

therapy techniques used. Other limitations of this study include the lack of granular information on use of chemotherapy. Although the receipt and timing of chemotherapy were known, the specific chemotherapy agent, dose, and number of cycles administered were not. Finally, the NCDB does not report cancer-specific survival, disease-specific survival, or quality of life outcomes, so OS was the only outcome that could be included.

We acknowledge that the findings of this study can only be considered hypothesis-generating because information regarding toxic effects of CMT, the granular details of the various chemotherapeutic regimens used, and the quality of delivery of radiotherapy are not readily available in the NCDB.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.urology.2019.05.062>.

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EDITORIAL COMMENT



The authors used the National Cancer Database (NCDB) to compare the survival of patients with muscle-invasive bladder cancer (MIBC) treated with either radical cystectomy (RC) or chemoradiotherapy (CRT).¹ The authors concluded that patients have better survival after RC than CRT. However, due to the innate limitations of registry-based observational studies, and potential bias in the patient selection, the validity and ability to apply this study's findings are limited.

Only randomization can truly control for known and unknown confounders when comparing treatment regimens. Although

investigators can use methods such as propensity-score weighting to attempt to account for some unknown confounding, the receipt of such drastically different treatment modalities is driven by multiple patient, clinician, and disease factors—all of which can create selection bias. In fact, a recent study compared the results of population-based observational studies with randomized trials in oncology comparing the same 2 treatment regimens and found no correlation between the observational studies and randomized trials beyond what would be expected with chance, regardless of the statistical methods used.² Therefore, it is not surprising, as the authors state, the results of other observational studies using population-based datasets are conflicting when it comes to comparing survival with RC and CRT. Interestingly, a recent publication comparing RC and CRT in an overlapping NCDB population found no difference in survival.³ Frankly, studies using this design and data source seem no better than flipping a coin when comparing survival.

Moreover, the definition of the CRT group in this study was prone to selecting patients inherently at risk for worse survival. The authors selected patients who received as low as 50 Gy—well below the standard doses used for curative radiotherapy (~64 Gy using 1.8-2 Gy/fraction).⁴ Although some hypofractionated regimens use 50 Gy, the use of these regimens is low in the NCDB.⁵ Furthermore, patients were defined as having concurrent chemotherapy if they received chemotherapy within 90 days of radiation. To our knowledge, there are no radiosensitizing chemotherapy platforms that allow such a large time gap between concurrent chemotherapy and radiotherapy, thereby further questioning what proportion of patients received standard, curative, concurrent CRT.

Another source of bias in this study is that the CRT group included patients who were not candidates for surgery due to comorbidity. Although the authors controlled for comorbidity using the NCDB's Charlson/Deyo comorbidity score, the data in this variable are limited. It is coded as 0, 1, 2, or ≥ 3 based on patient comorbidities. In this study, it was dichotomized to 0 or ≥ 1 —even further limiting the granularity. A patient with a score of ≥ 1 could be a patient with uncomplicated diabetes, or, could be a patient with hemiplegia, moderate to severe liver disease, dementia and a history of myocardial infarction. It's hard to believe this dichotomy can capture the impact of comorbidity on surgical candidacy or survival.

Ultimately, only a randomized trial can truly determine any differences in survival that exist between RC and CRT, but it's unlikely we will get an answer to this question anytime soon. Perhaps there are more practical avenues to pursue, such as optimizing the outcomes with each modality. For example, A031501 (NCT03244384) is determining the role of adjuvant immunotherapy after RC. In the setting of CRT, SWOG/NRG 1806 (NCT03775265) is studying the role of concurrent and adjuvant immunotherapy in node-negative MIBC, and ECOG/NRG 8185 is under development to study this approach in node-positive MIBC. These studies will hopefully improve the outcomes in patients undergoing either modality.

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Author Reply

“Striving to better, oft we mar what’s well.”

Williams Shakespeare

We agree with the authors URL-19-01203.¹ that well-designed adequately powered trials, evenly distributes the confounders among the control and intervention groups, thereby minimizing the potential for selection bias. Thus, randomized trials are widely encouraged as the ideal methodology for causal inference. However, some clinical scenarios have not, cannot, and will never be addressed in the context of a randomized trial.² The role of chemoradiotherapy (CRT) in muscle-invasive bladder cancer is a clear example.

We have recently reported screening logs from the recruitment phase of pilot feasibility trial (ClinicalTrials.gov Identifier: NCT02716896) to determine whether CRT offers overall survival similar to that of radical cystectomy (RC) in patients with muscle-invasive bladder cancer. Our results from this trial indicated that the number of patients eligible to receive chemotherapy and in whom cystectomy and radiation therapy were both valid options was not as high as previously reported in retrospective CRT series. Many patients were excluded after transurethral resection of bladder tumor. Our preliminary data indicate that only a very small subset of patients with muscle-invasive bladder cancer are ideal candidates for CRT.³

Thus, in the absence of randomized clinical trials, well-designed and analyzed observational studies are of utmost importance with benefits even surpassing randomized controlled trials.^{2,4}

We acknowledged in our article the inherent limitations in retrospective observational studies including risks of selection bias. To address the editorial comments on dichotomization of Charlson/Deyo score, we would like to highlight that the NCDB reports a modified index in which the variables are truncated to 0, 1, and >1 .⁴ Even when reported in a continuous manner as suggested, a patient with controlled DM would have the same score as a patient with myocardial infarction or heart failure.⁵ The editorial also questioned the selection criteria for patients with CRT. Interestingly, they mention in comment the reason