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Survival Claims From Observational Data on Cancer Therapy

TO THE EDITOR: In their analysis of radiation therapy for early-stage diffuse large B-cell lymphoma (DLBCL) using the National Cancer Data Base (NCDB) data, Vargo et al[1] started from nearly identical assumptions of and reached remarkably similar conclusions to our study of classic Hodgkin lymphoma (cHL).[2] The authors suggest that abandonment of consolidative radiation therapy (RT) negatively affects survival in DLBCL. However, when we contemplated a similar project, we encountered issues that led us to believe that the propensity score method applied to the NCDB data may not be suitable to answer this question. As laid out in a prior editorial statement in *Journal of Clinical Oncology*,[3] claims of treatment-related survival benefits from observational research are difficult and require extraordinary scrutiny. Statistical methods for causal inference rely on strong assumptions that are often unappreciated by clinically oriented readers. Important differences between cHL and DLBCL serve well to illustrate this jeopardy.

Propensity score analysis, sometimes simplistically described as a two-step method (confounder balancing followed by outcome modeling),[4] in fact requires important feasibility prerequisites.[5] The positivity assumption demands that every patient has a nonzero probability of receiving the counterfactual treatment. We limited our cHL analysis to a specific period (2003 to 2006), when national guidelines recommended combined-modality therapy (CMT) for all patients with early-stage cHL[6] regardless of favorable/unfavorable category or tumor bulk. This allowed us to frame the comparative question as adherence or nonadherence to guidelines, which coincided with the use or nonuse of CMT. In contrast, guidelines for DLBCL have emphasized three clinically determined scenarios. All patients without adverse risk factors (as delineated by the practice-defining Southwest Oncology Group trial SWOG 8736[7]), were recommended to receive abbreviated chemotherapy (ie, three cycles) with RT, and those with bulky disease, extended chemotherapy (six to eight cycles) with RT. These separate abbreviated and extended chemotherapy populations can be identified in the NCDB data, and the median times from first chemotherapy to RT were 82 and 143 days, respectively (Fig 1A). Chemotherapy alone (as an alternative to abbreviated chemotherapy with RT) was acceptable only for patients with adverse risk factors. Thus, according to the guideline, all patients with good prognoses should be in the combined-modality arm, which violates the positivity assumption and results in a fatal selection bias.

Additional differences are apparent between cHL and DLBCL in epidemiology, presentation, and response to chemotherapy. First, a majority of cHL occurs among younger adults, whereas the median age of patients with DLBCL is 67 years. Performance status and ability to receive anthracycline-based chemotherapy are major determinants of survival in DLBCL. In contrast to Vargo et al,[1] Odejide et al[8] compared extended rituximab-based immunochemotherapy alone with the clinically relevant strategy of abbreviated chemotherapy plus RT in older patients and, after adjustment for nonlinear effects of age and for performance status, found no significant difference between those treatment approaches (hazard ratio, 1.02; 95% CI, 0.76 to 1.38).[8] Second, extranodal origin is exceedingly rare in cHL but is common (> 40%) in DLBCL. We observed a marked variation in the use of RT by primary site, which reflects specific clinical indications uncaptured by the simple nodal/extranodal distinction (Fig 1B). Of note, despite the recommendation for scrotal RT in testicular DLBCL, it was not administered to 46% of patients. Finally, although nearly all patients with cHL achieve complete remission during chemotherapy, interim evaluation in DLBCL will redirect up to 10% of patients with poor responses to salvage autologous stem-cell transplantation, which also biases any survival comparisons. A quantitative sensitivity analysis for such unobserved confounding should occur as the final step of the propensity score method, and several approaches to achieve this have been proposed.[9]

In summary, although we agree that consolidative RT may be essential in many occurrences of early-stage DLBCL, the analysis by Vargo et al[1] is unlikely to provide a true marginal estimate of its effect on survival for all patients. Population-based data may allow assessment of system- or policy-related phenomena, including adherence to treatment guidelines in selective settings where it coincides with delivery of specific therapy, but we advise extreme caution when direct survival advantage of a treatment is asserted from such data. Even instrumental variable analysis, sometimes advertised as a method to overcome unobserved confounding, results in biased estimates when applied to the impact of medical treatments on mortality.[10] Decisions about cancer therapy are made specifically with anticipated survival benefits in mind and, in most instances, current registry data do not capture the complexity of this process. For the assessment of treatment efficacy in DLBCL, much more comprehensive data sets will be needed to incorporate validated clinical and molecular prognostic markers. Initiatives such as the American Society of Clinical Oncology CancerLinQ raise our hope of approaching this capability.

