# Advances in the Management of Muscle-Invasive Bladder Cancer Through Risk Prediction, Risk Communication, and Novel Treatment Approaches

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**Abstract:** Although level I evidence supports the use of neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy for the management of patients with muscle-invasive bladder cancer (MIBC), these treatment modalities are utilized in only a subset of patients. The reasons for lack of implementation of these treatment standards are multiple; patients may be considered ineligible for cisplatin or too old for safe cystectomy. Better means of determining a patient's probability of recurrence with surgery alone, or likelihood of benefit with neoadjuvant chemotherapy, are clearly needed. Models have been developed to individualize estimates of non–organ-confined disease based on pretreatment variables. It is critical that clinicians are able to effectively communicate complex risk-related data to patients to facilitate a shared medical decision.

Keywords
Muscle-invasive bladder cancer, cisplatin, personalized therapy

## Introduction

In 2012, approximately 73,510 patients in the United States were diagnosed with bladder cancer, and approximately 14,880 patients succumbed to the disease.[1] Although the majority of patients (approximately 85%) will have clinically localized disease at the time of diagnosis, up to 50% of patients who present with muscle-invasive disease will ultimately develop metastatic recurrence. The median survival of patients with metastatic bladder cancer is only approximately 14 months.[2]

The development of novel therapeutic approaches to the management of bladder cancer has lagged far behind other malignancies (Figure 1). Since 1995, there has been 1 new drug approved for the treatment of bladder cancer in the United States, an intravesical therapy for the treatment of non–muscle-invasive disease. (Note: Vinflunine has been approved for second-line treatment of metastatic bladder cancer by the European Medicines Agency.) There are multiple potential reasons for the lack of progress, including disease biology, lack of funding, and lack of investigator interest. However, bladder cancer is also largely a disease of the elderly (median age of diagnosis, 73 years), and

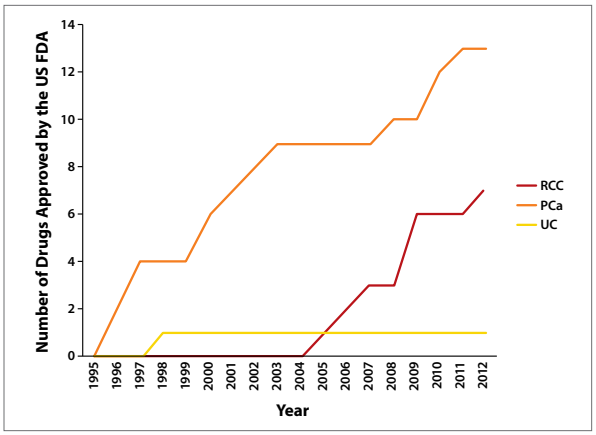


**Figure 1.** New drug approvals for genitourinary cancers between 1995 and 2012. RCC=renal cell carcinoma; PCa=prostate cancer; UC=urothelial cancer; US FDA=US Food and Drug Administration.

patients often have smoking-related comorbidities. Over the past decade, there has been an increasing appreciation for the significant disconnect between the efficacy of "gold standard" therapies for this disease, and the effectiveness of such treatments when applied to the general population of patients with bladder cancer.

This review will focus on the management of muscle-invasive bladder cancer (MIBC) as a paradigm for addressing the difficulties in translating level I evidence to "real world" patients. MIBC was selected for discussion for 2 major reasons: (1) Only approximately 8–10% of patients with metastatic bladder cancer have radiographic evidence of metastases at the time of presentation—the vast majority initially present with clinically localized disease; and (2) MIBC is potentially curable, particularly with combined modality approaches. It is in this clinical disease state where, arguably, the largest impact on the natural history of bladder cancer may occur.

## Neoadjuvant Chemotherapy and Radical Cystectomy: Gold Standard Management for MIBC?

Surgical removal of the bladder, with pelvic lymph dissection, is potentially curative in patients with MIBC. In large surgical series, the vast majority of patients with pathologically organ-confined disease are cured with this approach, although patients with evidence of pathologic lymph node involvement fare significantly worse.[3] However, radical cystectomy is a major operation often associated with a significant recovery period. This procedure requires a skilled surgeon and adequate support team, factors that have contributed to an increasing regionalization of care.[4]

Due to these considerations, as well as the older age of most patients with bladder cancer, only a minority of patients with muscle-invasive disease are undergoing cystectomy. This issue has been addressed in population-based studies using Surveillance Epidemiology and End Results (SEER) data and data derived from the National Cancer Data Base (NCDB).[5,6] In an NCDB analysis, more than 40,388 patients with MIBC diagnosed between 2003 and 2007 were analyzed with regards to patterns of care.[5] Notably, only 42.9% of patients were treated with cystectomy, and this proportion decreased significantly with increasing age.

