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Effective Use of Reconstructed Survival Data for Individual-Level Correlation Assessment in Oncology: A Case Study in Metastatic-Hormone Sensitive Prostate Cancer (mHSPC)

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Background

- A surrogate endpoint (SE) is an intermediate outcome that is used as a direct substitute or predictor of a final "true" outcome of interest in clinical trials or real-world settings.[1]
- Surrogate endpoints are increasingly appealing in clinical research as they can be measured earlier or with fewer resources than the true endpoint. Their use can accelerate the evaluation of new therapies, particularly in oncological settings where lengthy follow-up is often needed to obtain statistically mature overall survival (OS) data due to recent improvements in standard of care.[2]
- Elston and Taylor proposed a three-level hierarchical framework for evaluating the validity of SEs as follows: 1) biological plausibility of a causal mechanism between the surrogate and true endpoints, 2) association between the surrogate and the true endpoints at the individual patient level, and 3) association between treatment effects on the surrogate and true endpoints across multiple clinical trials.[1]
- While the association between treatment effects can be assessed using published aggregate-level data, the individual level association requires individual patient data (IPD) from at least one clinical trial or real-world cohort. This requirement is frequently a barrier to the assessment of second criterion proposed by Elston and Taylor because procurement of IPD from external sources is often costly and difficult due to privacy concerns and regulatory barriers.
- Additionally, even when IPD are available, the standard Copula-based approach cannot estimate the Pearson's correlation coefficient due to the censored nature of survival data.[4] The standard Copula-based approach may also be prone to convergence and interpretation issues due to their sophisticated structural forms.
- Alternatively, pseudo IPD can be reconstructed from the published Kaplan-Meier (KM) curves.[3] However, this procedure can only be used to reconstruct the survival data for the SE and true endpoint separately. To investigate the association between the SE and true endpoint using existing correlation measures, the reconstructed survival data for the surrogate and true endpoint need to be paired.[5]
- A potential solution to this problem is the application of a three-state illness-death model. This approach has been investigated previously in simulating paired survival data in metastatic gastric cancer[6] and in metastatic melanoma.[5]

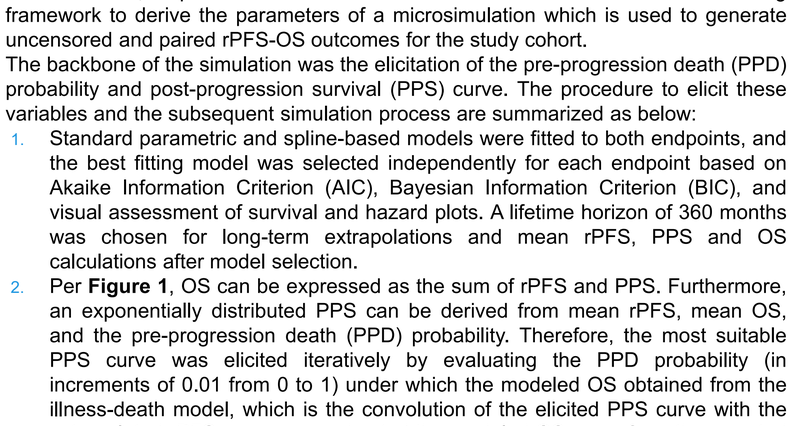
Objective

- To devise a novel framework for indirectly estimating individual-level correlation using reconstructed survival data, with an application in metastatic hormone-sensitive prostate cancer (mHSPC).
- To investigate the robustness of the proposed indirect approach to the key parameters elicited from the aggregate level data.

