy to 3 cycles of cisplatin and methotrexate (CM) or three cycles of methotrexate, vinblastine, epirubicin, and cisplatin (M-VEC).[11] The median progression-free survival was 43.4 months in the CM arm and 49.7 months in the M-VEC arm, yielding a hazard ratio [HR] for disease progression of 1.13 (90% confidence interval [CI], 0.86–1.48). The median overall survival (OS) was 47.1 months in the CM arm and 51.8 months in the M-VEC arm, yielding an HR for death of 1.10 (90% CI, 0.88–1.44). Leukopenia was more common with the four-drug regimen, but the rates of febrile neutropenia, infection, and treatment-related deaths were the same with both regimens. This study was powered to accept as much as a 50% increase in progression-free survival as being noninferior.[11][Level of evidence: 1iiA]

In patients who are not willing or able to undergo radical cystectomy, definitive radiation therapy is an option that yields a 5-year survival of approximately 30%.[12, 13, 14] Approximately 50% of patients have dysuria and urinary frequency during treatment, which resolves several weeks after treatment, and 15% report acute toxic effects of the bowel. In addition, compared with patients treated with radical cystectomy, those treated with definitive radiation therapy report less sexual dysfunction.[15] Randomized trials, conducted from the 1950s through the 1980s, of definitive radiation therapy (with salvage cystectomy only for incomplete response or failure) versus preoperative radiation therapy followed by cystectomy have found similar or worse survival in patients who received definitive radiation therapy. [1, 16, 17]

Systemic chemotherapy has been incorporated with definitive radiation therapy to develop a more effective bladder-sparing approach for patients with locally advanced disease. The utility of this multimodality approach was confirmed in a prospective, randomized comparison of radiation therapy and chemoradiation therapy, which reported an improved rate of local control when cisplatin was given in conjunction with radiation therapy, even though there was no improvement in the rate of distant metastases or OS.[18][Level of evidence: 1iiA] In some nonrandomized studies, 50% or more of patients who had bladder-preserving therapy (i.e., initial transurethral resection of as much tumor as possible followed by concurrent chemoradiation therapy) were alive at 5 years, and 75% of those survivors had an intact bladder.[3, 4, 19] In a phase III study, the Radiation Therapy Oncology Group evaluated the potential benefit of adding two cycles of neoadjuvant methotrexate, cisplatin, and vinblastine administered prior to concurrent cisplatin and radiation therapy, but neoadjuvant chemotherapy was associated with increased hematologic toxic effects and yielded no improvement in response rate, freedom from distant metastases, or OS compared with chemoradiation therapy alone.[6] Because no randomized trials have directly compared the bladder-preserving chemoradiation therapy approach with radical cystectomy, it is not clear if the former is as effective as the latter. Choice of treatment should be guided by a patient's overall medical condition and by consideration of the adverse effects of therapy.

Treatment options:

1. Radical cystectomy with or without pelvic lymph node dissection.[7]
2. Neoadjuvant platinum-based combination chemotherapy followed by radical cystectomy.[8]
3. External-beam radiation therapy (EBRT) with or without concurrent chemotherapy.[3, 4, 5, 6, 12, 13, 14, 18]
4. EBRT with interstitial implantation of radioisotopes.[20]
5. Segmental cystectomy (in highly selected cases).[21]

References:

1. Sell A, Jakobsen A, Nerstrøm B, et al.: Treatment of advanced bladder cancer category T2 T3 and T4a. A randomized multicenter study of preoperative irradiation and cystectomy versus radical irradiation and early salvage cystectomy for residual tumor. DAVECA protocol 8201. Danish Vesical Cancer Group. Scand J Urol Nephrol Suppl 138: 193-201, 1991.

2. Jenkins BJ, Caulfield MJ, Fowler CG, et al.: Reappraisal of the role of radical radiotherapy and salvage cystectomy in

the treatment of invasive (T2/T3) bladder cancer. Br J Urol 62 (4): 343-6, 1988.