Two randomized trials and a meta-analysis have demonstrated that neoadjuvant cisplatin-based combination chemotherapy results in an improvement in survival in patients with MIBC.[7-9] In the Southwestern Oncology Group (SWOG) 8710 trial comparing 3 cycles of methotrexate, vinblastine, and doxorubicin plus cisplatin (MVAC) followed by cystectomy with cystectomy alone, the neoadjuvant chemotherapy arm achieved a median survival of 77 months compared with 46 months with surgery ($P$=.06 by a 2-sided stratified log-rank test).[9] Similar results were demonstrated in an international randomized trial of neoadjuvant cisplatin, methotrexate, and vinblastine followed by local therapy versus local therapy alone. In this study, neoadjuvant chemotherapy was associated with a statistically significant 16% reduction in the risk of death (hazard ratio [HR], 0.84; 95% confidence interval [CI], 0.72–0.99; $P$=.037).[8]

Are patients with MIBC receiving neoadjuvant chemotherapy? A patterns-of-care analysis was performed utilizing NCDB data on 7,161 patients with stage III bladder cancer diagnosed between 1998 and 2003.[10] Among these patients, perioperative chemotherapy was administered to 11.6% of patients, with only 1.2% receiving neoadjuvant chemotherapy. A single-center analysis performed by Raj and colleagues revealed that only 17% of patients with MIBC received neoadjuvant chemotherapy, despite "adequate" renal function (calculated creatinine clearance ≥60 mL/min) in 67% of patients.[11] A questionnaire of European centers designed to estimate practice patterns demonstrated that only 9–20% of patients with MIBC were considered for neoadjuvant chemotherapy.[12]

## Identifying Barriers to Optimal Care

There are several possible explanations for the finding that only approximately half of patients with MIBC undergo cystectomy and for the dismal uptake of neoadjuvant chemotherapy. As mentioned, bladder cancer is a disease of the elderly. The majority of patients have a history of smoking and smoking-related comorbidities. Renal impairment, due to age; comorbidities; and tumor-related ureteral obstruction are frequently present. A study of 1,284 patients with MIBC evaluated the

proportion of patients who would be considered ineligible for cisplatin-based perioperative chemotherapy due to impaired renal function alone.[13] In this study, cisplatin-ineligibility was defined as a calculated creatinine clearance/glomerular filtration rate of less than 60 mL/min/1.73 $m^2$. Importantly, this analysis revealed that more than 40% of patients older than 70 years would have been considered ineligible for cisplatin. Although impaired renal function may explain the lack of uptake of neoadjuvant therapy in a significant subset of patients, this factor alone does not provide adequate explanation for a large proportion of patients who are not receiving combined modality care.

Prospective studies are required to determine the precise reasons for the poor uptake of neoadjuvant chemotherapy. Feifer and colleagues, in association with the Bladder Cancer Advocacy Network Muscle Invasive Bladder Cancer Quality of Care Consortium, have prospectively evaluated patterns of care in a phase I study across a number of academic institutions.[14] This study, which evaluated 4,972 patients, revealed that perioperative chemotherapy was integrated in 12.4% of patients, slightly better than reported in the NCDB study, but still quite dismal considering these were mostly large volume referral centers. Notably, approximately one-third of patients treated with perioperative chemotherapy were treated with non–cisplatin-based regimens. This study has now expanded to a phase II portion that is prospectively collecting data on the reasons why neoadjuvant chemotherapy was not administered, and will provide critical data regarding approaches to optimize quality care.

## Risk Predicting and Communication

Often-cited reasons for lack of administration of neoadjuvant chemotherapy include statements such as, "My patient is not at high enough risk" and "My patient does not want chemotherapy." Discussions regarding perioperative chemotherapy are an exercise in risk prediction and communication. Risk can be defined as the product of probability × consequence.[15] The probability is simply the numerical chance of an event's occurrence, which can often be quantified. However, the consequence, or severity, of the event is subjective, variable dependent on the individual, and difficult to quantify. There are several "probabilities" relevant to perioperative chemotherapy that could be individualized to enhance shared decision-making. What is the likelihood that a particular patient will develop recurrent disease with surgery alone? What is the likelihood that a particular patient will benefit from neoadjuvant chemotherapy? What is the likelihood that a particular patient will develop severe chemotherapy-related toxicities?

