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Incorporating cure effect into copula models for long-term survival projections: a case study in previously treated advanced esophageal squamous cell carcinoma (aESCC)

Daniel J. Sharpe,[1] Georgia Yates,[1] Tuli De,[2] Prianka Singh,[3] Murat Kurt[3]

[1]Parexel, London, United Kingdom; [2]Parexel, Billerica, MA, United States; [3]Bristol Myers Squibb, Princeton, NJ, United States

Background

- Mixture cure models (MCMs) are commonly used to extrapolate survival outcomes in studies where long-term survivorship is deemed clinically plausible[1-3]
- A common criticism of MCMs is the sensitivity of the cure fraction estimates, and hence survival extrapolations, to the length of available follow-up[4,5]
  - specifically, there is sometimes a tendency for MCMs to overestimate cure fractions in earlier data cuts
- Here, we describe an approach based on copula models[6] to extrapolate overall survival (OS) outcomes with MCMs more conservatively, by using an effective progression-free survival (PFS) cure fraction to support OS projections
  - The method offers a strategy to improve robustness and clinical plausibility of MCM predictions when OS data mature slowly or when there is clinical belief that patients with progressed disease cannot be "cured"
  - The method implicitly accounts for excess hazard in patients with progressed disease (vs progression-free patients) and concomitantly estimates patient-level PFS-OS correlation coefficients in the presence of a cure effect
- We demonstrate the method with an application to observations in the nivolumab arm from the final data cut of the phase III ATTRACTION-3 study in previously treated advanced esophageal squamous cell carcinoma (aESCC)[7]

Methods

Bivariate copula mixture cure survival models

- A bivariate survival copula $C(\theta)$ for PFS-OS outcomes links a pair of marginal survival functions for each of the endpoints, $S_{\mathrm{OS}}(t_{\mathrm{OS}})$ and $S_{\mathrm{PFS}}(t_{\mathrm{PFS}})$, to express the joint OS-PFS survival function $S(t_{\mathrm{OS}}, t_{\mathrm{PFS}})$, via a coupling parameter θ[8]
- Here, we employ MCMs to represent the marginal OS and PFS functions. These two models share a cure fraction parameter, π, which is an effective PFS cure fraction
- Correlation coefficient estimates can be sensitive to the choice of copula function[8,9]. We identified a suitable candidate set of copula functions, namely: Clayton, Frank, Hougaard, Joe, and Plackett copulas. All these copulas allow correlation strength ranging from independence to perfect positive dependence, have a single coupling parameter, and together display diverse tail dependence characteristics[6]

Model estimation, selection, and outputs

- Parameters of the survival copula models were estimated by maximum likelihood and the preferred bivariate MCM was chosen based on goodness-of-fit (Akaike information criterion [AIC]) and visual fit to Kaplan-Meier curves
- We used marginal MCMs chosen from univariate fits to OS and PFS endpoints separately[10]. Namely, we employed MCMs wherein OS and PFS for the "uncured" patients were represented by gamma and log-normal distributions, respectively. The parameters of these distributions were then re-estimated under the copula likelihood
- Quality-adjusted life years (QALYs) over a 20-year horizon were estimated from alternative partitioned survival models (PSMs) based on the preferred bivariate MCM, independent univariate MCMs with separate cure fractions, and univariate standard parametric models (SPMs), using local discounting schemes and tariffs from nine selected countries

Results

- The selected (lowest-AIC) bivariate MCM was based on the Hougaard copula (Table 1). The estimated cure fraction from this bivariate MCM was 5.2% [95% confidence interval (CI): 2.7-9.8%], which compares favorably with the estimated PFS cure fraction from the univariate MCMs (4.4% [95% CI: 2.1-8.8%] and is substantially more conservative than the OS cure fraction from the univariate MCMs (10.4% [95% CI: 6.2-17.1%])
- The bivariate MCMs with shared cure fraction yield significantly more conservative OS extrapolations than the conventional univariate MCMs. PFS extrapolations from the bivariate MCMs are slightly less conservative than from the univariate MCMs (Fig. 1)
- QALYs estimated from the PSM based on the bivariate MCM with shared cure fraction are consistently more conservative than from the PSM based on the univariate MCMs and less conservative than from the PSM based on univariate SPMs (Table 2)
- For any given country, there is an increased (decreased) contribution to the total QALYs from the progression-free (progressed disease) state, respectively, in bivariate MCMs with shared cure fraction vs univariate MCMs with separate cure fractions (Table 3)

Table 1. Key estimates and goodness-of-fit statistics from bivariate MCMs based on various copulas, and independent univariate MCMs

Model	Cure fraction (%) [95% CI]	5-year OS (%) [95% CI]	5-year PFS (%) [95% CI]	ΔAIC
Clayton	6.8 [3.8-11.7]	6.9 [5.2-10.9]	6.4 [4.2-10.6]	35.0
Frank	6.2 [3.5-10.7]	6.6 [4.5-11.1]	5.9 [3.3-10.7]	23.2
Hougaard	5.2 [2.7-9.8]	6.0 [3.7-10.4]	4.8 [2.6-9.4]	0.0
Joe	5.3 [2.8-9.9]	6.6 [4.8-10.5]	5.0 [2.8-9.5]	9.1
Plackett	6.3 [3.6-10.8]	6.6 [4.1-10.3]	5.9 [3.1-9.5]	18.3
Univariate MCMs	4.4 [2.1-8.8]	10.1 [6.9-16.9]	4.1 [2.3-7.7]	-

