

Bladder Cancer: Narrowing the Gap Between Evidence and Practice

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The American Cancer Society estimates that bladder cancer (BC) accounted for more than 14,000 deaths in 2008. At only 14 months, the median survival for patients with metastatic BC has not significantly changed during the last two decades. No new agents have been approved for BC treatment for more than a decade, few new therapies are being tested in this area, and research in BC has historically been underfunded. In addition, several therapeutic interventions known to influence survival have not been widely adopted into practice.

Cystectomy is often delayed in patients with high-risk non-muscle-invasive BC. In muscle-invasive disease, mounting evidence supports the importance of a more extensive surgical approach and the beneficial role of neoadjuvant chemotherapy on survival; however, a wide gap remains between evidence and practice. Even in academic centers, only a few patients with muscle-invasive disease undergo a more extended lymph node dissection and receive neoadjuvant chemotherapy. A recent study¹ evaluating the integration of chemotherapy for BC in the United States using the National Cancer Database revealed that only 11.6% of patients received any perioperative chemotherapy, most of those in the adjuvant setting.

Given these challenges, two imperatives are before us: (1) improving patient outcomes by defining and implementing optimal standards of care, and (2) identifying and prioritizing specific strategies to advance development of more effective therapies for patients with BC.

NON-MUSCLE-INVASIVE DISEASE

Because at least 70% of all BC initially presents as non-muscle-invasive disease, the urologist must determine a treatment strategy that balances the risk of recurrent, invasive disease (occurring in > 15% of patients), with the risk of overtreatment.^{2,3} Transurethral resection (TUR) with surveillance cystoscopy is sufficient therapy for most low-grade noninvasive tumors. Most will recur within 5 years, but will rarely invade or result in death. A single dose of perioperative intravesical chemotherapy will reduce the risk of recurrence and is more effective for index and solitary tumors. No agent appears to be superior.⁴ The impact of perioperative intravesical chemotherapy is

modest, with a 10% to 15% reduction in recurrence rates. Findings on subsequent cystoscopies, usually performed at 3-month intervals, assist in determining the clinical course of these tumors.^{5,6} Adjuvant therapy is generally reserved for those patients with multiple or multifocal recurrence or who demonstrate progression in stage or grade.

High-Risk Non-Muscle-Invasive Urothelial Carcinoma

Certain subgroups of patients, however, have a higher risk and should be considered for intravesical therapy after TUR and perioperative chemotherapy. These subgroups include patients with tumors classified as high grade, and patients with carcinoma in situ. In addition, patients with large lesions (> 3 cm), multifocal tumors, evidence of lamina propria invasion, or recurrence within 2 years have been shown to be at increased risk.⁶ Although aggressive intervention with intravesical therapy in this high-risk group leads to response rates up to 85%,^{7,8} recurrence rates are more than 50% within the first year and 90% by 5 years. In addition, up to 50% of high-risk lesions will progress to muscle-invasive disease despite intravesical therapy.³

Several morphologic and pathologic features can alter the prognosis of non-muscle-invasive disease. Flat, diffusely infiltrating tumors have a more than two-fold increased progression risk compared with papillary lesions.^{9,10} Tumors at the bladder neck, within the prostatic urethra, or at the ureteral orifices are more difficult to completely resect and accurately stage. Radical cystectomy (RC) should be offered in the presence of these adverse features because of the increased risk of understaging and progression with intravesical therapy.

Patients with high-grade or T1 tumors should undergo repeat TUR at 4 weeks to ensure accurate staging and complete eradication of all gross disease before proceeding to intravesical therapy. A randomized clinical trial has demonstrated that recurrence can be reduced as much as 37% with repeat resection, even when postoperative chemotherapy is used.^{11,12} Complete resection requires visualizing all the tumor, and fluorescent cystoscopy seems to reduce residual tumor at repeat resection.¹³

Intravesical *Bacillus Calmette-Guérin* (BCG) is widely accepted as the most effective therapy for patients with high-risk non-muscle-invasive transitional-cell carcinoma compared with chemotherapy or

TUR alone and will delay recurrence and progression, decreasing the need for immediate cystectomy.¹⁴ Usually, intravesical BCG is administered as a 6-week induction course. There is now strong evidence that a course of induction therapy followed by a course of maintenance therapy leads to significantly better outcomes than induction therapy alone,¹⁵ though not all maintenance BCG schedules provide the same benefit. The Southwest Oncology Group (SWOG) 8507 6 + 3 maintenance regimen results in a 20% absolute reduction in the recurrence rate that persists for at least 5 years. This regimen consists of 3-week miniseries of BCG instillation at 3, 6, and 12, and then every 6 months up to 36 months after initial BCG induction.¹⁶ In contrast, the use of monthly or quarterly schedules of BCG after induction therapy is not associated with improvements during a single 6-week induction course.