There are currently no optimal models to determine the probability that a patient will develop recurrence after surgery, based on information that is available at the time that neoadjuvant treatment decisions are made. Pathologic features, such as non–organ-confined disease or lymph node involvement, correlate well with the risk of recurrence and disease-specific survival. However, this information is available only after surgery. Models have been developed to individualize estimates of non–organ-confined disease based on pretreatment variables. Green and colleagues developed a nomogram comprised of clinical stage, presence of lymphovascular invasion on biopsy, and abnormal imaging (presence of hydronephrosis and/or non–organ-confined disease) that predicted ≥pT3Nany or pTanyN+ disease with an area under the receiver operating characteristic curve (AUC) of 0.828.[16] A model comprised of serum levels of the tumor markers CEA, CA 125, and CA 19-9 in patients with MIBC was developed and externally validated, predicting non–organ-confined disease with an AUC of 0.79.[17] Smith and associates sought to develop a gene expression model, based on primary tumor tissue, that could be utilized to predict pathologic lymph node status in patients with MIBC.[18] Importantly, this group first developed a gene set that could be sufficiently analyzed in both fresh-frozen and paraffin-embedded tissue. A 20-gene model was developed and externally validated, which predicted the likelihood of pathologic lymph node involvement with an AUC of 0.67 (95% CI, 0.60–0.75). Importantly, this gene expression model was also predictive of disease-specific survival.

A patient who is shown to be at high risk for recurrence after cystectomy will not necessarily derive a benefit from neoadjuvant chemotherapy. Research from Lee and colleagues has focused on developing gene expression models of chemotherapy sensitivity.[19] The coexpression extrapolation (COXEN) bioinformatics approach utilizes publicly available gene expression and drug sensitivity data from the National Cancer Institute (NCI)-60 cell line panel, and integrates gene expression data from human tumors of interest to determine which genes are most commonly co-expressed.[19] A gene expression model can then be developed to predict sensitivity to a single chemotherapeutic agent or a multidrug regimen. The COXEN approach has been retrospectively applied to a cohort of patients with bladder cancer who had been treated with neoadjuvant MVAC.[20] In this study, the gene expression model score correlated with the likelihood of achieving tumor downstaging, and the 3-year overall survival for those with favorable gene expression model scores was 81% versus 33% for those with less favorable scores ($P$=.002). The COXEN approach will be further evaluated in a planned SWOG neoadjuvant study to determine the gene expression model score's ability to

**Figure 2.** Outcomes at 5 years after neoadjuvant chemotherapy and/or cystectomy in patients with muscle invasive bladder cancer. This figure illustrates 100 patients. Light gray shading represents deceased patients, black shading represents patients alive treated with cystectomy alone, and darker gray shading represents additional patients alive with the use of neoadjuvant chemotherapy. The data are derived from the Southwest Oncology Group (SWOG) trial 8710.[9]

predict pathologic complete responses in patients with MIBC randomized to either dose-dense MVAC or gemcitabine (Gemzar, Lilly) plus cisplatin.

Better means of determining an individual's probability of recurrence with surgery alone, or likelihood of benefit with neoadjuvant chemotherapy, are clearly needed. However, it is critical that we are also able to effectively communicate these complex data to patients to facilitate a shared medical decision. How should we communicate risk to patients? Should we speak about *P* values, number needed to treat, hazard ratios? Several studies suggest that patients and health care providers have difficulty with numeracy, or quantitative literacy. In one such study, 50% of participants were unable to convert 1% to 10 in 1,000, while in another, participants had difficulty determining which was the higher risk, 1 in 27 versus 1 in 37.[21,22] Health care providers are also prone to framing or presenting information in such a way that inappropriately influences decisions. Best practices in risk communication suggest that most patients prefer that risk be communicated in a graphical format and that absolute differences, rather than relative differences, should be conveyed. Figure 2 illustrates the results of the SWOG neoadjuvant MVAC study (8710) in graphical format. Are we presenting discussions of neoadjuvant chemotherapy in this light to our patients? Would more effective risk communication impact the dismal rates of uptake of neoadjuvant chemotherapy?

## Developing Therapeutic Approaches in MIBC for the "Real World"

As noted, a large proportion of patients with MIBC do not receive perioperative cisplatin-based chemotherapy because they are considered cisplatin-ineligible.[23,24] Treatments that reduce the risk of recurrence and that can be safely and widely applied to the general population of patients with MIBC are urgently needed. One novel approach in this regard is DN24-02, an autologous cellular immunotherapy product designed to stimulate an immune response against human epidermal growth factor receptor 2 (HER2)/neu. In an ongoing trial, patients with urothelial cancer who are postsurgery, deemed at high risk of relapse, and have at least 1+ HER2/neu expression by immunohistochemistry are being randomized to 3 treatments with DN24-02 versus placebo (NCT01353222).[25] The primary endpoint of this trial is overall survival.