3. Kachnic LA, Kaufman DS, Heney NM, et al.: Bladder preservation by combined modality therapy for invasive bladder cancer. J Clin Oncol 15 (3): 1022-9, 1997.

4. Housset M, Maulard C, Chretien Y, et al.: Combined radiation and chemotherapy for invasive transitional-cell carcinoma of the bladder: a prospective study. J Clin Oncol 11 (11): 2150-7, 1993.

5. Tester W, Porter A, Asbell S, et al.: Combined modality program with possible organ preservation for invasive bladder carcinoma: results of RTOG protocol 85-12. Int J Radiat Oncol Biol Phys 25 (5): 783-90, 1993.

6. Shipley WU, Winter KA, Kaufman DS, et al.: Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with selective bladder preservation by combined radiation therapy and chemotherapy: initial results of Radiation Therapy Oncology Group 89-03. J Clin Oncol 16 (11): 3576-83, 1998.

7. Smith JA, Crawford ED, Blumenstein B, et al.: A randomized prospective trial of pre-operative irradiation plus radical cystectomy versus surgery alone for transitional cell carcinoma of the bladder: a Southwest Oncology Group study. [Abstract] J Urol 139(4, Part 2): 266A, 1988.

8. Grossman HB, Natale RB, Tangen CM, et al.: Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 349 (9): 859-66, 2003.

9. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. International collaboration of trialists. Lancet 354 (9178): 533-40, 1999.

10. Advanced Bladder Cancer Meta-analysis Collaboration.: Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. Lancet 361 (9373): 1927-34, 2003.

11. Lehmann J, Retz M, Wiemers C, et al.: Adjuvant cisplatin plus methotrexate versus methotrexate, vinblastine, epirubicin, and cisplatin in locally advanced bladder cancer: results of a randomized, multicenter, phase III trial (AUO-AB 05/95). J Clin Oncol 23 (22): 4963-74, 2005.

12. Gospodarowicz MK, Hawkins NV, Rawlings GA, et al.: Radical radiotherapy for muscle invasive transitional cell carcinoma of the bladder: failure analysis. J Urol 142 (6): 1448-53; discussion 1453-4, 1989.

13. Yu WS, Sagerman RH, Chung CT, et al.: Bladder carcinoma. Experience with radical and preoperative radiotherapy in 421 patients. Cancer 56 (6): 1293-9, 1985.

14. Jahnson S, Pedersen J, Westman G: Bladder carcinoma--a 20-year review of radical irradiation therapy. Radiother Oncol 22 (2): 111-7, 1991.

15. Henningsohn L, Wijkström H, Dickman PW, et al.: Distressful symptoms after radical radiotherapy for urinary bladder cancer. Radiother Oncol 62 (2): 215-25, 2002.

16. Miller LS: Bladder cancer: superiority of preoperative irradiation and cystectomy in clinical stages B2 and C. Cancer 39 (2 Suppl): 973-80, 1977.

17. Horwich A, Pendlebury S, Dearnaley DP, et al.: Organ conservation in bladder cancer. Eur J Cancer 31 (Suppl 6): S208-9, 1995.

18. Coppin CM, Gospodarowicz MK, James K, et al.: Improved local control of invasive bladder cancer by concurrent cisplatin and preoperative or definitive radiation. The National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 14 (11): 2901-7, 1996.

19. Rödel C, Grabenbauer GG, Kühn R, et al.: Combined-modality treatment and selective organ preservation in invasive bladder cancer: long-term results. J Clin Oncol 20 (14): 3061-71, 2002.

20. van der Werf-Messing BH, van Putten WL: Carcinoma of the urinary bladder category T2,3NXM0 treated by 40 Gy external irradiation followed by cesium137 implant at reduced dose (50%). Int J Radiat Oncol Biol Phys 16 (2): 369-71, 1989.

21. Skinner DG: Current perspectives in the management of high-grade invasive bladder cancer. Cancer 45 (7 Suppl): 1866-74, 1980.

1866-74, 1980.

