ENHANCING THE ASSESSMENT OF PATHOLOGICAL COMPLETE RESPONSE AND EARLY DISEASE-FREE SURVIVAL AS SURROGATE ENDPOINTS FOR OVERALL SURVIVAL IN NEOADJUVANT RANDOMIZED CLINICAL TRIALS FOR EARLY BREAST CANCER: A BAYESIAN TRIVARIATE MODEL

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Introduction

To streamline the drug approval process, the use of surrogate endpoints is a cost-effective alternative to waiting for results on overall survival (OS) to assess the efficacy of a novel treatment in a randomized clinical trial (RCT). Validation of a surrogate endpoint involves establishing associations between the surrogate and final outcomes at both patient and trial levels. Pathological complete response (pCR) is supported by regulatory agencies as surrogate endpoint for OS in neoadjuvant RCTs for early stage breast cancer (BC), even if its correlation with survival has been proven only at patient level. [1] A recent meta-analysis conducted by our group [2] showed the limited value of pCR as surrogate endpoint for OS at trial level, hindering its reliability in predicting true clinical outcomes before trial completion. In contrast, late invasive disease-free survival (iDFS) is considered a reliable surrogate endpoint for OS but requires a longer follow-up than pCR to achieve optimal surrogacy. Thus, the use of late iDFS as a surrogate endpoint is less convenient than using pCR.

Aims

We aim to evaluate the surrogacy value for OS at trial level of a combined endpoint that incorporates both pCR and an early evaluation of iDFS. Our hypothesis is that combining pCR data with early iDFS can enhance the surrogacy for OS in neoadjuvant RCTs for early BC without waiting for final iDFS results.

Methods

As proposed by Elia et al. [3], a Bayesian trivariate model can be used to model jointly treatment effects on two surrogate endpoints, pCR (Y_{1i}) and early iDFS (Y_{2i}), and a final outcome, OS (Y_{3i}), which are assumed to be correlated and normally distributed:

$$\begin{pmatrix} Y_{1i} \\ Y_{2i} \\ Y_{3i} \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_{1i} \\ \mu_{2i} \\ \mu_{3i} \end{pmatrix}, \Sigma_i \right), \; \Sigma_i = \begin{pmatrix} \sigma_{1i}^2 & \sigma_{1i}\sigma_{2i}\varrho_{wi}^{12} & \sigma_{1i}\sigma_{3i}\varrho_{wi}^{13} \\ \sigma_{2i}\sigma_{1i}\varrho_{wi}^{12} & \sigma_{2i}^2 & \sigma_{2i}\sigma_{3i}\varrho_{wi}^{23} \\ \sigma_{3i}\sigma_{1i}\varrho_{wi}^{13} & \sigma_{3i}\sigma_{2i}\varrho_{wi}^{23} & \sigma_{3i}^2 \end{pmatrix}$$

μ_{ki} (k=1,2,3) represent the true treatment effects, σ_{ki}^2 their corresponding variances, and ϱ_{wi}^{kp} the within-study correlations between the estimates. Assuming a positive correlation between Y_{2i} and Y_{3i} and a negative correlation between Y_{1i} and both Y_{2i} and Y_{3i}, informative uniform prior distributions are given to between-study correlations as $\rho_{bet}^{13}, \rho_{bet}^{12} \sim U(-1,0)$ and $\rho_{bet}^{23} \sim U(0,1)$. [4] Other model parameters, including those involved in the dependence among means, are given non-informative prior distributions. To perform an early assessment of iDFS, individual patient data (IPD) are crucial to estimate treatment effects

