Estimation of overall survival from initial progression-free survival data

A Bayesian parametric copula-based approach leveraging earlier-phase trial data

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Background

- In phase III oncology studies, overall survival (OS) data are typically unavailable to decision-makers at the time of early interim analyses.
- Reimbursement submissions based on interim data for a surrogate endpoint such as progression-free survival (PFS) present high decision risk, since payers require lifetime OS estimates to evaluate cost-effectiveness[1-3].

Objectives

- We proposed that a prior representation of the **joint PFS-OS distribution**, determined by estimating a **parametric copula model** from **earlier-phase trial data**, can be combined with an **extrapolated PFS distribution** for the current (phase III) trial to yield **estimated OS probabilities** in the absence of OS data.
  - We conducted a **simulation study** to assess the **sensitivity** of the proposed novel method to **parametric model specification**.

Methods

Bayesian copula-based OS prediction model

- Estimates from a parametric copula model[4-6] fitted to PFS-OS data in the earlier-phase trial provide an **informative multivariate normal prior distribution** for outcomes in the phase III trial.
- A parametric distribution is then used to extrapolate the PFS density in the phase III trial, and OS is estimated by numerical integration of the **weighted conditional distributions** for OS given PFS[7,8].

Simulation study

- PFS-OS data were simulated for phase II (N=150; 36 months min. follow-up [fu]) and III (N=300; 18 and 36 months min. fu at interim PFS and final analyses, resp.) trials of patients with metastatic cervical cancer treated with first-line immunochemotherapy[9], via a multistate model.
- OS was estimated using parametric models based on Weibull (or log-normal (sensitivity analysis)) marginals and five candidate copulas encompassing archetypal tail behaviors for PFS-OS association[10].

Results

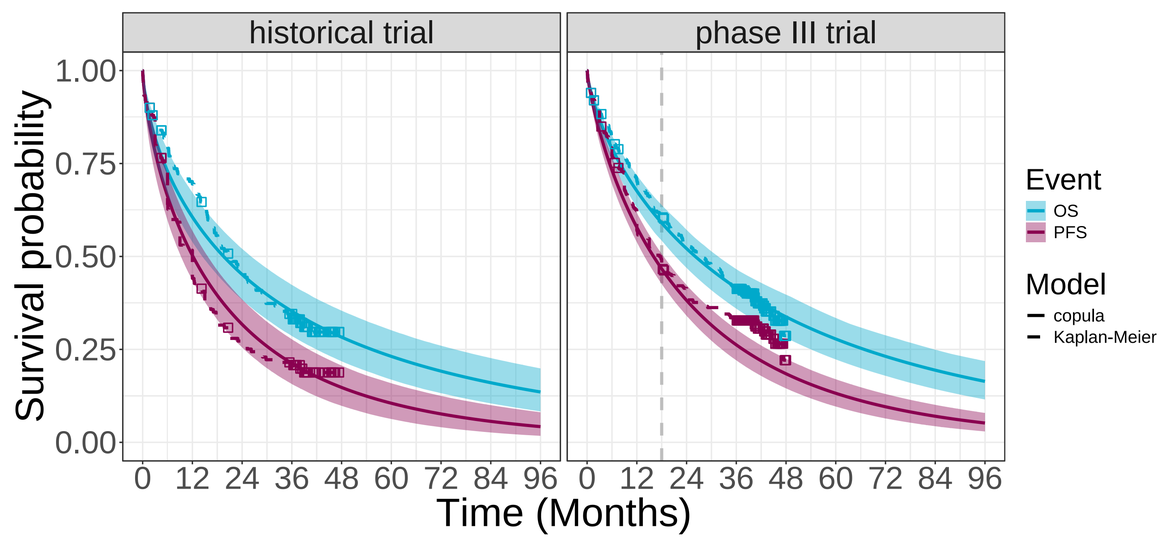
- The simulated phase II trial datasets typically featured a heavy right-tail dependence pattern (with the Joe and Hougaard copulas being favored per average DIC; Table 1) with strong patient-level PFS-OS association (average Kendall's tau coefficient estimated from the Joe copula: 0.65).
- For all five copula functions examined, uncertainty in the OS estimates was reasonable (e.g., for the Joe model, average bounds of the 95% CrIs were 35.4-44.8%) (Fig. 1).
  - Achievement of satisfactory posterior uncertainty was facilitated by the extended follow-up duration of the phase II study.
- The error in the estimated 3-year OS probabilities varied substantially across the alternative copulas (Table 1), with the Joe copula having the highest accuracy (range in mean absolute error: 5.8-9.0%).