Stage IV Bladder Cancer

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Stage IV bladder cancer is defined by the following TNM classifications:

- T4b, N0, M0
- Any T, N1–N3, M0
- Any T, Any N, M1

Currently, only a small fraction of patients with stage IV bladder carcinoma can be cured. The potential for cure is restricted to patients with stage IV disease with involvement of pelvic organs by direct extension or metastases to regional lymph nodes.[1] These patients may undergo radical cystectomy with pelvic lymph node dissection. The extent of lymph node dissection during cystectomy is controversial [2] as there are no data from prospective trials demonstrating improved outcomes with lymph node dissection. Definitive radiation therapy with or without concurrent chemotherapy, evaluated mainly in patients with locally advanced (T2–T4) disease, appears to have minimal curative potential in patients with regional lymph node metastases.

Prognosis is so poor in patients with stage IV disease that consideration of entry into a clinical trial is appropriate. The focus of care for many stage IV patients is on palliation of symptoms from bladder tumor that is often massive. Urinary diversion may be indicated, not only for palliation of urinary symptoms, but also for preservation of renal function in candidates for chemotherapy. Platinum-based combination chemotherapy regimens are the standard of care. A prospective, randomized trial of methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) compared with cisplatin, cyclophosphamide, and doxorubicin demonstrated improved response and median survival rates (48 weeks vs. 36 weeks, $P = .003$) with the former regimen.[3] Results from a randomized trial that compared M-VAC with single-agent cisplatin in advanced bladder cancer also showed a significant advantage with M-VAC in both response rate and median survival (12.5 months vs. 8.2 months, $P = .002$).[4] The (outpatient) regimen of paclitaxel and carboplatin achieved response rates in the range of 50% in single-institution phase II trials.[5, 6][Level of evidence: 3iiiDiv] However, when this regimen was evaluated in a multicenter phase II study conducted by the Southwest Oncology Group, the response rate was only 21%.[7][Level of evidence: 3iiiDiv] Gemcitabine has shown activity in phase II trials of patients with metastatic bladder cancer.[8] In a multicenter, randomized, phase III trial comparing the combination of gemcitabine/cisplatin (GC) with the M-VAC regimen in 405 patients with advanced or metastatic bladder cancer, GC yielded similar response rates, time-to-progression, and overall survival (OS) (hazard ratio [HR] = 1.04; 95% confidence interval [CI], 0.82–1.32; $P = .75$) compared with M-VAC, but GC had a better safety profile and was better tolerated than M-VAC. Although this study was not designed to show the equivalence of the two regimens, the similar efficacy and reduced toxic effects of GC make it a reasonable alternative in patients who may not tolerate the M-VAC regimen.[9][Level of evidence: 1iiA]

The European Organisation for Research and Treatment of Cancer Group conducted another randomized trial that studied 263 patients with advanced bladder cancer and evaluated the efficacy of a high-dose-intensity M-VAC regimen given every 2 weeks with granulocyte colony-stimulating factor (G-CSF) compared to a classic M-VAC regimen given every 4 weeks.[10] Although there was no significant difference in OS at a median follow-up of 3.2 years (HR = 0.80; 95% CI, 0.60–1.06; $P = .122$), an update at a median follow-up of 7.3 years reported that the high-dose intensity M-VAC regimen was associated with improved OS (HR = 0.76; 95% CI, 0.58–0.99; $P = .042$), with a 5-year survival rate of 22%, compared to 14% in patients treated with the classic M-VAC regimen. The high-dose intensity M-VAC regimen was also associated with higher response rates (72% vs. 58%, $P = .016$), improved median progression-free survival (9.5 months vs. 8.1 months, $P = .017$), and decreased neutropenic fever (10% vs. 26%, $P < .001$), though only 19% of patients treated with a classic M-VAC regimen ever received G-CSF.[10][Level of evidence: 1iiA] An imbalance in baseline prognostic factors (i.e., visceral metastases were found in 37 patients randomly assigned to the high-dose M-VAC regimen and 47 patients assigned to the classic M-VAC regimen) may account, in part, for these results. Ongoing studies are evaluating new chemotherapy combinations.

