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Multimodal therapies for muscle-invasive urothelial carcinoma of the bladder

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Abstract

Purpose of review—To evaluate the current literature for processes of care and outcomes of multimodal therapies for muscle-invasive urothelial carcinoma of the bladder.

Recent findings—Treatments for high-risk bladder cancer remain an active area of investigation. Despite evidence of the benefits, the use of chemotherapy, either neoadjuvant or adjuvant, remains underutilized. Given patient preference or baseline comorbidities, multimodal bladder-preserving strategies have been employed by several institutions, with rates of overall survival similar to radical cystectomy series. Late complications associated with these treatments were recently described. Future management strategies for solid tumors will incorporate a personalized approach based upon molecular diagnostic tools to predict risk of recurrence, progression, and response to specific therapeutic agents.

Summary—Multimodal paradigms for muscle-invasive urothelial carcinoma have demonstrated favorable clinical outcomes relative to radical cystectomy alone. Further work through properly conducted randomized trials and accurate individual-level risk assessments will facilitate the determination of the optimal candidates and timing for these treatments.

Keywords

bladder cancer; chemotherapy; multimodal therapy; radiation; review

INTRODUCTION

Urothelial carcinoma of the bladder remains a significant public health problem in the United States, with over 69 000 expected new cases and an estimated 10 670 deaths due to the disease in 2011 [1]. Known risk factors for the development of urothelial carcinoma include smoking, pelvic radiation, and a number of occupational exposures including aniline dyes, aromatic amines, nitrites, acrolein, coal, and arsenic [2,3]. Histopathology is of paramount importance in the management of urothelial carcinoma, and as such, careful attention must be paid to depth of invasion. Approximately 70% of new bladder cancer cases fail to invade the detrusor muscle (muscularis propria) and are managed with combination therapy including serial cystoscopy, transurethral resection (TUR), and intravesical chemotherapy and/or immunotherapy. Nonetheless, 50–70% of the nonmuscle invasive tumors will recur and 10–20% will progress to ultimately become muscle invasive [4,5].

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Conflicts of interest

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Radical cystectomy, pelvic lymphadenectomy, and urinary diversion remain the gold standard treatment for patients with muscle-invasive urothelial carcinoma (T2+). Recurrence rates following surgical extirpation remain unacceptably high, between 30 and 45% [6,7], with 5-year overall survival following radical cystectomy of 45–66% [6,7,8,9]. Given the modest long-term cure rates from surgical monotherapy, considerable attention has been paid to multimodality treatment for muscle-invasive urothelial carcinoma. This review will discuss the advances in the administration of perioperative systemic chemotherapy and the role of combined radiotherapy and chemotherapy.

NEOADJUVANT CHEMOTHERAPY FOR MUSCLE-INVASIVE UROTHELIAL CARCINOMA OF THE BLADDER

The past 20 years have witnessed mounting high-quality evidence for the administration of cisplatin-based neoadjuvant chemotherapy (NAC) for muscle-invasive urothelial carcinoma. The largest trial, conducted by the Medical Research Council (MRC)/European Organization for Research and Treatment of Cancer (EORTC), randomized 976 patients to radical local therapy or three cycles of neoadjuvant cisplatin, methotrexate, and vinblastine (CMV). At a median follow-up of 8 years, investigators documented a 16% reduction in all-cause mortality and a 23% reduction in death or metastasis in those patients receiving neoadjuvant CMV compared to those undergoing local therapy alone. NAC, in this study, resulted in increased 3-year survival from 50 to 56%, improved 10-year survival from 30 to 36%, and enhanced median survival of 7 months [10].

These findings are consistent with the data from the Southwest Oncology Group (SWOG), who randomized 317 patients to immediate radical cystectomy or three cycles of neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin followed by radical cystectomy. At a median follow-up of 8.7 years, patients receiving neoadjuvant MVAC enjoyed a median survival of 77 months, compared to 46 months in the immediate cystectomy group. Proportional hazards modeling revealed a 33% increase in the risk of death among patients in the immediate cystectomy cohort when compared to those receiving neoadjuvant MVAC [11].

