Disease-Free Survival Versus Overall Survival As a Primary End Point for Adjuvant Colon Cancer Studies: A Commentary

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In this issue of the Journal of Clinical Oncology, Sargent et al.1 evaluated disease-free survival with 3 years of follow-up (DFS3 years) as a surrogate for overall survival with 5 years of follow-up (OS5 years) and conclude that it is an appropriate primary end point to replace OS in phase III clinical trials of adjuvant fluorouracil (FU)-based therapies for colon cancer.

In most definitive studies of the benefits of potential cancer therapies, OS is the primary end point because (1) it has obvious clinical importance, (2) survival of an individual patient can be unambiguously assessed, and (3) even if a patient does not return for follow-up evaluation, survival information can be obtained from death registries such as that provided by the United States Social Security Administration. These advantages are balanced by several disadvantages: (1) use of OS as the primary end point may prolong evaluation of new therapies because of the long follow-up time required to obtain adequate information for assessment; (2) studies of long duration may be weakened by decreasing patient compliance over time and increasing losses to follow-up; (3) because of this, long-term studies are more expensive to conduct; (4) studies of long duration may delay approval and dissemination of effective therapies and postpone pursuit of alternative research strategies when a therapy proves to be ineffective.

For these reasons, investigators have considered the use of clinical end points that are surrogates for the true end point and that require less time to evaluate and may be less costly to assess. There are, however, significant statistical challenges to be addressed when considering use of a surrogate end point. Although the true end point is assumed to be causally related to the effectiveness of treatment, that relationship must be verified for a surrogate. Additionally, there are critical assumptions about the relationship between the surrogate and the true end point that require verification.2-6

In the current study, the authors analyzed data from 18 different trials in which there were 43 different treatment arms with a total of nearly 21,000 patients. Their evaluation of DFS as a surrogate is strengthened by their consideration of the relationship between DFS3 years and OS5 years at 3 levels: the patient, the treatment arm, and the trial. An end point that is a good surrogate at the level of the patient but not at the level of the trial is not useful for hastening evaluation of new therapies. One that meets the criteria of a good surrogate at the level of the trial but not at the level of the patient has no clinical value. One that is valid only for some treatment arms may distort the effects of therapy and is, obviously, not a useful surrogate. In this study, DFS3 years is shown to be an appropriate surrogate for OS5 years at each level of analysis.

Although future studies of FU-based adjuvant therapy for patients with stages II and III colon cancer may comfortably use DFS3 years as a primary end point replacing OS5 years, casual readers are cautioned against generalizing these results to all colon cancer trials or to cancer clinical trials in general. These results depend on specific features of the disease and the current state of diagnosis and therapy. For example, colon cancer diagnosed at stages II and III has poor prognosis and, if the disease recurs, it is likely to result in imminent death, median survival time being approximately 1 year. DFS may not be an appropriate surrogate clinical end point for diseases in which treatment for recurrence is more often successful in prolonging survival. If there are significant advances in treatment for recurrence, then the statistical association between DFS and OS will be weakened, and one of the critical assumptions needed for determination of a surrogate end point will be violated.

As the authors point out, if new diagnostic methods detect recurrent disease sooner than current methods, then there will be an apparent decrease in time to recurrence and an apparent increase in time from recurrence to death. Without advances in treatment for recurrence, advances in diagnosis may require consideration of other time points.
for DFS and OS, although the underlying relationship between DFS and OS is unlikely to be altered.

Sargent et al\textsuperscript{1} not only provide important results on the choice of clinical end points for clinical researchers, but they also provide a model for the careful evaluation of possible clinical surrogates for true clinical end points.

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