Methods

- In the Phase III trials evaluating new therapies in mHSPC, it can take approximately a decade to achieve mature OS data. Therefore, Halabi et al. (2024) investigated both individual-level and trial-level association between radiographic progression-free survival (rPFS) and OS in mHSPC by pooling IPD from nine trials.
- To validate the predictive performance of a three-state illness-death model in assessing the individual-level surrogacy between rPFS and OS in the same patient population, we reconstructed pseudo IPD[3] for both endpoints from the digitized KM curves published by Halabi et al. (2024).[7] Reconstructed pseudo IPD were based on 6,390 patients pooled across nine trials in the evidence base.
- Reconstructed, unpaired rPFS and OS data were used in a survival modeling framework to derive the parameters of a microsimulation which is used to generate uncensored and paired rPFS-OS outcomes for the study cohort.
- The backbone of the simulation was the elicitation of the pre-progression death (PPD) probability and post-progression survival (PPS) curve. The procedure to elicit these variables and the subsequent simulation process are summarized as below:
  1. Standard parametric and spline-based models were fitted to both endpoints, and the best fitting model was selected independently for each endpoint based on Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and visual assessment of survival and hazard plots. A lifetime horizon of 360 months was chosen for long-term extrapolations and mean rPFS, PPS and OS calculations after model selection.
  2. Per **Figure 1**, OS can be expressed as the sum of rPFS and PPS. Furthermore, an exponentially distributed PPS can be derived from mean rPFS, mean OS, and the pre-progression death (PPD) probability. Therefore, the most suitable PPS curve was elicited iteratively by evaluating the PPD probability (in increments of 0.01 from 0 to 1) under which the modeled OS obtained from the illness-death model, which is the convolution of the elicited PPS curve with the extrapolated rPFS curve, approximated the modeled OS curve from the reported data as closely as possible. The iterative procedure relied on a moment-matching approach.
  3. Paired rPFS-OS data were simulated for 6,390 patients [the sample size of patients across all trials in Halabi et al. (2024)] by (1) randomly determining whether each patient progressed or died before progression per the PPD probability, (2) sampling their rPFS and PPS durations from their respective curves (i.e., PPS = 0 if death occurred before progression), and (3) combining simulated rPFS and PPS to calculate OS.
  4. Finally, the paired rPFS-OS data were used to calculate Kendall's (τ), Spearman's (ρ) and Pearson's (r) correlation coefficients between the two endpoints.
- This process was repeated 100 times, then each correlation coefficient (τ, ρ and r) and its standard error were estimated by the sample mean and standard deviation across iterations on the Fisher-transform scale.
- Sensitivity analyses were conducted by varying the following three parameters around their base-case values or estimates: PPD probability by ±10%, hazard rate of PPS by ±10%, and time horizon by ±60 months.

Figure 1: Structure of three-state death-illness model used to estimate paired rPFS and OS data.



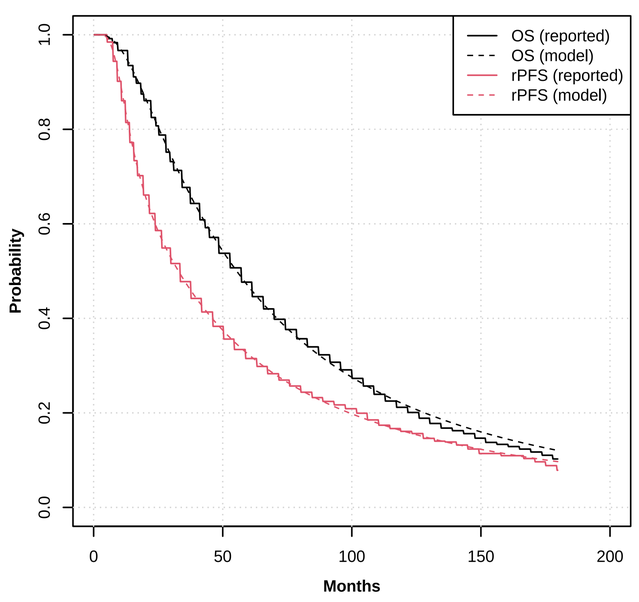
* – Not reported by the study.

Abbreviations: OS – Overall Survival, rPFS – Radiographic Progression-Free Survival, p – Pre-progression death probability, PPS – Post-Progression Survival, TTP – Time to Progression.

