Bayesian multi-parameter evidence synthesis for informed extrapolations of time-to-event outcomes in multistate models

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Background

- Extrapolations in multistate (time-inhomogeneous Markov) models fitted to immature trial data present high uncertainty and potential inaccuracy in cost-effectiveness analyses[1,2]

Objectives

- We developed a novel approach to generate informed extrapolations of outcomes in multistate models, based on prior expectation for occupation probabilities of health states at selected times, via a Bayesian multi-parameter evidence synthesis (B-MPES) framework[3-6]

Methods

Synthetic trial data and multistate model structure

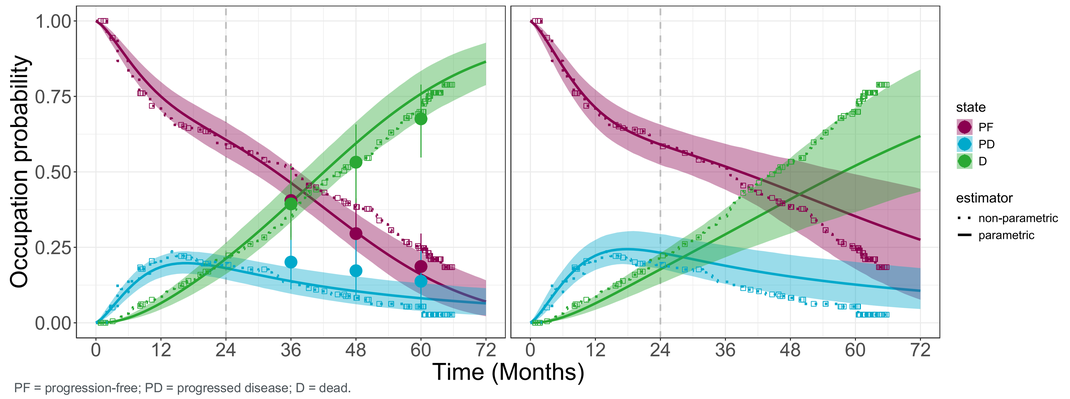
- Parametric models were used to simulate data for overall survival (OS), time to progression (TTP), and progression-free survival (PFS), emulating features of outcomes for high-risk patients with advanced ovarian cancer treated with first-line PARP inhibitor (PARPi) +/- bevacizumab (BEV) [7]
- Data were simulated for interim (2-y) and final (5-y) analyses of a trial of PARPi+BEV (*N*=200), and 5-y data for a historical trial of BEV (*N*=200) with somewhat poorer outcomes
- TTP, OS, and PFS outcomes were represented by a continuous-time semi-Markov multistate model[8-11] for a three-state irreversible progressive illness-death process, parameterized by Weibull transition intensity functions

Specifying prior expectation for health state occupation probabilities

- Prior expectation for the occupation probabilities of a set of health states at time t, $\boldsymbol{\pi}(t)$, was expressed via the concentration parameters $\boldsymbol{\alpha}(t)$ of a Dirichlet distribution, and this external information was applied for selected (annual) timepoints $\boldsymbol{t}_{\text{ext}}$,

$$\boldsymbol{\pi}(t) \sim \text{Dirichlet}\big(\boldsymbol{\alpha}(t)\big), \qquad \forall\, t \in \boldsymbol{t}_{\text{ext}}. \quad (1)$$

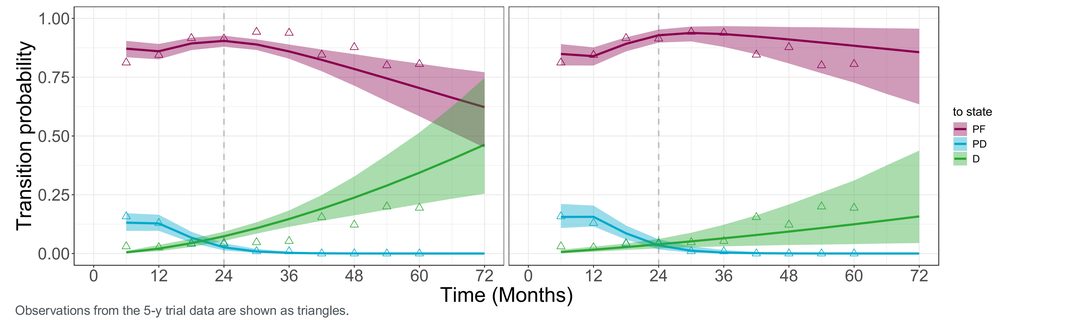
- In Eq. (1), the sum of the concentration parameters is an effective sample size that reflects the *a priori* uncertainty,[6] which was here scaled to half the number of patients at risk in the historical trial data at 2 years (*n*=58)
- To extrapolate from the 2-y trial data, prior expectation for state occupation probabilities was applied for each subsequent year, i.e., $\boldsymbol{t}_{\text{ext}} = \{36, 48, 60 \text{ mo.}\}$
  - The concentration parameters, $\boldsymbol{\alpha}(t)$ in Eq. 1, were derived by applying 12-mo. transition probabilities (Aalen-Johansen estimates) from the historical trial data to the observed 24-mo. state occupation probabilities in the current trial
  - This strategy partially addresses between-study confounding in absolute occupation probabilities
- Informed (B-MPES) and naïve (vague prior) models were fitted to the 2-y trial data, and extrapolated estimates for state occupation probabilities were compared to observations from the 5-y trial data