Not only are many patients considered cisplatin-ineligible, but as previously cited, a large proportion of patients with MIBC are not undergoing cystectomy. In a potentially practice-altering trial, James and colleagues randomized 350 patients with MIBC to treatment with radiation therapy alone or radiation therapy with concurrent 5-fluorouracil and mitomycin.[26] The primary endpoint of the trial was locoregional disease-free survival. The study met its primary endpoint, with an improvement in locoregional disease-free survival (HR, 0.68, 95%

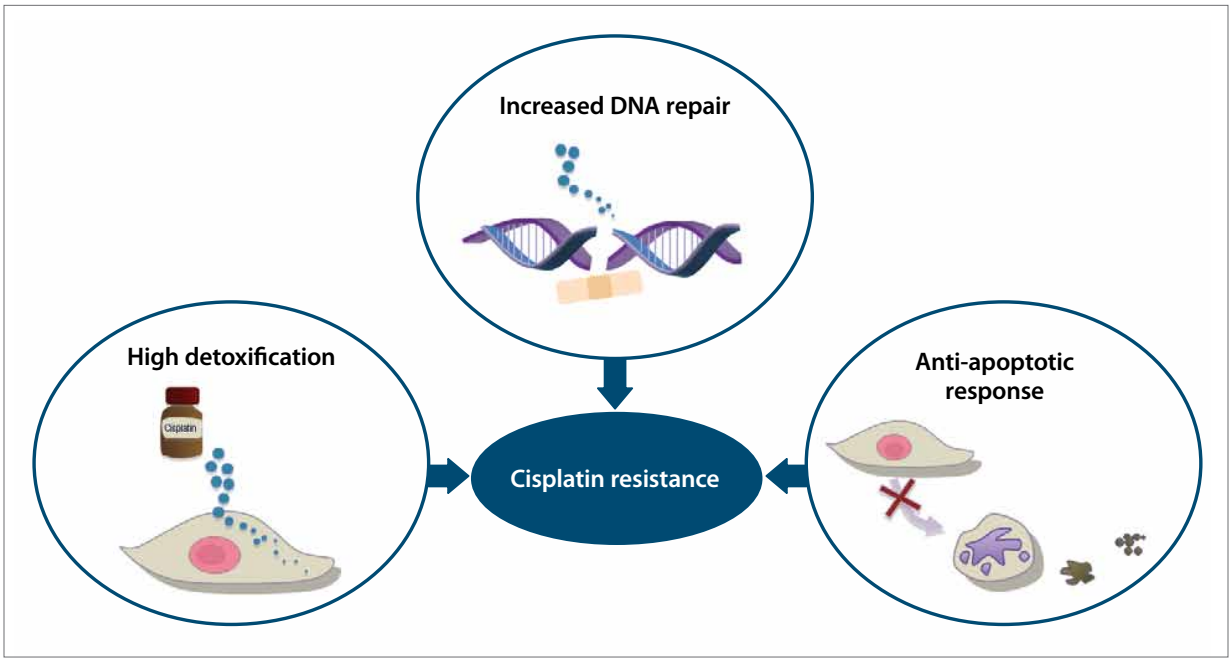


**Figure 3.** Mechanisms of cisplatin resistance in muscle-invasive bladder cancer. Alterations in DNA repair, drug detoxification, and apoptotic pathway deregulation are shown.

CI, 0.48–0.96; *P*=.03). Notably, the 5-year overall survival for patients treated with chemoradiation was 48%, comparable to results from many large cystectomy series.

Refining the selection of patients most likely to benefit from radiation may further optimize this approach. Immediately following exposure to radiation, DNA double-strand breaks are detected by the MRE11-RAD50-NSB1 complex, which results in recruitment of signaling and repair proteins.[27] Choudhury and coworkers performed a study to assess whether expression of a panel of DNA damage–signaling proteins (MRE11, RAD50, NBS1, ATM, and H2AX), as identified by immunohistochemistry in pretreatment samples from patients with MIBC, could be used as predictive or prognostic biomarkers.[28] Protein expression was analyzed in 3 cohorts of patients: 2 cohorts treated with radiation alone and 1 cohort treated with cystectomy. In an initial cohort of patients treated with radiation, low tumor MRE11 expression was associated with an inferior cancer-specific survival (CSS) compared with high expression (43.1% vs 68.7% 3-year CSS; *P*=.012). Importantly, this finding was confirmed in a prospective cohort of patients treated with radiation (3-year CSS, 43.0% vs 71.2%; *P*=.020). In the cystectomy cohort, MRE11 was not associated with CSS, and high MRE11 in the combined radiation cohorts had significantly better CSS compared with high expression in the cystectomy cohorts (69.9% vs 53.8%, 3-year CSS; *P*=.021). These findings suggest that MRE11 may indeed represent a predictive biomarker for radiation therapy in patients with MIBC.