Chemotherapy for patients not eligible for cisplatin

The only regimens that have shown a survival benefit in randomized controlled trials have been the cisplatin-based multiagent regimens MVAC, high-dose MVAC, and CMV; gemcitabine plus cisplatin is generally accepted as equivalent to MVAC based on the data discussed above.[3, 4, 10, 11, 12] Optimal treatment of patients who are not eligible for cisplatin-based chemotherapy caused by renal insufficiency or poor performance status is thus unknown. One common practice has been to substitute carboplatin for cisplatin to reduce nephrotoxicity and gastrointestinal toxicity. Two small randomized trials comparing cisplatin-based regimens to carboplatin-based regimens have been published.[13, 14] One trial reported a lower complete response rate, while the other trial reported shorter disease-specific survival with the carboplatin-based regimen

complete response rate, while the other trial reported shorter disease-specific survival with the carboplatin-based regimen. However, these studies were underpowered, and the one that showed a disease-specific survival difference included an anthracycline in the cisplatin arm but not in the carboplatin arm. If carboplatin-based regimens are less effective than cisplatin regimens, which only prolong survival by several months, then carboplatin-based regimens may have no survival benefit.

Several less nephrotoxic regimens have been studied in clinical trials, but most of these trials have not focused on patients with renal impairment or poor performance status. Published regimens that have been studied in trials limited to patients with a medical contraindication to cisplatin include gemcitabine plus carboplatin, single-agent docetaxel, and single-agent paclitaxel.[15, 16, 17, 18, 19, 20] In general, outcomes of studies in patients unfit for cisplatin have been inferior to those of cisplatin-based regimens with reported median survival times of less than 1 year. A randomized phase II/III trial comparing gemcitabine plus carboplatin (GCa) to methotrexate, carboplatin and vinblastine (M-CAVI) reported that in the phase II portion of the trial, the response rate was 42% with GCa compared to 30% with M-CAVI.[16] However, patients with a performance status of 2 and a creatinine clearance less than 60 mL/min had a response rate of only 26% and 20%, respectively and a severe acute toxicity rate of 26% and 25%, respectively. These regimens were judged to be nonbeneficial for patients meeting both those criteria.

Many other doublet and singlet noncisplatin chemotherapy regimens, such as gemcitabine plus paclitaxel, have been studied in healthier subjects with advanced-stage urothelial carcinoma.[21, 22, 23, 24] Studies of these regimens have reported longer survival in unselected subjects than in subjects selected on the basis of impaired renal function and/or poor performance status. In the absence of any published randomized controlled trials showing improved outcomes with a noncisplatin regimen, it is impossible to know whether any of those regimens benefit patients.

For patients with T4b, N0, M0 and Any T, N1–N3, M0 disease:

Treatment options:

1. Radical cystectomy with pelvic lymph node dissection.[2, 25, 26]
2. External-beam radiation therapy (EBRT).[27, 28]
3. Urinary diversion or cystectomy for palliation.
4. Chemotherapy as an adjunct to local treatment as seen in the RTOG-8512 trial, for example.[29, 30, 31, 32, 33]

For patients with Any T, Any N, M1 disease:

Standard treatment options:

1. Chemotherapy alone or as an adjunct to local treatment.[3, 4, 9]
2. EBRT for palliation.
3. Urinary diversion or cystectomy for palliation.

Treatment options under clinical evaluation:

- Other chemotherapy regimens appear active in the treatment of metastatic disease. Chemotherapy agents that have shown activity in metastatic bladder cancer include paclitaxel, docetaxel, ifosfamide, gallium nitrate, gemcitabine, and pemetrexed.[34, 35, 36][Level of evidence: 3iiiDiv]

References:

1. Vieweg J, Gschwend JE, Herr HW, et al.: The impact of primary stage on survival in patients with lymph node positive bladder cancer. J Urol 161 (1): 72-6, 1999.