In addition to the SWOG and MRC/EORTC trials, pooled data from the Nordic Collaborative Group evaluated survival following neoadjuvant cisplatin/doxorubicin or cisplatin/methotrexate and confirmed a 20% improvement in risk of death, favoring the NAC cohort. This combined analysis showed an absolute survival benefit of 8% at 5 years [12]. These data have been corroborated by a meta-analysis performed by the Advanced Bladder Cancer Meta Analysis Collaboration who documented a 5% absolute overall survival benefit conferred to those patients receiving cisplatin-based NAC compared to those not receiving chemotherapy. These data demonstrated a 5-year survival of 50 and 45%, respectively.

Despite the preponderance of evidence favoring the use of NAC, utilization of this strategy has been poor. Recent data from the National Cancer Database revealed only 9% of patients received NAC. However, the rate of administration did increase from 6% in 2003 to 13% in 2007, likely reflecting the incorporation of randomized trial data into clinical practice [13]. Numerous studies from both the USA and Canada have corroborated the dismal rates of utilization [14,15], prompting the identification of referral for NAC as a quality measure in bladder cancer care. Possible reasons for the low uptake of the neoadjuvant paradigm include potential concerns for overtreatment of low-risk patients, surgical delay in chemotherapy nonresponders, and concerns over rendering elderly patients unsuitable for radical cystectomy [16]. Systems-based quality improvement efforts must be undertaken to improve delivery of NAC to appropriate patients with muscle-invasive bladder cancer.

ADJUVANT CHEMOTHERAPY

The data supporting the administration of adjuvant chemotherapy for urothelial carcinoma are less robust than the corresponding data for NAC. Nonetheless, many physicians treating muscle-invasive bladder cancer favor this approach given the ability of pathologic staging to further stratify patients into risk groupings for likelihood of progression. Furthermore, adoption of an adjuvant paradigm facilitates the separation of patients with pT2 disease from those with pT3, pT4, or node positive disease, each of whom is at high risk of progression [4].

Given the limitations of available level I evidence including small sample sizes, variable chemotherapeutic regimens, short follow-up, and early study termination, the most widely cited evidence evaluating adjuvant platinum-based chemotherapy is a meta-analysis conducted by the Advanced Bladder Cancer Consortium. This systematic review included 491 patients from six trials representing 90% of all patients randomized to adjuvant cisplatin-based combination trials. This study revealed a 25% relative decrease in the risk of all-cause mortality in patients who received adjuvant chemotherapy, corresponding to an absolute survival benefit of 9%. Additionally, these data revealed a 32% relative improvement in disease-free survival, corresponding to an absolute benefit of 12% [17]. The Advanced Bladder Cancer (ABC) investigators caution that the small number of patients in this series limits the analysis, and as such, they state that there is insufficient evidence upon which to base treatment decisions. Although these data may be somewhat limited, nonrandomized observational data have corroborated the survival benefit documented in the ABC meta-analysis [18].

The adjuvant chemotherapy paradigm poses a unique set of challenges in patients with advanced bladder cancer. Recent data suggest high rates of perioperative morbidity, with 64% of patients suffering a complication [19] and 26.6% requiring readmission [20] within 90 days of surgery. Indeed, impairments in functional status following cystectomy have been shown to prevent the administration of adjuvant chemotherapy in nearly 30% of patients [19,21]. These data must be considered when discussing the merits of combined multimodality treatment for muscle-invasive bladder cancer.

ORGAN PRESERVATION

Despite the aforementioned advances realized by combination chemotherapy and radical cystectomy for muscle-invasive urothelial carcinoma, many patients are too ill or unwilling to undergo radical surgery. Progress in multimodal treatment for carcinomas of the breast, larynx, rectum, esophagus, and extremity soft-tissue sarcomas has fostered interest in organ preservation for urothelial carcinoma [22,23]. Notwithstanding concerns regarding the multifocality and high rate of concomitant upper tract disease [24], rates of overall survival between radical cystectomy and strategies employing multimodal treatments with salvage cystectomy are similar [25–27].

