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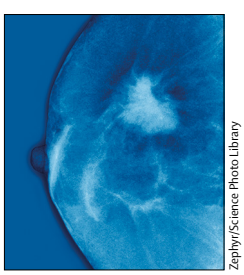
Endpoint selection in HER2-positive early breast cancer



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Compared with definitive endpoints such as overall survival, the use of intermediate endpoints such as disease-free survival improves the efficiency of trial design, resulting in studies requiring smaller sample sizes and shorter follow-up. In oncology, the validation of intermediate endpoints as adequate surrogates of definitive outcomes is challenging.[1] In early-stage breast cancer, evidence supporting the surrogacy of intermediate endpoints and definitive outcomes such as overall survival is scarce. Disease-free survival is a composite endpoint typically comprising locoregional and distant recurrences as well as new contralateral breast cancers, second cancers, and death from any cause. Disease-free survival has been used frequently as a primary endpoint in trials of early-stage breast cancer despite scarce data supporting its adequacy as a surrogate for overall survival.

In an Article in *The Lancet Oncology*, Everardo Saad and colleagues[2] aimed to validate disease-free survival as a surrogate for overall survival in patients with HER2-positive, early-stage breast cancer using individual patient data from several large randomised trials of HER2-targeted therapy. After a systematic review, they identified eight trials on this topic with available data (21 480 patients, 3233 deaths, and 5371 disease-free survival events). The availability of individual patient data allowed the investigators to explore both trial-level and patient-level surrogacy of disease-free survival. Results showed that disease-free survival correlated strongly with overall survival at the trial level (R_2=0·75) and also predicted for the net benefit of treatment at the patient level (r_s=0·90). The inclusion of both trial-level and patient level correlation is a major strength of the analysis and provides robust support for the adequate surrogacy of disease-free survival and overall survival in HER2-positive, early-stage breast cancer. However, before disease-free survival is embraced as the optimal primary endpoint in this setting, several limitations of the analysis need to be considered.

The surrogacy of disease-free survival was less strong among studies with small numbers of events. This aspect is concerning, because during the past decade the frequency of events in clinical trials has fallen substantially in HER2-positive, early-stage breast cancer. For example, the 3-year disease-free survival in the trastuzumab group of the 2005 combined analysis of the National Surgical Adjuvant Breast and Bowel Project B-31 and North Central Cancer Treatment Group N9831 trials was 87·1%.[3] By contrast, in the 2017 report of the APHINITY trial, the proportion of patients in the trastuzumab-only group with events was almost halved, with a 3-year invasive disease-free survival of 93·2%.[4] In a lower-risk cohort of predominantly lymph node-negative, HER2-positive breast cancer, the 7-year disease-free survival was 93·3%.[5] Whether disease-free survival will retain robust surrogacy in a more contemporary setting with low event frequencies is uncertain.

Another important consideration is that despite a strong estimate for treatment-level association between disease-free survival and overall survival, the confidence intervals for estimates were wide. Whereas subgroup data defined by lymph node status and hormone receptor status yielded similar results, there was a weaker association in hormone receptor-positive disease than in hormone receptor-negative disease, which is unsurprising. Among HER2-positive breast cancers, there is a well-established difference in the timing of disease-free survival events between

hormone receptor-positive disease and hormone receptor-negative disease, with the hormone receptor-positive group having a lower proportion of disease-free survival events earlier in follow-up.[3] Data show that disease-free survival events occurring later in follow-up are more likely to be contralateral breast cancers and non-breast cancer deaths and are less likely to be locoregional and distant recurrences.[6] The possible influence of non-breast cancer death on the surrogacy of disease-free survival is supported by data in Saad and colleagues' analysis showing both improved patient-level and improved trial-level association between disease-free survival and breast cancer-specific survival (which excludes deaths unrelated to breast cancer) compared with overall survival (which is agnostic to cause of death). This finding highlights the importance of competing risks of death in the interpretation of trials over long-term follow-up.

With many registration trials in early breast cancer using disease-free survival as the primary endpoint, a question that needs to be answered is whether the data reported by Saad and colleagues can be extrapolated to other settings. Triple-negative breast cancer is associated with a high frequency of disease-free survival events similar to that seen in HER2-positive disease untreated with trastuzumab. However, the magnitude of relative treatment effect in this subgroup is smaller.[7] For hormone receptor-positive, HER2-negative disease, the low event frequency and higher proportion of disease-free survival events unrelated to breast cancer would probably result in reduced performance of disease-free survival as a surrogate for overall survival.

Saad and colleagues should be congratulated for their work to assess the use of disease-free survival as a primary endpoint in a defined subgroup of early-stage breast cancer, and for providing a blueprint for the validation of disease-free survival in this setting. Attempts to validate disease-free survival as a surrogate for overall survival should be pursued in a broader group of breast cancers while ensuring (as in Saad and colleagues' analysis) that assessment includes not only the strength and consistency of correlation between the surrogate and definitive endpoints at the trial level, but also the prediction of the net effect of treatment at a patient level.

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Improving the outcomes of checkpoint inhibitors in breast cancer

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Checkpoint inhibitors have revolutionised the way that cancer is treated in all developed countries, with numerous checkpoint inhibitors approved to treat multiple tumour types. Unfortunately, the results for checkpoint inhibitors in breast cancer have been less successful. Most of the positive results to date in this setting have been reported in triple-negative breast cancer, which comprises only 15% of breast cancers, but is known to induce a higher level of endogenous immune response than other breast cancer