

## Systemic Therapy for Invasive Bladder Cancer: The Value Proposition

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*Disclosures of potential conflicts of interest may be found at the end of this article.*

The report from Yin et al. in this issue of *The Oncologist* is an important reminder of the utility of neoadjuvant cisplatin-based chemotherapy for invasive, clinically nonmetastatic bladder cancer [1]. In their updated analysis, these investigators suggest that the hazard ratio from this treatment strategy has improved to 0.87, from approximately 0.93; the analysis now includes more than 3,000 cases, some with longer follow-up. It is a pity that there has been a need to justify a treatment that my colleagues and I first tested more than 30 years ago [2, 3] and proved, with level 1 evidence, in two hallmark trials that were initiated more than 20 years ago [4–6] and were even confirmed by an early meta-analysis [7]. That said, updating of information is useful, in that Yin et al. have confirmed and extended the 10-year trends and added important case experience.

Why is this worthy of publication? First, there is an increasing focus on the value proposition in oncology, at a time when costs of treatment are burgeoning and patients are being expected to shoulder much higher proportions of the cost. Increasingly, health planners are looking at the ratio of outcome versus cost [8] and questioning the use of treatments that simply do not provide meaningful increments in survival when compared with physical or fiscal expenditure [9]. The American Society of Clinical Oncology and the European Society of Medical Oncology have issued remarkably similar documents that have attempted to measure “value” in oncology in a structured fashion [9, 10]; these have produced complex algorithms, but they do begin to address a thoughtful and critical appraisal of the return on investment for the expenditure of resources by the individual patient and the community at large. In that context, a hazard ratio for neoadjuvant treatment of bladder cancer of 0.87 is compelling, particularly with median survival figures measured in years rather than months. That said, the upper boundary of 0.95 in the confidence interval suggests that continued follow-up of this domain will be necessary.

The second reason that this study is important is that the reaffirmation of the important effect of neoadjuvant chemotherapy sets into stark contrast the proliferation of underpowered and inaccurate reports that have attempted to equate the usefulness of adjuvant chemotherapy in the same setting, as discussed in detail elsewhere [11]. Although the European Organisation for Research and Treatment of Cancer

took on the tough challenge of a randomized trial of cystectomy versus cystectomy plus adjuvant chemotherapy, which was also open in North America, investigators in Europe and the U.S. chose not to support this seminal trial, which closed early because of lack of accrual [12].

Dr. Sternberg and her colleagues reported the available information, showing the presence of a progression-free survival benefit, which was not surprising (given the known activity of cisplatin-based chemotherapy for bladder cancer). However, once salvage chemotherapy had been given to patients relapsing after initial cystectomy-only treatment, no statistically significant difference in survival was observed, although there was a small trend in favor of adjuvant chemotherapy [12]. They also reported the unexpected finding that the real effect of adjuvant chemotherapy was seen in node-negative disease, which might indicate that chemotherapy was partially compensating for suboptimal surgery. Another explanation could also have been that four cycles of adjuvant chemotherapy were sufficient to improve survival for node-negative disease but were not adequate to affect node-positive tumors. Whichever is true, the bottom line is that overall survival was not significantly affected by the expenditure of resources required from the patient and the community when four cycles of adjuvant chemotherapy was delivered.

One of the frustrating aspects of this discussion is the range of attempts to convince our profession of the utility of this adjuvant approach despite the absence of real data. Thus, there have been several meta-analyses, all of which have included a seminal German study that compared cystectomy without salvage chemotherapy to cystectomy plus adjuvant chemotherapy [13, 14]; inclusion of this study prejudices the outcome clinically and statistically. In addition, the situation has been confused by post hoc large database studies (which have ignored randomization and have attempted to use statistical ploys and/or propensity matching to overcome the absence of real level 1 data) [15]. Bladder cancer is a heterogeneous disease, and the population of patients being treated is even more heterogeneous, so that propensity matching essentially reflects the “garbage in/garbage out” principle. In planning treatment of invasive disease, it is important to consider conventional predictors of outcome, such as grade and stage, solid growth pattern, size, aneuploidy

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**Table 1.** Design rules for neoadjuvant bladder cancer trials