RADICAL TRANSURETHRAL RESECTION OR PARTIAL CYSTECTOMY PLUS CHEMOTHERAPY

In light of the improvements in all-cause mortality attributed to NAC regimens, several investigators have explored the role of bladder preservation in those select patients who achieve complete clinical response (cT0) on restaging TUR after NAC. In 1998, Herr *et al.* [28] evaluated 111 patients with muscle invasive urothelial carcinoma, 54% of whom achieved a cT0 response on restaging TUR after prior chemotherapy. Of this group, 72% opted for bladder preservation. At the completion of 10 years of follow-up, 74% were alive and 58% had an intact bladder. By comparison, only 65% of the radical cystectomy patients were alive at the completion of follow-up. As with many studies, it is difficult to ascertain

whether these differences were due to treatment effect or confounding by indication. In a further analysis, de Vere White *et al.* [29] evaluated 77 patients who received three cycles of gemcitabine, paclitaxel, and carboplatin for muscle-invasive bladder cancer. After restaging TUR, 46% achieved an apparent complete clinical response. Of this subset, 33% received prompt cystectomy, which noted a disturbingly high proportion (60%) of residual tumor in the bladder specimen. Despite the mitigating fact that these patients received non-platinum-based chemotherapy, the authors urge consideration to definitive local therapy despite apparent cT0 pathology.

In 2011, Koga *et al.* [30] evaluated 183 patients with muscle-invasive urothelial carcinoma, 83 of whom were considered initial candidates for partial cystectomy, based on post-TUR criteria of small volume and well circumscribed tumors that did not involve the bladder neck or trigone. This subset then received concurrent cisplatin and radiotherapy over 4 weeks to 40 Gy total. A total of 65 patients ultimately underwent partial cystectomy with pelvic lymph node dissection, 71% of whom remained with an intact bladder. The remainder underwent completion cystectomy because of persistent muscle-invasive disease. In the highly selected partial cystectomy cohort, 5-year cancer-specific survival (CSS) and recurrence-free survival were both 100% after a median follow-up of 45 months.

TRIMODAL THERAPY: TRANSURETHRAL RESECTION, RADIATION THERAPY, AND CHEMOTHERAPY

Despite the successes noted in bimodal strategies, the most common approach to bladder preservation has utilized trimodal therapy. Selection criteria for this paradigm should assess tumor histology, stage, hydronephrosis, multifocality, presence of carcinoma in situ, extent of tumor, and existence of disease outside the bladder [31]. Management is initiated with an aggressive TUR, with an aim for complete tumor resection. This is followed by external beam radiation to the pelvis, with dosing to 40–45 Gy and concomitant radiosensitizing chemotherapy, such as 5-fluorouracil, cisplatin, gemcitabine, or paclitaxel. The addition of chemotherapy has the dual benefit of enhancing the radiotherapy and systemically treating micro-metastatic disease [32]. After completion of this course of treatment, patients proceed to repeat TUR. Those with persistent disease are typically referred for cystectomy, whereas responders often receive an additional radiation course of 20–25 Gy. Cystoscopic surveillance continues at 3–6 months intervals. These protocols have largely been developed at Massachusetts General Hospital (MGH) and via cooperative institutions such as the Radiation Therapy Oncology Group (RTOG) [33].

RTOG 85-12 was the initial trial to introduce this standardized trimodal paradigm. In a cohort of 42 patients, 4-year survival was 64% utilizing concomitant cisplatin and induction radiotherapy of 40 Gy. As delineated above, responders were allocated to further radiotherapy, whereas those patients with persistent disease were referred for cystectomy [34]. In a follow-up series, RTOG 95-06, 34 patients with muscle invasive bladder cancer received complete TUR, combination cisplatin and 5-fluorouracil, and twice-a-day radiotherapy at 3 Gy per fraction for a total dose of 24 Gy. Those patients with complete clinical response received consolidation chemotherapy and repeat radiation to a total dose of 44 Gy. A total of 67% of patients had clinical resolution of disease with 83% survival at 3 years [35].

More recently, investigators have evaluated the addition of alternative chemotherapeutic agents such as gemcitabine and paclitaxel. In a series of 80 patients receiving concomitant cisplatin and paclitaxel with hyperfractionated radiotherapy to 21 Gy, the complete response rate was 81%. Responders received adjuvant gemcitabine with cisplatin and consolidation radiotherapy to 45 Gy total. Actuarial 5-year overall survival was 56% and disease-specific survival was 71% [36]. Similarly, in 2011, Caffo *et al.* [37] presented the combined results

of two small, prospective trials, totaling 26 patients, who received concurrent gemcitabine and cisplatin with fractionated radiotherapy to 54 Gy. Actuarial 5-year overall survival in this series was 70% with a disease-specific survival of 79% and an intact bladder proportion of 74%.