Results

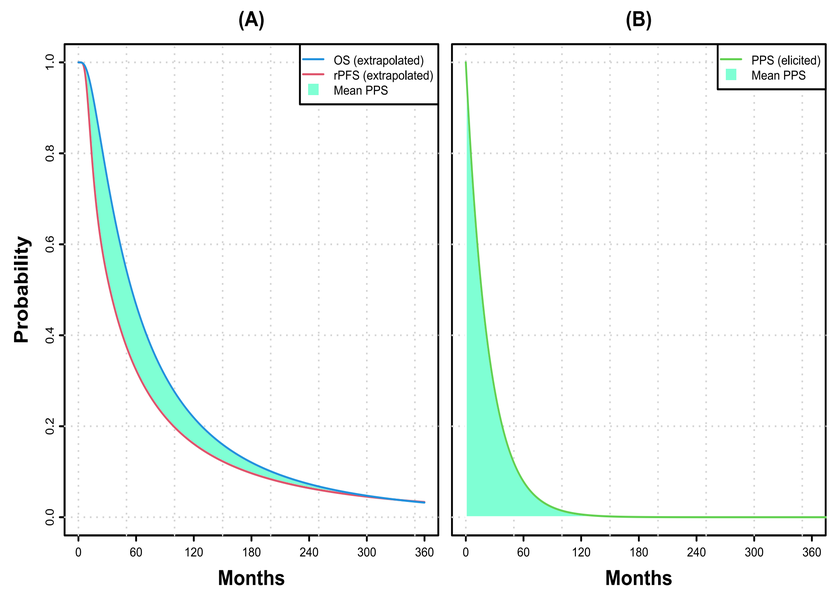
- The spline normal model was identified as the best fitting distribution for both rPFS and OS (one and two knots, respectively), and this was also confirmed visually (**Figure 2**). There was a slight overestimation in the tail of the reported OS curve with the selected fit, but otherwise the modelled curves and their corresponding hazards closely captured the trend in the observed KM curves and underlying smoothed hazard rates, respectively, throughout the follow-up for both endpoints.
- The PPD probability was estimated as 22%, which translated to a monthly PPS hazard rate of 0.042 under the exponential distribution assumption. For the estimated PPD probability and PPS hazard rate, the modeled OS from the three-state illness-death model matched the extrapolated OS from the observed data closely. The elicited PPS curve and the corresponding mean PPS are illustrated in **Figure 3**.
- Estimated rPFS, OS, and PPS curves from the first batch of the simulation process are compared to the corresponding extrapolated and elicited curves using reported data in **Figure 4**. The simulated curves closely matched the extrapolated curves for all three outcomes (i.e. rPFS, PPS and OS), indicating that the process of simulating correlated data did not impact the marginal distributions of any of the three outcomes. Estimates for Pearson's r, Kendall's τ, and Spearman's ρ are presented in **Table 1**.
  - In the primary analysis, the simulation procedure estimated a Pearson's r of 0.965 (95% CI: 0.961, 0.968), a Kendall's τ of 0.707 (95% CI: 0.695, 0.719), and a Spearman's ρ of 0.857 (95% CI: 0.847, 0.867).
  - The estimated Kendall's τ was slightly conservative compared to the Kendall's τ of 0.83 (95% CI: 0.82, 0.84) obtained from Copula-based methods using actual IPD pooled across trials in the original meta-analysis.[4]
- Sensitivity analysis results were consistent with the primary analysis, demonstrating insensitivity of the results to moderate variations in the estimates of the PPD probability and PPS hazard, as well as the choice of time horizon when estimating mean rPFS and mean OS.

Figure 2: Comparison of reported and modeled curves for rPFS and OS.



Abbreviations: OS – Overall Survival, rPFS – Radiographic Progression-Free Survival.