We recommend that after re-resection, patients with high-risk tumors undergo BCG induction therapy followed by maintenance therapy using the 6 + 3 SWOG regimen. Furthermore, although full-dose BCG is less well tolerated in the long-term maintenance setting, reduced-dose BCG markedly improves the ability of most patients to receive this full regimen.¹⁶

Treating BCG Failures

Despite the approach taken, more than 40% of patients with high-risk superficial disease will eventually experience treatment failure with adequate BCG.¹⁴ Early cystectomy should be considered in the face of BCG failure in these patients because they are at high risk of developing muscle-invasive or metastatic disease. Patients with persistent T1 BC despite a single course of BCG should be cautioned against additional BCG or second-line therapy and guided toward an RC because they have a real chance of experiencing disease progression if cystectomy is delayed.³ Unfortunately, up to 50% of patients who undergo RC in this scenario experience disease recurrence after surgery, a sobering testimony to the double-edged sword of attempting bladder preservation in the absence of a truly effective intravesical therapy. Thus, effective second-line therapy for non-muscle-invasive BC is critically needed to avoid early RC.

Several agents have been studied as second-line intravesical therapy for refractory superficial BC. Although complete response rates range from 20% to 50%, durable disease-free intervals have not been maintained. Intravesical valrubicin and gemcitabine have been tested in phase I and II studies.^{17,18} Intravesical taxane therapy (docetaxel) has also met with some success, best when combined with a maintenance course where a 13-month disease-free rate of 46% has been reported.¹⁹ Interferon alfa-2b (IFN- α -2b) is well tolerated as monotherapy for superficial BC and has shown some dose-related clinical efficacy after BCG failure, although the durability of the response is limited. IFN- α -2b has been combined with BCG in an attempt to enhance the cellular immune response to BCG and improve response.²⁰ The combination was effective in some cases of BCG-refractory disease, but many with initial responses later experienced relapse and ultimately required cystectomy.

Initial reports of combining mitomycin and BCG indicated no added benefit over either agent alone.²¹⁻²⁵ However, a recent report in a cohort of high-risk patients with T1 tumors found that the combination of BCG and electromotive mitomycin reduced the recurrence rate by 16%, the progression rate by 12.6%, the risk for death from BC by 10.6%, and the risk for death from any cause by 10.9% compared

with BCG alone, without increased morbidity.²⁵ This approach has not been evaluated in the setting of BCG failure.

Photodynamic therapy may also be effective in patients with refractory CIS, but the logistics and poor availability of equipment and expertise continue to render this therapy investigational.²⁶ Mitomycin with microwave-induced hyperthermia is another approach that seems to be more effective than standard mitomycin when used as adjuvant therapy, but it has not been tested in refractory patients.^{27,28}

Although intravesical BCG may be safely offered to many patients with high-risk disease, early cystectomy should be considered in patients considered at high risk for progression, because survival may be compromised once progression occurs. Clearly, more effective intravesical therapies are necessary to improve overall survival and provide an alternative to RC. A number of novel approaches are being tested, including intravesical maintenance gemcitabine, doublets of intravesical agents, and intravesical gene therapy.

OPTIMIZING MANAGEMENT OF MUSCLE-INVASIVE DISEASE

RC and Pelvic Lymph Node Dissection

The current standard approach for treating muscle-invasive BC in the United States is RC and bilateral pelvic lymph node dissection (PLND). However, a preponderance of evidence indicates that the quality of the RC and the extent of PLND affect staging and survival. Although there has been significant controversy regarding the importance of the extent of PLND in patients undergoing an RC, patients undergoing a more extensive dissection seem to have a lower risk for disease recurrence and improved overall survival.²⁹⁻³¹ Data from Stein et al^{32,33} detailed the results of an extended lymphadenectomy that includes a dissection from the inferior mesenteric artery superiorly down to the inguinal ligaments bilaterally, including the presacral lymph nodes. This extensive dissection seemed to be associated with a survival benefit, arguably due to both accurate staging that allowed judicious use of adjuvant chemotherapy and a therapeutic effect by resecting small-volume nodal disease.³³

Data from a post hoc analysis of a SWOG study,³⁴ which compared cystectomy with or without neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC), reported that a more extensive PLND (≥ 10 lymph nodes) was associated with significantly improved overall survival compared with a more limited dissection. An extensive PLND is recommended in these high-risk individuals.

Although there is no Level 1 evidence in support of this approach or a universally accepted standard for what constitutes an extensive PLND, it is important that surgeons adopt a standardized approach to the performance of PLND, if for no other reason than to eliminate surgical technique as a source of bias when interpreting outcomes after cystectomy.

We, therefore, recommend a nodal dissection that includes the obturator, bilateral external, and internal iliacs, as well as the bilateral common iliacs and presacrals. The lower para-aortic nodes between the bifurcation and the inferior mesenteric artery base usually contain only a couple of lymph nodes, and we do not feel strongly that they need to be routinely included in all dissections. This recommendation is supported by a multicenter study reported by Leissner et al,³⁵ in which extended PLND was performed on 290 patients with cT-T4 BC undergoing RC. The incidence of lymph node metastases was stage

dependent, and 27.9% of patients had documented metastasis. No patients had an isolated metastasis above the aortic bifurcation.