SUPERFICIAL RECURRENCE AFTER TRIMODAL TREATMENT

Regardless of the type of treatment, patients with a diagnosis of urothelial carcinoma and an intact bladder require vigilant follow-up. For those patients with persistent or recurrent muscle invasive bladder cancer, the recommendation is to proceed to radical cystectomy. The data are less clear on the best course of management for superficial disease recurrence after trimodal therapy. In 2003, Pieras *et al.* [38] evaluated a select cohort of 51 patients who underwent bladder preservation with bimodal TUR and carboplatin with vinblastine. A total of 82% of these patients were considered responders and elected bladder preservation. Of this group, 18 patients (43%) were noted to have superficial recurrence at the time of referral for bladder preservation. The authors noted no difference in CSS between those patients with superficial recurrence (94% CSS) compared to those without disease recurrence (89% CSS). Comparably, Zietman *et al.* [39] in a series of 190 patients enrolled at Massachusetts General Hospital and treated with trimodal therapy noted a 26% rate of superficial recurrence and also found no significant difference in 5-year survival between those with superficial recurrence and those that remained free of disease. Importantly, however, after 8 years of follow-up, 61% of recurrence-free patients were alive with an intact bladder, while survival with a functional bladder was a mere 34% for those with superficial recurrence. Thus, the management of patients with superficial recurrence after bladder preservation remains a clinical quandary.

PELVIC TOXICITY AFTER BLADDER-PRESERVING THERAPIES

The benefits of bladder-sparing therapies are manifest only if they outweigh the risks. Evidence from quality-of-life studies suggest that patients undergoing bladder preservation enjoy continued appropriate bladder function and sustained sexual function after treatment [40]. Not surprisingly, given their leadership role, researchers at RTOG and MGH have described their experience with complications after trimodal therapy. In 285 patients after a mean follow-up of 5.4 years, 6% of patients experienced late grade III genitourinary toxicities, such as frequency and dysuria, whereas less than 2% of patients experienced late grade III bowel toxicities, such as diarrhea or colic. The median duration of these complications was 7 months, which typically decreased over time. Importantly, there were no late grade IV complications, such as severe hemorrhagic cystitis or bowel necrosis in this series. No patients required a cystectomy because of treatment-associated complications [41].

FUTURE DIRECTIONS

‘The overarching goal of personalized medicine is to optimize medical care and outcomes for each individual, to include treatments, medication types and dosages, and/or prevention strategies that may differ from person to person – resulting in an unprecedented customization of patient care’ [42]. The future key to multimodal therapy will be the ability to precisely and prospectively determine those individuals at highest risk for disease progression and mortality, so that they can be targeted for more aggressive approaches. To this end, future treatment strategies for various solid tumors will incorporate a personalized approach based upon molecular diagnostic tools to predict risk of recurrence, progression, and response to specific therapeutic agents. Investigators have already begun to develop molecular instruments to better identify patients at high risk for nodal disease. Smith *et al.* [43] recently reported the validation of a gene-expression model (GEM) for the prediction of nodal metastasis at the time of radical cystectomy. When incorporated into a multivariable

model comprising known predictors of nodal disease, the gene-expression score remained highly predictive of the presence of lymph node metastases. Shah *et al.* [44[■]] recently described the dual challenges of improving the paradigm by which we treat bladder cancer – enhancing our ability to accurately stage patients and refining our ability to predict which patients will respond to particular chemotherapy regimens. Progress in pretreatment risk-stratification and prediction of individual tumor response will allow practitioners to tailor treatment strategies to individual patients' risk profiles, predicted response, treatment goals, and specific utility functions.