Rule	Specifics	Effect of failure to observe rules
1	Incorporate complex biology	Failure of single-agent chemotherapy in randomized neoadjuvant trials
2	Avoid variable constants	Effect of suboptimal surgery: <ul style="list-style-type: none"> <li>• Worse survival curves for control groups</li> <li>• Possible effect in adjuvant trials (e.g., N0 disease with limited node sampling)</li> <li>• Effect of neoadjuvant gemcitabine-cisplatin vs. MVAC</li> </ul>
3	Repetition doesn't make it right	Serial reports and overviews of studies of chemoradiation: <ul style="list-style-type: none"> <li>• Dilutes effect of long-term follow-up in survival curves</li> <li>• Large numbers still do not prove superiority</li> </ul>
4	Randomization trumps historical controls	Phase II neoadjuvant trials suggested possible survival benefit from single-agent chemotherapy <sup>a</sup>
5	If it doesn't make sense, it's probably wrong	Use of disease-free interval as primary parameter for adjuvant trials Misinterpretation of meta-analyses of adjuvant therapy—inclusion of inappropriate sets of data Failure to implement level 1 clinical trials data in treatment of invasive disease Underpowered phase III trial suggesting immunotherapy fails in invasive bladder cancer

<sup>a</sup>By comparison, phase III trials proved clinical and statistical benefit of neoadjuvant chemotherapy.

Abbreviation: MVAC, methotrexate, vinblastine, doxorubicin, cisplatin.

Adapted from [18], with permission.

and genomic heterogeneity, lympho-vascular invasion, and the presence of hydronephrosis. There is simply no way that propensity matching can account for this level of variation, particularly given the modest numbers of cases included in the recent published exercises. When one compounds this with a consideration of the huge potential costs [11] engendered in an unproven approach with, at best, marginal survival effect and significant morbidity, the argument simply becomes fatuous.

The other important consideration in the work of Yin et al. [1] is their attempted comparison of the methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) and gemcitabine-cisplatin (GC) regimens in the neoadjuvant context, and their conclusion that GC is inferior. Once again, the question is important because GC has become a standard approach since the demonstration that it is less toxic than MVAC in the metastatic setting [16], with a hazard ratio of 1.09 (which is not “noninferior”). Further confusion on this issue has been created by another propensity-matched retrospective analysis of pooled data from 28 centers (which included data dredging from several prior reports) [17]. Despite different median survival figures (MVAC, 35.5 months; GC, 26.8 months;  $p = .17$ ) and absence of central pathology or surgical quality review, with only 212 heterogeneous cases, these authors concluded that MVAC and GC were not different, and this study has been used as the basis for routine introduction of GC in the neoadjuvant setting.

When I contemplate the respective levels of rhetoric and reason in the profusion of publications on invasive bladder

cancer, I keep coming back to my five basic rules regarding the design of trials for invasive bladder cancer (Table 1) [18]:

- Understand the complex biology of invasive bladder cancer when designing trials.
- Variable constants can impair outcomes (e.g., understand the importance of optimal surgery, radiotherapy, or chemotherapy in the design of these studies).
- Repetition is not the best way to prove a concept.
- Randomized trials prove more than historical comparisons (or retrospective analyses with so-called propensity matching).
- If it doesn't make sense, it's probably wrong.

Fortunately, carefully designed and completed studies, such as the work of Yin et al. [1], despite some obvious methodological issues acknowledged by the authors, allow us to build structure and confidence around a decision that neoadjuvant MVAC chemotherapy followed by definitive local treatment should be the treatment of choice for otherwise healthy and robust patients with T2b–T4 invasive bladder cancer. Randomized clinical trials may not be easy or convenient, but they remain the mainstay of thoughtful, well-designed science that allows us to advance with confidence.

#### DISCLOSURES

**Derek Raghavan:** Gerson Lehrman, Caris Life Sciences (C/A).

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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**EDITOR'S NOTE:** See the related article, “Neoadjuvant Chemotherapy for Muscle-Invasive Bladder Cancer: A Systematic Review and Two-Step Meta-Analysis,” by Ming Yin et al. on page 708 of this issue.

**For Further Reading:** David D. Chism, Michael E. Woods, Matthew I. Milowsky. Neoadjuvant Paradigm for Accelerated Drug Development: An Ideal Model in Bladder Cancer. *The Oncologist* 2013;18:933–940.

**Implications for Practice:** Recent recommendations to use the neoadjuvant setting in breast cancer as an accelerated drug development pathway make a similar approach in bladder cancer very appealing. The current article will review the rationale for consideration of bladder cancer as the ideal neoadjuvant model for accelerated drug development. Several factors including the ease of bladder tumor tissue collection performed as standard of care, the use of pathologic response as an intermediate marker for overall outcome, and a richer understanding of the important molecular pathways involved in bladder cancer development and progression make the neoadjuvant paradigm particularly relevant. The ability to conduct clinical trials that require fewer patients and efficiently explore disease biology will undoubtedly lead to the development of novel therapies and have a profound effect on every day medical practice.