Early Efficacy End Points in Neoadjuvant Rectal Cancer Trials: Surrogacy Revisited

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Rectal cancer constitutes one of the prime examples for the success of multimodal treatment. Preoperative fluorouracil (5-FU)-based chemoradiotherapy (CRT) or short-course radiotherapy (SCRT) followed by total mesorectal excision (TME) has substantially reduced locoregional recurrence and, partly, increased disease-free survival (DFS) and overall survival (OS).[1,2] Multiple potential combinations of radiotherapy platforms (SCRT, CRT); induction, concurrent, and consolidation chemotherapy (as part of total neoadjuvant treatment [TNT]); neoadjuvant chemotherapy with selected use of SCRT/CRT, as demonstrated in the recently presented PROSPECT trial; adjuvant cytotoxic chemotherapy, different molecular targeted agents, immunotherapeutic agents, and the spectrum of nonoperative management (NOM) to a range of minimal/radical surgical resections; and all their varying combinations, sequences, and intervals have emerged and provide a challenge for research in multimodal rectal cancer treatment.[1-6]

Designing the best possible clinical trials of these interventions will entail the use of the most reliable end points to capture the respective treatment benefits.[7-9] To reduce costs and speed up clinical implementation of new treatment strategies, clinical trials increasingly focus on early and easily obtained surrogate markers. In rectal cancer neoadjuvant trials, outcome measures reflecting tumor response at a given timepoint during or shortly after treatment have been widely used as surrogate markers assuming a close correlation between the surrogate and more relevant time-to-event end points, such as DFS and OS. Some of these early end points are pathology-based such as pathologic complete response (pCR) and tumor regression grading (TRG).[10] The neoadjuvant rectal score (NAR), a formula incorporating pretreatment and pathologic TN categories [5 ypN − 3(cT-ypT) + 12)^2/9.61], has also gained attraction since the NRG trial platform uses NAR as their primary end points although its accuracy and validity depend on the reliability of initial baseline clinical staging.[11] More recently, clinical complete response (cCR) and near clinical complete response (ncCR) have been adopted as early efficacy end points within NOM and organ preservation approaches although there is large heterogenicity in their timing and definitions.[3,12]

To formally validate these early end points as surrogates for intermediate- (eg, 3-year DFS) or long-term end points (5 year-OS), a two-level statistical approach is generally required, which consists in checking whether (1) the surrogate is associated with the final end point in individual patients and (2) the effect of the treatment on the surrogate can be used to reliably predict the treatment effect on the final end point.[13] While individual-level surrogacy can be easily tested with individual patient data from any patient series, including nonrandomized series, treatment- or trial-level surrogacy requires a meta-analysis of several randomized trials for which hazard ratios are available on both the surrogate and the final end point.[13]

It has been known for a long time that achieving a pCR confers excellent prognosis in the neoadjuvant treatment of rectal cancer. Maas et al[14] demonstrated a strong correlation of pCR with 5-year DFS (hazard ratio [HR], 0.44 [95% CI, 0.34 to 0.57]; $P < .0001$) in a pooled analysis of individual patient data after neoadjuvant CRT and surgery (17 different data sets, 3,105 patients). Most reports confirm, on the basis of a Cox model, an independent prognostic value of pCR for DFS/OS on the level of individual patients treated with a given therapy (individual-level surrogacy).[15]

Intriguingly, however, on the level of comparative trials, differences in early tumor response end points did not imply superior time-to-event outcomes (trial-level surrogacy). For example, pCR poorly correlated with 5-year OS ($R = 0.2$ [95% CI, 0.29 to 0.78]; $P = .5$) at the trial level in a meta-analysis of 22 randomized trials involving 10,050 patients treated with neoadjuvant CRT or SCRT.[16] This discrepancy between the strength of association at the individual level and the trial level has sparked debate and controversy. How is it possible that a surrogate, such as pCR, is strongly prognostic for the final end point at an individual level and a given treatment improves pCR, yet the same treatment does not significantly improve the final outcome at the trial level? This paradoxical situation exists and has been discussed in the statistical and medical literature.[13,17]

As recently discussed by Buyse et al,[13] to serve as a surrogate, an end point should ideally be on the *causal pathway* between treatment and final end point.[18] This would—in a perfect situation—imply that the treatment effect on the final end point is indirect and entirely mediated by the effect on the surrogate. In the opposite situation, the treatment would have direct effects on the surrogate and on the final end point, but these effects would be completely independent of each other. Such a situation is undesirable because the treatment effect on the surrogate cannot be used to predict the treatment effect on the final end point. More plausible situations likely to be seen in practice are characterized by both direct and indirect effects of the treatment on the final end point. Estimation of direct and indirect treatment effects requires methods of causal inference,[19] but when data from multiple randomized clinical trials are available, the method most commonly used to assess surrogacy is to perform a meta-analysis of these trials to estimate both individual-level and trial-level surrogacy.[9] The meta-analytic approach can also be used to rule out the surrogate paradox, a situation in which the effect of treatment on the surrogate is positive and the surrogate and the final outcomes are strongly positively correlated (high individual-level surrogacy), but the effect of treatment on the final outcome is negative.[20,21]

