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What Constitutes a Valid Surrogate End Point in Cancer Clinical Trials?

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Historically, novel postneoadjuvant therapies for patients with early breast cancer have been assessed in multiyear trials. In an effort to address the unmet need of postneoadjuvant therapies in high-risk populations, the US Food and Drug Administration established guidelines for expediting the drug approval process by using pathologic complete response (pCR) as the end point. Previous randomized neoadjuvant trials have suggested that this end point may predict long-term outcome in patients with early-stage breast cancer.[1]

In this issue of *JAMA Oncology,* the I-SPY2 Trial Consortium[2] investigated the association between pCR and survival end points, event-free survival (EFS) and distant recurrence-free survival (DRFS), using data from the I-SPY2 trial, which applied a bayesian adaptive trial design to assess 9 novel neoadjuvant therapeutic combinations for breast cancer. The authors concluded that there is a strong individual-level association between pCR and the survival end points; however, they did not provide the evidence needed to validate pCR as a surrogate outcome for EFS and DRFS.

Methodological literature on surrogate end points has highlighted the importance of showing 2 types of associations for proving any candidate surrogate end point as the true end point:

- I-Association: The association between the surrogate end point (eg, pCR) and the true end point (eg, EFS or DRFS).
- T-Association: The association between the effect of treatment on the surrogate end point (eg, odds ratio for pCR), and the effect of treatment on the true end point (eg, hazard ratio for EFS or DRFS).[3-5]

I-Association can be shown with individual-level data from clinical trials, and the I-SPY2 Trial Consortium examined this association by comparing pCR with EFS and DRFS across multiple test drugs and a control regimen. T-Association requires trial-level data with a sufficient number of patients and number of events per treatment type.[6] To validate T-

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association, the I-SPY2 Trial Consortium would have needed to provide a figure comparing the odds ratio for pCR to the hazard ratio for EFS across multiple studies. Given that I-SPY2 is a multicenter platform trial, the I-SPY2 Trial Consortium[2] could have provided a plot, similar to that from Cortazar and Geyer,[7] with 9 circles representing each of the novel therapeutic combinations, the size of each circle representing the corresponding sample size, and a linear line based on a general linear model depicting the correlation between the odds ratio for pCR and the hazard ratio for EFS.

If the plot based on the I-SPY2 trial showed a strong association, then the I-SPY2 Trial Consortium[2] could have concluded that pCR is a validated surrogate. Unfortunately, the I-SPY2 trial has a small number of patients and events per treatment type, making it difficult to evaluate T-association. In addition, the small number of events would have translated to large confidence limits around the summary measures of trial-level association owing to the large sampling error for each data point in a trial-level analysis. A possible remedy for this situation would be to use meta-analytic technology or collaborate with other cancer drug trialists to accumulate more data with larger sample sizes, although this does not necessarily guarantee a strong association. In fact, to date, other researchers, including Cortazar and Geyer,[7] who have examined the potential of using pCR as a surrogate end point for long-term outcomes in breast cancer have found weak associations.

The difficulties of evaluating T-association stem from how the disease pathways and mechanism of the treatment affect the true clinical outcome and the surrogate end point. For example, the surrogate end point may not be in the causal pathway of the true end point, or the surrogate end point may not be in the pathway of the treatment's effect on the true endpoint. Bothofthese examples would result in a strong conclusion of the surrogate end point being invalid. Having a causal pathway in which the intervention's effect on the true end point is mediated through its effect on the surrogate end point would give the greatest potential for validating the surrogate end point. But even in this setting, the surrogate end point could still result in misleading conclusions because the effect on the true end point could be overestimated or underestimated.[6]

In cancer prevention trials, the clinical trial for finasteride, which was prescribed to patients with high-risk prostate cancer, used a surrogate end point, presence of prostate cancer shown by biopsy after 7 years of follow-up, in place of the true end point, elimination of symptomatic disease or reduction in mortality rate. Using this surrogate end point decreased the sample size needed to detect prevention effects by 50000 compared with using the true end point. Although this is a substantial decrease in sample size, researchers discovered that finasteride reduced the incidence of positive biopsy results because of the treatment's effect on prostate-specific antigen levels, which altered the pattern of biopsy sampling and affected the rate of false-positive results. Thus, it is possible that finasteride did not have any effect on the true end point, making it difficult to conclude the effectiveness of finasteride based on the surrogate end point.[6]

In the end, there is no shortcut to performing rigorous and reproducible science. When it comes to expediting the drug approval process, surrogate end points remain a strong option when the validity of the surrogate can be proved with I-association and T-association. If

researchers are not careful, surrogate end points could lead to misleading conclusions that may result in ineffective treatments for patients.

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