Table 1: Copula OS prediction model performance, with bias and uncertainty calculated based on estimated 3-year OS probabilities (vs Kaplan-Meier).

Copula function	Mean absolute error (%)	95% CrI coverage rate	Average 95% CrI widths (%)	Average DIC (phase II study)	Average τ_K (phase II study)
Clayton	9.0	72%	10.3	1720.7	0.70
Frank	7.1	74%	8.7	1695.5	0.71
Hougaard	6.0	78%	8.9	1652.6	0.72
Joe	5.8	81%	9.4	1650.8	0.65
Plackett	7.6	74%	9.8	1680.8	0.71

τ_K = Kendall's tau; CrI = credible interval; DIC = deviance information criterion. Results are from 100 simulated datasets.

Figure 1: Estimates from the parametric copula-based OS prediction model.



Note: illustrated results are taken from a single representative iteration of the simulation study, using the Joe copula. OS in the phase III study was estimated based on interim PFS data, with 18 mo. minimum follow-up.

- The coverage rates of the 95% CrIs for 3-year OS ranged from 72-81% across copulas (Table 1). The main source of error was apparent between-study differences in PFS-OS association strength, driven by uncertainty from the limited sample size of the phase II study.
  - A minority of iterations contributed high error owing to the reliance on PFS extrapolations given the immature PFS data at the interim analysis.
- In the sensitivity analysis using log-normal marginals, the Joe copula again yielded the smallest mean absolute error in 3-year OS (range: 6.3-9.6%) and highest coverage rates (range: 70-80%).

Discussion

- Estimated OS probabilities were **moderately sensitive** to the choice of marginal and copula distributions. Therefore, it is recommended to employ the **candidate set of copulas** used herein, and to perform a sensitivity analysis using alternative marginal models.
  - Even short-term OS predictions can be sensitive to long-term PFS extrapolations.
  - **Bias from mis-specification of the copula** appears typically **smaller** than the error arising from between-study differences in the PFS-OS correlation pattern or from small sample size of the earlier-phase study data, as explored in previous simulation studies[8].

Conclusions

- The model provides an interpretable approach to **generate plausible OS probabilities** from initial PFS data. It is predicated on **strong prognostic relevance** of progression events and a **highly similar PFS-OS dependence pattern** between phase III & II studies.

References

[1] Bujkiewicz S, et al. Methods for evaluation of surrogate endpoints for health technology assessment decision making: a good practices report of an ISPOR task force. *Value Health* 29(5):711-24.
[2] Buyse M, et al. Surrogacy beyond prognosis: the importance of "trial-level" surrogacy, *Oncologist* 2022; 27(4):266-71.
[3] Belin L, et al. Progression-free survival as a surrogate for overall survival in oncology trials: a methodological systematic review. *Br J Cancer* 2020; 122: 1707-14.
[4] Weber EM, Titman AC. Quantifying the association between progression-free survival and overall survival in oncology trials using Kendall's tau. *Stat Med* 2019; 38(5):703-19.
[5] Fu H, et al. Joint modeling of progression-free survival and overall survival by a Bayesian normal induced copula estimation model. *Stat Med* 32(2):240-54.
[6] Escalera G, Carrière JF. Fitting competing risks with an assumed copula. *Stat Methods Med Res* 2003; 12(4):333-49.
[7] Sharpe DJ, et al. A novel copula-based method to predict overall from progression-free survival in phase III trials using earlier-phase data. Poster presentation at DIA Europe 2026, 24-26 Mar 2026, Rotterdam, Netherlands.
[8] Sharpe DJ, Tate AE, De T, He B, Vanderpuye-Orgle J, Davé K. Predicting overall survival from interim progression-free survival data in a phase III trial: a novel copula-based model and case study in microsatellite instability-high metastatic colorectal cancer. (Submitted).
[9] Ogasawara A, Hasegawa K. Recent advances in immunotherapy for cervical cancer. *Int J Clin Oncol* 2025; 30(3):434-48.
[10] Sharpe DJ, et al. Bivariate copula models with event-free cure effect for survival extrapolations and individual-level correlation analysis. *Stat Med* 2026 (in press).

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