CONCLUSION

It has been repeatedly demonstrated in multiple series that urothelial carcinoma is responsive to both chemotherapy and radiation. The challenge has been two-fold – to determine in which patients these modalities should be added to, or replace, radical surgery and the optimal timing of these alternate treatment strategies. The key to solving these choices will be further work through properly conducted randomized trials and additional efforts to accurately and reliably assess an individual's disease-related risk.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

1. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. *CA Cancer J Clin.* 2011; 61:212–236. [PubMed: 21685461]
2. Wein, AJ.; Louis, R.; Kavoussi, MD., et al. *Campbell-Walsh urology.* W B Saunders Co; Philadelphia: 2011.
3. Scardino, PT.; Linehan, WM.; Zelefsky, MJ., et al., editors. *Comprehensive textbook of genitourinary oncology.* Lippincott Williams & Wilkins; Philadelphia: 2011.
4. Kaufman DS, Shipley WU, Feldman AS. Bladder cancer. *Lancet.* 2009; 374:239–249. [PubMed: 19520422]
5. Rübber H, Lutzeyer W, Fischer N, et al. Natural history and treatment of low and high risk superficial bladder tumors. *J Urol.* 1988; 139:283–285. [PubMed: 3339726]
6. Stein JP, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1054 patients. *J Clin Oncol.* 2001; 19:666–675. [PubMed: 11157016]
7. Madersbacher S, Hochreiter W, Burkhard F, et al. Radical cystectomy for bladder cancer today – a homogeneous series without neoadjuvant therapy. *J Clin Oncol.* 2003; 21:690–696. [PubMed: 12586807]

- 8■. Yafi FA, Aprikian AG, Chin JL, et al. Contemporary outcomes of 2287 patients with bladder cancer who were treated with radical cystectomy: a Canadian multicentre experience. *BJU Int*. 2011; 108:539–545. [PubMed: 21166753] [A recent evaluation of 2287 patients from multi-institutional series in a universal healthcare system. Five-year overall survival was 57%. Local recurrence rates were 6%. A total of 3.1% of patients received neoadjuvant chemotherapy, whereas 19.4% received adjuvant chemotherapy.]
9. Dalbagni G, Genega E, Hashibe M, et al. Cystectomy for bladder cancer: a contemporary series. *J Urol*. 2001; 165:1111–1116. [PubMed: 11257649]
- 10■. International Collaboration of Trialists; Medical Research Council Advanced Bladder Cancer Working Party (now the National Cancer Research Institute Bladder Cancer Clinical Studies Group); European Organisation for Research and Treatment of Cancer GenitoUrinary Tract Cancer Group; Australian Bladder Cancer Study Group; National Cancer Institute of Canada Clinical Trials Group; Finnbladder; Norwegian Bladder Cancer Study Group; Club Urologico Espanol de Tratamiento Oncologico Group. Griffiths G, Hall R, et al. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. *J Clin Oncol*. 2011; 29:2171–2177. [PubMed: 21502557] [A multicenter Phase III trial of 966 patients recruited between 1989 and 1995, randomized to three cycles of CMV or no chemotherapy. Neoadjuvant chemotherapy provides a small, but significant survival advantage.]
11. 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*. 2003; 349:859–866. [PubMed: 12944571]
12. Sherif A, Holmberg L, Rintala E, et al. Nordic Urothelial Cancer Group: Neoadjuvant cisplatinum based combination chemotherapy in patients with invasive bladder cancer: a combined analysis of two Nordic studies. *Eur Urol*. 2004; 45:297–303. [PubMed: 15036674]
- 13■. Fedeli U, Fedewa SA, Ward EM. Treatment of muscle invasive bladder cancer: evidence from the National Cancer Database; 2003 to 2007. *J Urol* 2011. 185:72–78. [A recent evaluation of national trends in utilization of chemotherapy from the National Cancer Database.]
14. Miles BJW, Fairey AS, Eliasziw M, et al. Referral and treatment rates of neoadjuvant chemotherapy in muscle-invasive bladder cancer before and after publication of a clinical practice guideline. *Can Urol Assoc J*. 2010; 4:263–267. [PubMed: 20694104]
15. Raj GV, Karavadia S, Schlomer B, et al. Contemporary use of perioperative cisplatin-based chemotherapy in patients with muscle-invasive bladder cancer. *Cancer*. 2011; 117:276–282. [PubMed: 20830767]
16. Feifer AH, Taylor JM, Tarin TV, Herr HW. Maximizing cure for muscle-invasive bladder cancer: integration of surgery and chemotherapy. *Eur Urol*. 2011; 59:978–984. [PubMed: 21257257]
17. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Adjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis of individual patient data Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. *Eur Urol*. 2005; 48:189–199. discussion 199–201. [PubMed: 15939530]
- 18■. Svatek RS, Shariat SF, Lasky RE, et al. The effectiveness of off-protocol adjuvant chemotherapy for patients with urothelial carcinoma of the urinary bladder. *Clin Cancer Res*. 2010; 16:4461–4467. [PubMed: 20651056] [A multicenter evaluation of 932 patients who received adjuvant chemotherapy demonstrating improved survival in recipients, particularly those in the highest risk quintile.]
19. Donat SM, Shabsigh A, Savage C, et al. Potential impact of postoperative early complications on the timing of adjuvant chemotherapy in patients undergoing radical cystectomy: a high-volume tertiary cancer center experience. *Eur Urol*. 2009; 55:177–185. [PubMed: 18640770]
- 20■. Stimson CJ, Chang SS, Barocas DA, et al. Early and late perioperative outcomes following radical cystectomy: 90-day readmissions, morbidity and mortality in a contemporary series. *J Urol*. 2010; 184:1296–1300. [PubMed: 20723939] [A large, single institution series of 753 patients, describing morbidity up to 90 days. Rates of readmission were up to 26%, whereas 30-day and 90-day mortality rates were 2.1 and 6.9%, respectively.]
21. Millikan R, Dinney C, Swanson D, et al. Integrated therapy for locally advanced bladder cancer: final report of a randomized trial of cystectomy plus adjuvant M-VAC versus cystectomy with