2. Konety BR, Joslyn SA, O'Donnell MA: Extent of pelvic lymphadenectomy and its impact on outcome in patients diagnosed with bladder cancer: analysis of data from the Surveillance, Epidemiology and End Results Program data base. J Urol 169 (3): 946-50, 2003.

3. Logothetis CJ, Dexeus FH, Finn L, et al.: A prospective randomized trial comparing MVAC and CISCA chemotherapy for patients with metastatic urothelial tumors. J Clin Oncol 8 (6): 1050-5, 1990.

4. Loehrer PJ Sr, Einhorn LH, Elson PJ, et al.: A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. J Clin Oncol 10 (7): 1066-73, 1992.

5. Vaughn DJ, Malkowicz SB, Zoltick B, et al.: Paclitaxel plus carboplatin in advanced carcinoma of the urothelium: an active and tolerable outpatient regimen. J Clin Oncol 16 (1): 255-60, 1998.

6. Redman BG, Smith DC, Flaherty L, et al.: Phase II trial of paclitaxel and carboplatin in the treatment of advanced

urothelial carcinoma. J Clin Oncol 16 (5): 1844-8, 1998.

7. Small EJ, Lew D, Redman BG, et al.: Southwest Oncology Group Study of paclitaxel and carboplatin for advanced transitional-cell carcinoma: the importance of survival as a clinical trial end point. J Clin Oncol 18 (13): 2537-44, 2000.

8. Bajorin DF: Paclitaxel in the treatment of advanced urothelial cancer. Oncology (Huntingt) 14 (1): 43-52, 57; discussion 58, 61-2, 2000.

9. 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 18 (17): 3068-77, 2000.

10. Sternberg CN, de Mulder P, Schornagel JH, et al.: 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 tumours. Eur J Cancer 42 (1): 50-4, 2006.

11. Bamias A, Aravantinos G, Deliveliotis C, et al.: Docetaxel and cisplatin with granulocyte colony-stimulating factor (G-CSF) versus MVAC with G-CSF in advanced urothelial carcinoma: a multicenter, randomized, phase III study from the Hellenic Cooperative Oncology Group. J Clin Oncol 22 (2): 220-8, 2004.

12. Mead GM, Russell M, Clark P, et al.: A randomized trial comparing methotrexate and vinblastine (MV) with cisplatin, methotrexate and vinblastine (CMV) in advanced transitional cell carcinoma: results and a report on prognostic factors in a Medical Research Council study. MRC Advanced Bladder Cancer Working Party. Br J Cancer 78 (8): 1067-75, 1998.

13. Petrioli R, Frediani B, Manganelli A, et al.: Comparison between a cisplatin-containing regimen and a carboplatin-containing regimen for recurrent or metastatic bladder cancer patients. A randomized phase II study. Cancer 77 (2): 344-51, 1996.

14. Bellmunt J, Ribas A, Eres N, et al.: Carboplatin-based versus cisplatin-based chemotherapy in the treatment of surgically incurable advanced bladder carcinoma. Cancer 80 (10): 1966-72, 1997.

15. Bellmunt J, de Wit R, Albanell J, et al.: A feasibility study of carboplatin with fixed dose of gemcitabine in "unfit" patients with advanced bladder cancer. Eur J Cancer 37 (17): 2212-5, 2001.

16. De Santis M, Bellmunt J, Mead B, et al.: Randomized phase II/III study assessing gemcitabine/carboplatin (GC) and methotrexate/carboplatin/vinblastine (M-CAVI) in previously untreated patients (pts) with advanced urothelial cancer ineligible for cisplatin based chemotherapy: phase II results of. [Abstract] American Society of Clinical Oncology 2008 Genitourinary Cancers Symposium, Feb 14-16, 2008, San Francisco, CA. A-288, 2008.

17. Dimopoulos MA, Deliveliotis C, Moulopoulos LA, et al.: Treatment of patients with metastatic urothelial carcinoma and impaired renal function with single-agent docetaxel. Urology 52 (1): 56-60, 1998.