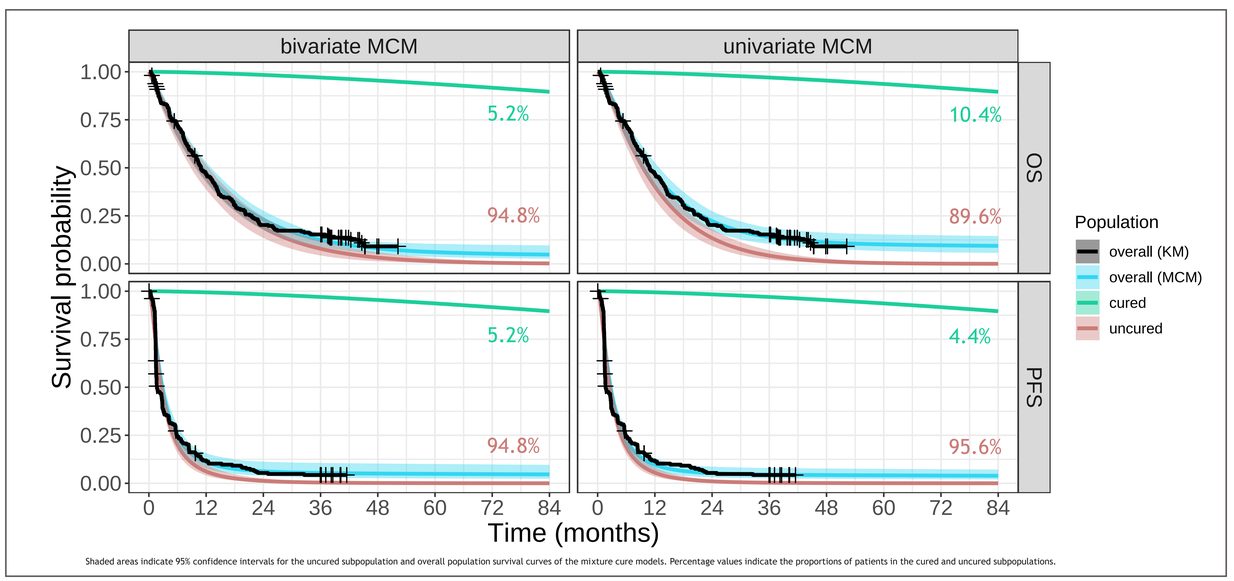
ΔAIC = relative Akaike information criterion; CI = confidence interval; MCM = mixture cure model.
The selected bivariate MCM is highlighted.

Table 2. QALY estimates from selected countries, estimated from alternative partitioned survival models

Country	QALY estimates by model		
	Bivariate MCM	Univariate MCMs	Univariate SPMs
UK	1.15	1.36	1.03
USA	1.32	1.60	1.21
Belgium	1.28	1.57	1.14
France	1.14	1.35	1.00
Netherlands	1.35	1.66	1.20
Sweden	1.46	1.81	1.38
Portugal	1.00	1.17	0.90
Australia	1.16	1.36	1.08
Canada	1.36	1.68	1.23

MCM = mixture cure model; QALY = quality-adjusted life year; SPM = standard parametric model.

Figure 1. OS and PFS curves from bivariate MCMs with shared cure fraction and univariate MCMs with separate cure fractions, compared to the Kaplan-Meier (KM) estimates



Shaded areas indicate 95% confidence intervals for the uncured subpopulation and overall population survival curves of the mixture cure models. Percentage values indicate the proportions of patients in the cured and uncured subpopulations.

Table 3. Contributions to QALY estimates from PSMs based on alternative parametric OS and PFS models, using local discounting schemes and tariffs for the USA

Model	Contributions to QALYs from state		
	Progression-free	Progressed disease	Total
Bivariate MCM	0.81	0.51	1.32
Univariate MCMs	0.72	0.88	1.60
Univariate SPMs	0.48	0.73	1.21

MCM = mixture cure model; PSM = partitioned survival model; QALY = quality-adjusted life year; SPM = standard parametric model.

Discussion

- The differences in QALYs calculated from the bivariate MCM with shared cure fraction vs the univariate MCMs with separate cure fractions is driven by opposing factors of more optimistic PFS extrapolations and more pessimistic OS extrapolations in the former model
  - on balance, since the OS extrapolations are affected more strongly by adopting the bivariate MCM formulation, the QALYs from the bivariate model are more conservative
- In general, bivariate MCMs could lead to more optimistic QALY estimates than conventional MCMs, dependent on the tumor area, quality of life data, and subsequent treatment pattern. For instance, the bivariate model may be more optimistic when there is a larger difference in utilities for progression-free vs progressed disease states, or a greater fraction of patients who are both progression-free and cured
- If post-progression relapses are common and expected to occur beyond the follow-up period of the study, conventional univariate MCMs are liable to perform poorly and the bivariate MCMs may offer a more reliable approach

Conclusions

- Bivariate copula MCMs for the joint modeling of OS-PFS outcomes employ an effective PFS cure fraction and therefore offer a more conservative method for incorporating the notion of cure to extrapolate OS outcomes
- This bivariate MCM formulation assumes that patients with progressed disease cannot be cured and implicitly accounts for the excess hazard experienced by patients with progressed disease (vs progression-free patients)
- The bivariate copula MCM approach can be especially useful when possibility of post-progression cure is believed to be remote or when OS data are immature

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Email: murat.kurt@bms.com