These concepts will be further analyzed in a planned Radiation Therapy Oncology Group trial in which patients with MIBC will receive radiation with concurrent 5-fluorouracil and mitomycin. In this study, pretreatment biomarkers, including MRE11, will be correlated with clinical outcomes.

## Overcoming Platinum Resistance

Neoadjuvant chemotherapy likely confers a "large benefit to a small subset" of patients with MIBC. An enhanced ability to risk-stratify patients could improve selection of this small subset likely to benefit, but improved therapy is required to extend this benefit to a larger population of patients with MIBC. Cisplatin, a first-in-class, platinum-based DNA-damaging agent, is a mainstay of treatment for metastatic bladder cancer and MIBC. In order to both select patients most likely to benefit from therapy and identify approaches to improve upon existing therapy, the investigation of mechanisms of resistance to cisplatin in MIBC is a clinical imperative. However, the identification of molecular regulators of cisplatin resistance with prognostic or therapeutic significance has been extremely limited, particularly with regard to MIBC.

To date, the mechanisms of resistance to cisplatin include alterations in drug metabolism, DNA repair, and apoptotic pathways (Figure 3). One early finding was that metallothioneins, cysteine-rich low-molecular weight proteins that bind to endogenous

and xenobiotic metals, confer cisplatin resistance in ovarian carcinoma cells.[29] The prognostic significance of metallothioneins was later demonstrated in MIBC, but such findings have yet to be translated to impact routine clinical care.[30-32] The majority of cisplatin DNA lesions are thought to be restored by nucleotide excision repair, and particular attention has focused on excision repair cross complementation group 1 (ERCC1). However, in MIBC, ERCC1 expression was shown to predict clinical outcome in some studies,[33,34] but not all.[35,36] The inconsistency of the results is likely due, at least in part, to the use of differing assays that vary in terms of reliability and reproducibility. Alterations in the apoptotic machinery of MIBC cells have also been linked to cisplatin resistance. Conflicting results have been published regarding the tumor suppressor protein p53, which has a central role in the induction of apoptosis.[37,38] High expression of the anti-apoptotic protein Bcl-2 has been associated with cisplatin resistance in both preclinical[39,40] and clinical studies.[41] Notably, Cooke and coworkers showed in a cohort of 51 patients with MIBC treated with neoadjuvant cisplatin-based chemotherapy that patients with Bcl-2–negative tumors had better prognosis.[41] Inhibition of DNA repair mechanisms[42] and downregulation of anti-apoptotic proteins[39] enhances cisplatin sensitivity in preclinical models. These studies imply that targeting these molecules may be a novel therapeutic strategy for the treatment of MIBC, although few drugs targeting anti-apoptotic proteins have entered clinical investigation in bladder cancer as of yet.

Germline variations may also play a role in platinum sensitivity. In an analysis of 205 patients with urothelial cancer, single nucleotide polymorphisms (SNPs) in 80 genes associated with urothelial cancer or platinum response were genotyped and found to correlate with a response to cisplatin-based or carboplatin-based therapy.[43] A multivariable model was developed, and after adjusting for clinical prognostic factors (performance status and presence of visceral metastases), 4 SNPs retained independent associations with response. Notably, the greater the SNP score, the lower the response rate (which was 84% in patients with a score of 0–1 vs 19% in patients with a score of 6–8).

In light of the scarcity of analytically validated and clinically qualified biomarkers of cisplatin sensitivity and resistance in MIBC, it is perhaps not surprising that the treatment and survival of patients has changed little over the past few decades. The identification of molecular regulators of cisplatin sensitivity and resistance in MIBC remains an important challenge, as improving the efficacy of therapy would also likely have a major impact on the utilization of systemic therapy in the neoadjuvant setting.

## Conclusions

The treatment of bladder cancer has been hampered by evasive advances in systemic therapy and barriers to effectively translating the advances that have been made to the general population of patients with this disease. A better appreciation for the disconnect between efficacy and effectiveness, however, has resulted in several recent novel approaches to optimize delivery of care that is potentially tailored not only to genomic characteristics of the patient's tumor, but also to the individual's comorbidities, functional status, and values/desires. Only when all of these aspects are integrated will we have truly entered the age of "personalized" care.

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