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Editorial

EDITORIAL

Disease-Free Survival is a Promising Surrogate for Overall Survival in Colorectal Cancer Studies

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I congratulate Yin et al. (1) on their well-conducted study validating the surrogacy of 3-year disease-free survival (DFS) for 5-year overall survival (OS) in the setting of adjuvant colorectal cancer studies. The thankfully long survival time in this setting makes phase III trials long and costly, requiring protracted follow-up times to rigorously assess efficacy in reducing OS. Thus, the identification and validation of earlier surrogate endpoints is of high clinical significance in this setting, and 3-year DFS is a practical choice.

The authors were able to obtain results and patient-level data from 9 large multicenter randomized trials from the ACCENT database (1), providing sufficient power to attack the important problem of validating surrogacy for this specific setting. Having 9 studies enabled them to have statistical power to assess trial-level surrogacy, and they were indeed able to demonstrate all of the prespecified criteria for effect size and confidence interval (CI) lower bound. The ability to extract patient-level data from these studies was an additional unique strength of this study, enabling the calculation of individual-level surrogacy. This analysis yielded a precise estimated correlation of 0.90 between 3-year DFS and 5-year OS (95% CI = 0.90 to 0.91), which provides further strength to the notion of using the surrogate measure to represent patient outcomes in this setting.

I had a mild concern that the removal of 1 small study out of the 9 studies weakened the surrogacy estimates somewhat, especially for the Copula measure. However, the fact that the trial surrogacy continued to increase at the later time points (6 years and 6.5 years) to very high levels helps overcome this concern and provides confidence that indeed strong evidence supports the use of the surrogate.

Another strength of the study is the investigation of surrogacy strength for later time points for OS, considering 6 and 6.5 years in addition to the standard 5 years. This is important for the setting of adjuvant therapy for colorectal cancer, given that the proportion of individuals alive at 5 years tends to be more than 90%. Demonstration of surrogacy for the later time points with 68% and 56% survival, respectively, provides additional evidence, and the strongly increasing surrogacy up to very high levels of 0.94 and 0.99 for the 2 measures is reassuring (1). It is not surprising that trial surrogacy might be slightly attenuated and have lower precision for the 5-year OS endpoint given the low event frequency by that time. That the prespecified surrogacy criteria were still met at the 5-year time point in spite of this fact, and increase greatly for later time points with substantially more events, reinforces the strong conclusions of validated surrogacy in this setting.

The authors considered surrogacy of 3-year DFS for OS at other time points (1); sadly however, they did not consider whether DFS at earlier time points would retain strong surrogacy for OS. This is unfortunate, as it would have been informative to see whether DFS at an earlier time point—say 2.5 years, 2 years, or even 1.5 years—provides sufficient information to be surrogate for 5-, 6-, or 6.5-year OS. If so, this could suggest that even earlier DFS time points could be considered in this setting, which could have resulted in further trial efficiency. Hopefully, this will be considered in future analyses.

In summary, this article by Yin et al. (1) strongly validates and reinforces the continued use of 3-year DFS as a surrogate endpoint for 5-year OS in adjuvant colorectal cancer therapy studies. This substantial contribution provides support for current practices and ensures more efficient assessment of new therapeutic strategies for this setting.

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Reference

1. Yin J, Salem ME, Dixon JG, Jin Z, et al. Reevaluating disease-free survival as an endpoint vs overall survival in stage III adjuvant colon cancer trials. *J Nat Cancer Inst*. 2021. doi: 10.1093/jnci/djab187.