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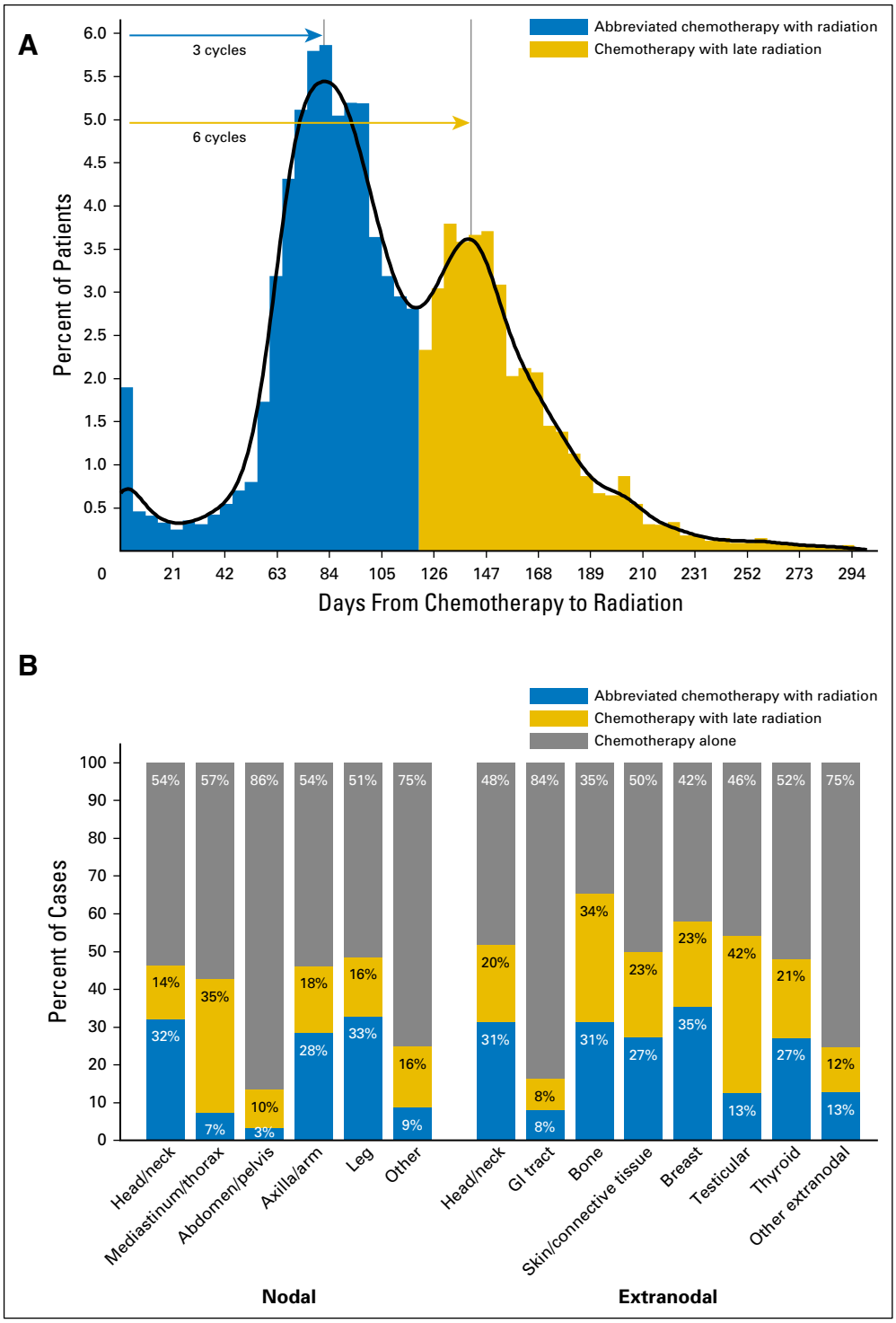

Fig 1. (A) Distribution of time from the initial chemotherapy to the start of radiation among patients with early-stage diffuse large B-cell lymphoma (DLBCL); the 21-day intervals correspond to the number of standard chemotherapy cycles. (B) Variation in the use of abbreviated (three cycles) or extended (six cycles) chemotherapy with or without radiation in early-stage DLBCL by primary site of disease; data from the National Cancer Data Base (2004 to 2012).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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