18. Dreicer R, Gustin DM, See WA, et al.: Paclitaxel in advanced urothelial carcinoma: its role in patients with renal insufficiency and as salvage therapy. J Urol 156 (5): 1606-8, 1996.

19. Linardou H, Aravantinos G, Efstathiou E, et al.: Gemcitabine and carboplatin combination as first-line treatment in elderly patients and those unfit for cisplatin-based chemotherapy with advanced bladder carcinoma: Phase II study of the Hellenic Co-operative Oncology Group. Urology 64 (3): 479-84, 2004.

20. Yang MH, Yen CC, Chang YH, et al.: Single agent paclitaxel as a first-line therapy in advanced urothelial carcinoma: its efficacy and safety in patients even with pretreatment renal insufficiency. Jpn J Clin Oncol 30 (12): 547-52, 2000.

21. Sternberg CN, Calabrò F, Pizzocaro G, et al.: Chemotherapy with an every-2-week regimen of gemcitabine and paclitaxel in patients with transitional cell carcinoma who have received prior cisplatin-based therapy. Cancer 92 (12): 2993-8, 2001.

22. Vaughn DJ: Chemotherapeutic options for cisplatin-ineligible patients with advanced carcinoma of the urothelium. Cancer Treat Rev 34 (4): 328-38, 2008.

23. Kaufman DS, Carducci MA, Kuzel TM, et al.: A multi-institutional phase II trial of gemcitabine plus paclitaxel in patients with locally advanced or metastatic urothelial cancer. Urol Oncol 22 (5): 393-7, 2004 Sep-Oct.

24. Calabrò F, Lorusso V, Rosati G, et al.: Gemcitabine and paclitaxel every 2 weeks in patients with previously untreated urothelial carcinoma. Cancer 115 (12): 2652-9, 2009.

25. Thrasher JB, Crawford ED: Current management of invasive and metastatic transitional cell carcinoma of the bladder. J Urol 149 (5): 957-72, 1993.

26. Grossman HB, Natale RB, Tangen CM, et al.: Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 349 (9): 859-66, 2003.

27. Jahnson S, Pedersen J, Westman G: Bladder carcinoma--a 20-year review of radical irradiation therapy. Radiother Oncol 22 (2): 111-7, 1991.

28. Coppin CM, Gospodarowicz MK, James K, et al.: Improved local control of invasive bladder cancer by concurrent cisplatin and preoperative or definitive radiation. The National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 14 (11): 2901-7, 1996.

29. Kachnic LA, Kaufman DS, Heney NM, et al.: Bladder preservation by combined modality therapy for invasive bladder cancer. J Clin Oncol 15 (3): 1022-9, 1997.

30. Tester W, Porter A, Asbell S, et al.: Combined modality program with possible organ preservation for invasive bladder carcinoma: results of RTOG protocol 85-12. Int J Radiat Oncol Biol Phys 25 (5): 783-90, 1993.

31. Logothetis CJ, Johnson DE, Chong C, et al.: Adjuvant chemotherapy of bladder cancer: a preliminary report. J Urol 139 (6): 1207-11, 1988.

32. 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 145 (3): 459-64; discussion 464-7, 1991.

33. Scher HI: Chemotherapy for invasive bladder cancer: neoadjuvant versus adjuvant. Semin Oncol 17 (5): 555-65, 1990.

34. Raghavan D, Huben R: Management of bladder cancer. Curr Probl Cancer 19 (1): 1-64, 1995 Jan-Feb.

35. Vogelzang NJ, Stadler WM: Gemcitabine and other new chemotherapeutic agents for the treatment of metastatic bladder cancer. Urology 53 (2): 243-50, 1999.

36. Sweeney CJ, Roth BJ, Kabbinavar FF, et al.: Phase II study of pemetrexed for second-line treatment of transitional cell cancer of the urothelium. J Clin Oncol 24 (21): 3451-7, 2006.