PF = progression-free; PD = progressed disease; D = dead.

Trial observations were calculated from the non-parametric Aalen-Johansen estimator. Squares indicate censoring. Shaded areas indicate 95% credible intervals of the parametric models. Points and whiskers show prior expectation and associated uncertainty (95% CIs) derived from the historical trial data, used in the B-MPES model.

Figure 1: Health state occupation probabilities from a B-MPES multistate model informed by historical trial data (left) and a naïve multistate model (right) fitted to 2-y trial data, compared to observations from the 5-y data.



Observations from the 5-y trial data are shown as triangles.

Figure 2: Trend in 6-month transition probabilities from the progression-free health state, estimated from a B-MPES model informed by historical trial data (left) and a naïve model (right) fitted to 2-y trial data.

Results

- Estimates for PFS and OS at 3 years and after were more conservative, less uncertain, and more accurate in the B-MPES vs the naïve model (Fig. 1, Table 1)
  - B-MPES and naïve models over- and under-estimated 6-month transition probabilities for death from the progression-free state, respectively (Fig. 2)
  - The naïve model overestimated the proportion of patients in the progressed disease state at 5 years (Fig. 1)
- The B-MPES model yielded more accurate estimates for post-progression survival (e.g., survival at 5 years after progression: 17.1% [95% CrI: 7.2-30.0%] B-MPES vs 22.6% [10.7-36.4%] naïve vs 13.5% observed)

Discussion

- The B-MPES model generally outperformed the naïve model but was conservative, reflecting the fact that the historical trial data did not fully capture the durable treatment benefit of PARPi for patients who survive beyond 2 years
- Confounding in conditional, long-term progression and survival outcomes is assumed to be tolerated by the variances of the Dirichlet distributions (Eq. 1)
- The proposed method offers a superior approach to generate informed joint PFS-OS distributions than can be achieved with partitioned survival models (PSMs)
  - Although, there are sometimes challenges in robustly estimating transition probabilities in multistate models[12]

Table 1: Posterior estimates [95% CrIs] for health state occupation probabilities (%) in the B-MPES and naïve multistate models fitted to 2-y data, compared to 5-y trial observations (Aalen-Johansen estimates) [95% CIs].

	Progression-free			Progressed disease			Dead		
Time (mo.)	B-MPES	Naïve	Obs.	B-MPES	Naïve	Obs.	B-MPES	Naïve	Obs.
36	46.4 [40.8-52.1]	51.8 [44.1-59.3]	51.7 [45.0-59.4]	13.8 [9.6-18.3]	18.9 [12.9-25.6]	13.6 [9.5-19.4]	39.8 [33.4-46.5]	29.3 [21.7-37.9]	34.7 [28.5-42.2]
48	30.1 [23.9-36.4]	43.7 [31.6-54.2]	38.4 [31.9-46.2]	10.5 [6.2-15.3]	15.4 [9.1-22.5]	8.4 [5.2-13.3]	59.5 [51.9-66.5]	40.9 [29.6-54.6]	53.3 [46.5-61.1]
60	16.0 [9.4-23.3]	35.3 [17.8-49.2]	24.7 [19.0-32.2]	8.1 [3.9-13.1]	12.7 [6.3-20.2]	6.3 [3.6-10.8]	75.9 [67.4-83.4]	52.1 [36.7-71.2]	69.0 [62.4-76.3]

Note: the historical trial data used in the B-MPES model had poorer outcomes than the current trial; % PF = 31.4, 22.9; 14.5; % D = 55.6, 65.2, 76.1 (at 36, 48, 60 mo.).

Conclusions

- Incorporating prior knowledge on expected longer-term occupation probabilities of health states at selected timepoints, within a B-MPES framework, can avoid speculation and reduce uncertainty in extrapolations from multistate models fitted to immature trial data
  - The approach can mitigate a major source of decision risk that commonly arises in cost-effectiveness analyses
  - The model has an intuitive appeal, since expected health state occupancy can be readily interpreted by clinical experts

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