Tumor response as measured by pCR, TRG, and NAR is a dynamic process associated with tumor-related factors, such as size, histology, and the molecular profile, and with treatment-related factors, such as radiotherapy (RT) dose, combination with chemotherapy, and the time interval between treatments and surgery/NOM.[10] In this scenario, some factors tend to be prognostic for both the surrogate and the final end point, which creates an apparent correlation between both the surrogate and survival at the individual level: patients with a small, biologically less aggressive tumor will tend to respond better to a given treatment and also have better DFS/OS.[15] Conversely, increasing the RT dose, applying RT-sensitizing systemic treatment, and/or prolonging the interval from completion of local treatment to response assessment will induce increased tumor regression of the primary rectal tumor with little or no effect on (subclinical) metastatic disease, not altering the natural course of the disease and, thus, DFS/OS. As such, the association between pCR and DFS/OS is affected by confounding factors rather than causal mechanisms.

In the recent RAPIDO randomized phase III trial, TNT with 5×5 Gy followed by consolidation chemotherapy and TME was superior to standard CRT and TME with or without adjuvant chemotherapy for the primary end point, disease-related treatment failure.[22] This was mainly due to a significant reduction in distant metastases in the TNT group. Intriguingly, despite a significantly increased pCR rate after TNT, the long-term follow-up at 5 years revealed a significantly increased rate of local recurrences.[23] Possible explanations for these findings include poorer quality of the TME specimen (possibly because of more fibrosis after intensified treatment) and local progression in poorly responding tumors during the longer interval to surgery. Thus, the causal pathway between more pCR and better long-term local control was likely confounded by impaired surgery because of fibrosis and/or more advanced tumors in the prolonged TNT interval.

In addition, surrogate-directed treatment adaptations might, in turn, have an impact on DFS/OS. For example, patients who fail to achieve a pCR on neoadjuvant therapy are often considered for (more aggressive) adjuvant chemotherapy, whereas patients with pCR are more likely to undergo observation only.[24] If adjuvant treatment prolongs DFS/OS, then a treatment with lower pCR may end up having the same DFS/OS and then a treatment with higher pCR.

The conceptual difficulties of surrogacy of pCR and correlation with DFS/OS in rectal cancer are mirrored by the same scenario in breast cancer, suggesting that this may be a general phenomenon rather than a tumor-specific one. Cortazar et al[25] from the US Food and Drug Administration (FDA) analyzed pCR as a potential surrogate for event-free survival in patients with operable breast cancer undergoing neoadjuvant therapy using data from 12 registrational randomized trials including 11,955 patients. Again, individual-level surrogacy was strong (HR, 0.44 [95% CI, 0.39 to 0.51]), whereas trial-level surrogacy was weak ($R^2 = 0.03$ [95% CI, 0.0 to 025]). Some dismissed these findings on account of the heterogeneity of the trials in terms of patient selection and treatments tested. Similar data were provided by the same group in a recent meta-analysis of 15 eligible trials including 3,980 patients with human epidermal growth factor receptor 2–positive, early breast cancer after a median follow-up of 62 months.[26] The treatment was adjusted for confounding, and the individual-level and trial-level correlations were essentially identical to those in the study by Cortazar et al[25] despite the inclusion of a more homogeneous patient subset. Similarly, albeit a strong association between major pathologic response (defined as 10% or less residual viable tumor) and OS has been previously shown in patients with resectable non–small-cell lung cancers after neoadjuvant chemotherapy,[27] to the best of our knowledge, a formal randomized trial meta-analysis to demonstrate trial-level

surrogacy of pCR for OS in NSCLC has not been reported to date.

In breast cancer, the FDA has stated that pCR is "reasonably likely to predict an effect on long-term outcomes," which is not the same as stating that it is a valid surrogate end point, but may be regarded as acceptable for accelerated approval in breast cancer, provided that evidence of benefit on long-term outcomes is generated to grant full approval.[28,29]

In conclusion, we suggest that early response assessment in neoadjuvant rectal cancer trials, on the basis of pCR, TRG, and NAR, may be pragmatically used in early phase II testing to identify promising interventions for further (randomized) phase II/III validation.[10] However, one has to acknowledge that trial-level surrogacy for pCR has not been demonstrated in rectal cancer and remains ambiguous from the point of view of strict surrogacy. As discussed here, the causal pathway between pCR and long-term oncologic outcomes is confounded by several treatment-, tumor-, and patient-related factors that affect the association between the surrogate and the clinical outcomes of interest.

Future aspects of surrogacy may include molecularly defined outcome measures on the basis of the assessment of circulating tumor DNA (ctDNA) and circulating free DNA (cfDNA) to detect minimal residual disease (MRD) to tailor (escalate/de-escalate) therapy and predict clinical outcomes.[30] A recent systematic review of 25 studies showed that the presence of MRD was significantly associated with worse oncologic outcomes.[31] Despite great promise, prospective validation of the potential of ctDNA and cfDNA for outcome prediction and guidance of therapeutic decisions in rectal cancer will be essential before any consideration is given to their routine use as a surrogate for true clinical end points in the clinic.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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