- both preoperative and postoperative M-VAC. *J Clin Oncol*. 2001; 19:4005–4013. [PubMed: 11600601]
22. Fernando SA, Sandler HM. Multimodality bladder preservation therapy for muscle-invasive bladder tumors. *Semin Oncol*. 2007; 34:129–134. [PubMed: 17382796]
 23. Balar A, Bajorin DF, Milowsky MI. Management of invasive bladder cancer in patients who are not candidates for or decline cystectomy. *Ther Adv Urol*. 2011; 3:107–117. [PubMed: 21904567]
 24. Herr HW, Cookson MS, Soloway SM. Upper tract tumors in patients with primary bladder cancer followed for 15 years. *J Urol*. 1996; 156:1286–1287. [PubMed: 8808855]
 25. 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 and Oncology Group 89-03. *J Clin Oncol*. 1998; 16:3576–3583. [PubMed: 9817278]
 26. Shipley WU, Kaufman DS, Zehr E, et al. Selective bladder preservation by combined modality protocol treatment: long-term outcomes of 190 patients with invasive bladder cancer. *Urology*. 2002; 60:62–68. [PubMed: 12100923]
 27. Houseset 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*. 1993; 1:2150–2157.
 28. Herr HW, Bajorin DF, Scher HI. Neoadjuvant chemotherapy and bladder-sparing surgery for invasive bladder cancer: ten-year outcome. *J Clin Oncol*. 1998; 16:1298–1301. [PubMed: 9552029]
 29. DeVere White RW, Lara PN Jr, Goldman B, et al. A sequential treatment approach to myoinvasive urothelial cancer: a phase II Southwest Oncology Group trial (S0219). *J Urol*. 2009; 181:2476–2480. [PubMed: 19371909]
 30. Koga F, Kihara K, Yoshida S, et al. Selective bladder-sparing protocol consisting of induction low-dose chemoradiotherapy plus partial cystectomy with pelvic lymph node dissection against muscle-invasive bladder cancer: oncological outcomes of the initial 46 patients. *BJU Int*. 2011 [Epub ahead of print]. [A recent analysis of 46 patients treated with partial cystectomy and chemoradiotherapy. In a highly select group, 5-year cancer-specific survival was 100%.]
 31. Rodel C, Grabenbauer GG, Kuhn R, et al. Combined-modality treatment and selective organ preservation in invasive bladder cancer: long-term results. *J Clin Oncol*. 2002; 20:3061–3071. [PubMed: 12118019]
 32. Seiwert TY, Salama JK, Vokes EE. The concurrent chemoradiation paradigm – general principles. *Nat Clin Pract Oncol*. 2007; 4:86–100. [PubMed: 17259930]
 33. Shipley W, Zietman A, Kaufman D, et al. Selective bladder preservation by trimodality therapy for patients with muscularis propria invasive bladder cancer and who are cystectomy candidates – The Massachusetts General Hospital and Radiation Therapy Group experiences. *Semin Radiat Oncol*. 2004; 15:36–41. [PubMed: 15662605]
 34. Tester W, Porter A, Asbell S, et al. Combined modality program with possible organ preservation for invasive bladder carcinoma: results of RTOG 85-12. *Int J Radiat Oncol Biol Phys*. 1993; 25:783–790. [PubMed: 8478228]
 35. Kaufman DS, Winter KA, Shipley WU, et al. The initial results in muscle invading bladder cancer of RTOG 95-06: phase I/II trial of transurethral surgery plus radiation therapy with concurrent cisplatin and 5-FU followed by selective bladder preservation or cystectomy depending on the initial response. *Oncologist*. 2000; 5:471–476. [PubMed: 11110598]
 36. Kaufman DS, Winter KA, Shipley WU, et al. Phase I–II RTOG study (99-06) of patients with muscle-invasive bladder cancer undergoing transurethral surgery, paclitaxel, cisplatin, and twice-daily radiotherapy followed by selective bladder preservation or radical cystectomy and adjuvant chemotherapy. *Urology*. 2009; 73:833–837. [PubMed: 19100600]
 37. Caffo O, Fellin G, Graffer U, et al. Gemcitabine and radiotherapy plus cisplatin after transurethral resection as conservative treatment for infiltrating bladder cancer: long-term cumulative results of 2 prospective single-institution studies. *Cancer*. 2011; 117:1190–1196. [PubMed: 20960501] [A small combined series of 26 patients demonstrating 70% overall survival at a median follow-up of 74 months.]