at defined timepoints. Thus, among the RCTs included in our previous meta-analysis [2], we included only those showing Kaplan-Meier (KM) curves for iDFS or DFS. IPD were reconstructed from digitized data from the published KM curves [5, 6] and early iDFS calculated by censoring observation times at 12 months. Original IPD are required to determine the joint distribution of early iDFS and OS time. Consequently, within-study correlations could not be derived from the published KM curves, and we assumed the same correlations across all studies (i.e., $\rho_{\mathrm{pCR-OS}} = -0.3,\ \rho_{\mathrm{pCR-iDFS}} = -0.4, \rho_{\mathrm{iDFS-OS}} = 0.5$). Treatment effects on iDFS, OS and pCR were modeled using hazard ratios (iDFS-HRs and OS-HRs) or odds ratios (pCR-ORs). Three bivariate models were also used to compare the surrogacy value of the combined endpoint with that of pCR on OS, pCR on iDFS and iDFS on OS. The surrogacy value was evaluated based on the estimated slope (required different from 0), variance (required equal to 0), and the adjusted R^2. All the analyses were performed using R v. 4.2.1 and OpenBUGS v. 3.2.

Results

Seven RCTs (10 pairwise comparisons and 7,639 patients) were included in the analysis. The bivariate model of pCR and early iDFS showed weak association (Table 1). The 95% credible interval (95% CI) for the slope contained 0, and the surrogate relationship was not strong (R^2_{adj}=0.34). The slope and the R^2_{adj} were slightly higher for the association of early iDFS and OS (slope=2.82 (95% CI, 0.08; 13.78) and R^2_{adj}=0.36 (95% CI: 0.00; 0.93)). From the trivariate meta-analysis, we obtained the associations between the treatment effects on pCR and early iDFS and the effect on early iDFS and OS. Results for the association between pCR and early iDFS were very similar to those obtained by the corresponding bivariate model. For the association between early iDFS and OS results were also comparable, even though in the trivariate model the adjusted R^2 was slightly lower (0.31 vs 0.36 in the bivariate model).

	Bivariate models		
	pCR - OS	**pCR - early iDFS**	**Early iDFS - OS**
Intercept	-0.30 [-0.70; 0.07]	-0.30 [-0.57; -0.06]	0.56 [-0.36; 3.08]
Slope	0.77 [0.02; 2.82]	-0.31 [0.00; 1.36]	2.82 [0.08; 13.78]
Variance	0.21 [0.04; 0.64]	0.03 [0.00; 0.18]	0.17 [0.01; 0.57]
Adjusted R^2	0.20 [0.00; 0.78]	0.34 [0.00; 0.97]	0.36 [0.00; 0.93]
	Trivariate model		
		pCR - early iDFS	**Early iDFS - OS**
Intercept		-0.26 [-0.52; 0.01]	0.34 [-0.38; 2.54]
Slope		-0.32 [-1.22; -0.01]	2.00 [0.08; 8.11]
Variance		0.04 [0.00; 0.22]	0.17 [0.02; 0.52]
Adjusted R^2		0.35 [0.00; 0.94]	0.31 [0.00; 0.93]

Table 1. Results from bivariate and trivariate models for the association between treatment effects on the surrogate endpoints (pCR or early-iDFS) and the final outcome (OS, or early-iDFS in one of the bivariate analyses). The results are posterior means and corresponding 95% credible intervals.

Conclusions

In a Bayesian meta-analytic framework, we evaluated the combination of two potential surrogate endpoints (pCR and early iDFS) as joint predictors of the final clinical outcome (OS) in early BC. In contrast to a meta-regression standard approach, this model accounts for measurement error around treatment effects on surrogate endpoints. [7] Overall, these results did not show any advantage in the use of the combination of the two surrogate endpoints. However, the use of aggregate data and pseudo IPD rather than original IPD

is an important drawback that undermines the robustness and reliability of the results. To address this concern, we have established a collaboration with the German Breast Group (GBG), renowned for conducting multiple trials in the neoadjuvant setting of early BC. Our plan is to apply the proposed methodology to original IPD from a total of 11 RCTs conducted by GBG, seven of which are already included in this preliminary aggregate data analysis. We anticipate that the use of real within-study correlations and early iDFS values will significantly enhance the accuracy and reliability of our results. While it is not uncommon to assume the same within-study correlation value across all studies [8, 9], the impact of this assumption has never been thoroughly studied. Furthermore, although validated and reliable algorithms have been used to reconstruct IPD, only original IPD allow for verifying data consistency and integrity.

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