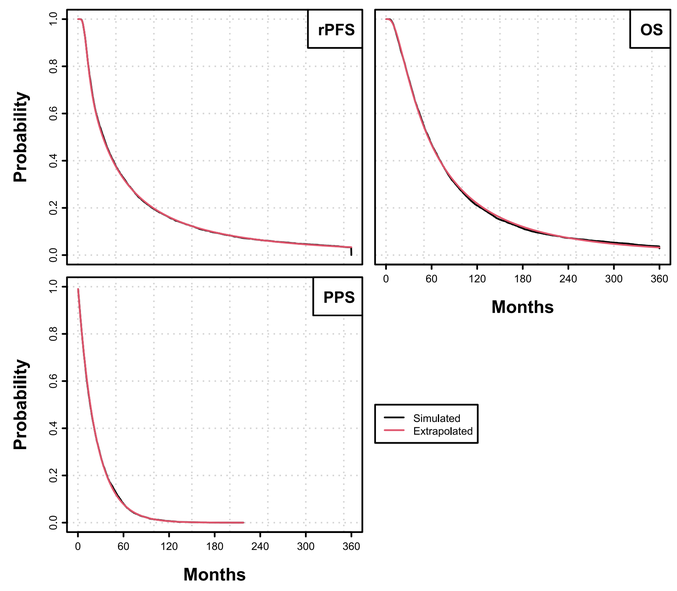
Figure 3: Estimated PPS and corresponding mean PPS from (A) time of randomization (B) estimated time of progression.



Note: Green shaded area represents mean PPS.

Abbreviations: OS – Overall Survival, PPS – Post-Progression Survival, rPFS – Radiographic Progression-Free Survival.

Figure 4: .Comparison of extrapolated and simulated curves for rPFS, OS and PPS.



Note: Simulated rPFS and PPS curves are derived by sampling from the extrapolated (rPFS) and elicited (for PPS) counterparts. Therefore, for these two outcomes, close approximations between the modeled curves from observed data and simulated curves are expected. However, the simulated OS curve is derived indirectly from the modeled rPFS and PPS curves, and estimated PPD probability. Therefore, a close approximation between the simulated and extrapolated OS curves is not guaranteed and close approximation between the two reflects the predictive ability of the procedure.

Abbreviations: OS – Overall Survival, PPS – Post-Progression Survival, rPFS – Radiographic Progression-Free Survival.

Table 1: Individual-level correlation estimates for base-case setting and sensitivity analyses.

Analysis	Pearson's r (95% CI)	Kendall's τ (95% CI)	Spearman's ρ (95% CI)
Primary	0.965 (0.961, 0.968)	0.707 (0.695, 0.719)	0.857 (0.847, 0.867)
p − 10%	0.966 (0.963, 0.969)	0.709 (0.700, 0.718)	0.859 (0.851, 0.867)
p + 10%	0.963 (0.959, 0.967)	0.706 (0.692, 0.719)	0.854 (0.843, 0.865)
h − 10%	0.958 (0.954, 0.962)	0.701 (0.686, 0.715)	0.846 (0.834, 0.858)
h + 10%	0.969 (0.967, 0.972)	0.715 (0.707, 0.722)	0.866 (0.859, 0.872)
Horizon − 60 months	0.958 (0.954, 0.961)	0.706 (0.694, 0.718)	0.857 (0.847, 0.867)
Horizon + 60 months	0.970 (0.966, 0.973)	0.709 (0.697, 0.721)	0.858 (0.848, 0.868)

Note: Pearson's correlation coefficient indicates stronger association between rPFS and OS as it's based on nominal durations of these endpoints rather than their ordered ranks.

Abbreviations: CI – Confidence Interval, p – Pre-progression death probability, h – Hazard rate for post-progression survival, OS – Overall Survival, rPFS – Radiographic Progression-Free Survival.

Conclusions

- This proposed approach can estimate both rank and product moment correlation coefficients without access to IPD and be generalized to other survival-based time-to-event SEs and cancer types. However, the approach is limited to predicting OS from endpoints such as PFS and recurrence-free or event-free survival, not other outcomes with binary nature (e.g., tumor response).
- Predictions from the proposed approach in this case study can be conservative due to independent sampling of rPFS and PPS in the simulation procedure. Despite the conservativeness of the results, sensitivity analyses highlighted the robustness of the simulation procedure to considerable variation in key parameters of the process.

References

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