38. Pias E, Palou J, Salvador J, et al. Management and prognosis of transitional cell carcinoma. Superficial recurrence in muscle invasive bladder cancer after bladder preservation. *Eur Urol*. 2003; 44:222–225. [PubMed: 12875942]
39. Zietman AL, Grocela J, Zehr E, et al. Selective bladder conservation using transurethral resection, chemotherapy, and radiation: management and consequences of Ta, T1, and Tis recurrence within the retained bladder. *Urology*. 2001; 58:380–385. [PubMed: 11549485]
40. Zietman AL, Sacco D, Skowronski U, et al. Organ conservation in invasive bladder cancer by transurethral resection, chemotherapy and radiation: results of a urodynamic and quality of life study on long-term survivors. *J Urol*. 2003; 170:1772–1776. [PubMed: 14532773]
41. Efsthathiou JA, Bae K, Shipley WU, et al. Late pelvic toxicity after bladder-sparing therapy in patients with invasive bladder cancer: RTOG 89-03, 95-06, 97-06, 99-06. *J Clin Oncol*. 2009; 27:4055–4061. [PubMed: 19636019]
42. Ginsburg GS, Willard HF. Genomic and personalized medicine: foundations and applications. *Transl Res*. 2009; 154:277–287. [PubMed: 19931193]
43. Smith SC, Baras AS, Dancik G, et al. A 20-gene model for molecular nodal staging of bladder cancer: development and prospective assessment. *Lancet Oncol*. 2011; 12:137–143. [PubMed: 21256081]
- 44■. Shah JB, McConkey DJ, Dinney CPN. New strategies in muscle-invasive bladder cancer: on the road to personalized medicine. *Clin Cancer Res*. 2011; 17:2608–2612. [PubMed: 21415213] [A thoughtful discussion about the history of bladder cancer and the future prospects of treatments tailored to individual patients.]

KEY POINTS

- Five-year overall survival for muscle-invasive urothelial carcinoma of the bladder after radical cystectomy is between 45 and 66%.
- Neoadjuvant chemotherapy confers a 6–8% survival advantage over the same timeframe, although it is dramatically underutilized.
- Adjuvant chemotherapy provides similar survival advantage, yet as many as 64% of patients may experience a posttreatment complication.
- Transurethral resection and concomitant chemotherapy can provide 5-year survival rates comparable to radical cystectomy in select patients; nonetheless, residual tumor rates may be alarmingly high.
- Trimodal therapy, employing transurethral resection, radiation treatment, and chemotherapy, results in similar 5-year survival rates to radical cystectomy; however, patients with disease recurrence and an intact bladder may have significantly worse survival.
- Grade III pelvic complications from trimodal therapy occur in 2–6% of patients.