Recurrent Bladder Cancer

The prognosis for any patient with progressive or recurrent invasive bladder cancer is generally poor. Management of recurrence depends on prior therapy, sites of recurrence, and individual patient considerations. Treatment of new superficial or locally invasive tumors that develop in the setting of previous conservative therapy for superficial bladder neoplasia has been discussed earlier in this summary. Recurrent or progressive disease in distant sites or after definitive local therapy has an extremely poor prognosis, and clinical trials should be considered whenever possible.

In patients with recurrent transitional cell carcinoma, combination chemotherapy has produced high response rates with occasional complete responses seen.[1, 2] Results from a randomized trial that compared M-VAC (methotrexate, vinblastine, doxorubicin, and cisplatin) with single-agent cisplatin in advanced bladder cancer show a significant advantage with M-VAC in both response rate and median survival.[3] The overall response rate with M-VAC in this cooperative group trial was 39%. Other chemotherapy agents that have shown activity in metastatic bladder cancer include: paclitaxel, ifosfamide, gallium nitrate, gemcitabine, and pemetrexed. Ifosfamide, gallium, and pemetrexed have shown limited activity in patients previously treated with cisplatin.[4, 5, 6, 7, 8, 9, 10, 11]

References:

1. Sternberg CN, Yagoda A, Scher HI, et al.: Methotrexate, vinblastine, doxorubicin, and cisplatin for advanced transitional cell carcinoma of the urothelium. Efficacy and patterns of response and relapse. Cancer 64 (12): 2448-58, 1989.

2. Harker WG, Meyers FJ, Freiha FS, et al.: Cisplatin, methotrexate, and vinblastine (CMV): an effective chemotherapy

regimen for metastatic transitional cell carcinoma of the urinary tract. A Northern California Oncology Group study. J Clin Oncol 3 (11): 1463-70, 1985.

3. Loehrer PJ Sr, Einhorn LH, Elson PJ, et al.: A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. J Clin Oncol 10 (7): 1066-73, 1992.

4. Roth BJ: Preliminary experience with paclitaxel in advanced bladder cancer. Semin Oncol 22 (3 Suppl 6): 1-5, 1995.

5. Witte RS, Elson P, Bono B, et al.: Eastern Cooperative Oncology Group phase II trial of ifosfamide in the treatment of previously treated advanced urothelial carcinoma. J Clin Oncol 15 (2): 589-93, 1997.

6. Einhorn LH, Roth BJ, Ansari R, et al.: Phase II trial of vinblastine, ifosfamide, and gallium combination chemotherapy in metastatic urothelial carcinoma. J Clin Oncol 12 (11): 2271-6, 1994.

7. Pollera CF, Ceribelli A, Crecco M, et al.: Weekly gemcitabine in advanced bladder cancer: a preliminary report from a phase I study. Ann Oncol 5 (2): 182-4, 1994.

8. Seidman AD, Scher HI, Heinemann MH, et al.: Continuous infusion gallium nitrate for patients with advanced refractory urothelial tract tumors. Cancer 68 (12): 2561-5, 1991.

9. Roth BJ: Ifosfamide in the treatment of bladder cancer. Semin Oncol 23 (3 Suppl 6): 50-5, 1996.

10. Bajorin DF: Paclitaxel in the treatment of advanced urothelial cancer. Oncology (Huntingt) 14 (1): 43-52, 57; discussion 58, 61-2, 2000.

11. Sweeney CJ, Roth BJ, Kabbinavar FF, et al.: Phase II study of pemetrexed for second-line treatment of transitional cell cancer of the urothelium. J Clin Oncol 24 (21): 3451-7, 2006.

Changes to This Summary (01/06/2012)

The PDQ cancer information summaries are reviewed regularly and updated as new information becomes available. This section describes the latest changes made to this summary as of the date above.

General Information About Bladder Cancer

Updated statistics with estimated new cases and deaths for 2012 (cited American Cancer Society as reference 1).