Integration of Chemotherapy

Multiagent chemotherapy seems to improve outcomes of patients presenting with muscle-invasive BC. Cure with RC is stage dependent. However, even in pathologically organ-confined BC (pT2), the 5-year survival rate is approximately 68%. Outcome is worse for those with extra-vesicular extension or lymph node involvement, with approximately 25% to 30% 5-year survival rates.³⁶ Failures after RC occur most frequently at distant sites, thus indicative of occult micrometastases present at diagnosis. Systemic relapses are fatal in most patients.

The objectives of neoadjuvant chemotherapy are to improve survival by early targeting of systemic micrometastases. Administration of chemotherapy before surgery improves the likelihood of administering planned doses³⁷ given an improved patient performance status and, theoretically, the potential for greater efficacy of chemotherapy in smaller-volume disease. One potential concern is that patients with chemotherapy-resistant disease may experience disease progression while receiving chemotherapy, delaying definitive local therapy; however, as two randomized trials have demonstrated, survival is positively affected by this approach.^{38,39}

Several randomized clinical trials have been conducted to evaluate neoadjuvant chemotherapy in BC.³⁸⁻⁴⁸ Although several failed to demonstrate a survival advantage, many of these studies have several design limitations that may limit useful interpretation, including small sample size, use of single-agent chemotherapy, and not standardizing local therapy.

The most well-known BC study in the United States is the Intergroup Trial 0080, in which more than 300 patients with muscle-invasive cT2-4a, N0, M0 BC were randomly assigned to treatment with RC alone or three cycles of neoadjuvant MVAC and RC.⁴⁸ Neoadjuvant MVAC resulted in a 60% improvement in BC-specific survival and an absolute 5-year overall survival benefit of 14% (57% v 43%) and improved median survival (77 v 47 months). The survival benefits were seen in all patient subsets.

Additional support for the role of neoadjuvant cisplatin-based combination chemotherapy is provided by long-term analysis of a large, randomized, phase III trial performed by the Medical Research Council/European Organisation for Research and Treatment of Cancer. At 7-year follow-up, survival was superior for those who received neoadjuvant chemotherapy compared with those undergoing cystectomy or radiation therapy alone.^{39,40} A subsequent meta-analysis of more than 3,000 patients in nine randomized controlled trials testing neoadjuvant cisplatin-based chemotherapy reported a 14% decrease in the relative risk of death, a 9% absolute improvement in disease-specific survival ($P < .0001$) at 5 years, and a 5% improvement in overall survival ($P = .003$).⁴¹

Despite this mounting evidence favoring a multimodal approach to muscle-invasive BC, practitioners are still reluctant to adopt this approach. In a review of more than 7,000 patients treated for stage III BC between 1998 and 2003, only 1.2% of patients actually received neoadjuvant treatment.⁴⁹

On the basis of the best Level 1 evidence to date, we recommend offering neoadjuvant chemotherapy to all appropriate patients with muscle-invasive disease (T2-T4). Patients should be appropriately counseled on the risks and the survival benefits of neoadjuvant chem-

otherapy before proceeding with RC or definite radiation therapy, and when feasible, efforts should be made to enter patients onto clinical trials.⁵⁰ Notwithstanding the theoretical advantage of better patient selection, there is no Level 1 evidence to support adjuvant chemotherapy, and the available data have not demonstrated a clear benefit of adjuvant chemotherapy.^{41,51,52} Specifically, the trials are limited by small sample size and thus are underpowered to demonstrate survival differences, early stopping of patient entry and premature closure, and statistical methodological limitation. Furthermore, there are limitations to the delivery of effective chemotherapy in the postoperative setting as a result of declines in patient performance status or a serious postoperative complication.⁵³ Current data also strongly support the need for definitive local therapy as the standard of care at this time, even in patients who achieve a cT0 after neoadjuvant chemotherapy.⁵⁴

Advancing Practice and Clinical Trials

Critical to advancing care for patients with BC is timely testing of new therapies and efficient utilization of patient resources. In addition to the conventional approach for drug development and trial designs, we recommend that the neoadjuvant setting be used to test novel agents and combinations, and that a more focused use of new technologies, such as gene expression models,⁵⁵ is used as a framework for trial design and drug assessment and discovery. It is critical that all involved in the care of patients with BC, including community oncologists and urologists and academia, refer patients to clinical trials to facilitate accrual. Because advanced urothelial cancer represents a relatively small component of most oncologists practices, accrual would be facilitated by better collaboration between academic centers and by referring patients for trials to centers focused on bladder cancer. And, most importantly, to improve care for our patients, it is crucial that we implement evidence-based practice and that basic and clinical research in this disease is supported and completed in a timely manner.

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