Poster #: MSR109

Can Jointly Modelling PFS and OS with Mixture Cure Models Overcome Data Immaturity Problems?

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Background & Objective

- Oncology trials are typically powered on progression-free survival (PFS). At the time of health technology assessment, therefore, the overall survival (OS) data are often immature. Mixture cure models (MCM) need a sufficiently long survival tail to capture a cured fraction. National Institute of Health and Care Excellence Technical Support Document guidance on extrapolating survival data indicates that external data may be used to reduce uncertainty.[1]
- The aim was to inform OS cure rates of the active and placebo arms by jointly modelling PFS and OS with an MCM by two different approaches.

Methods

- A trial in front-line renal cell cancer comparing ipilimumab plus nivolumab with sunitinib was used as example (Figure 1).[2]
- First, Bayesian log-logistic MCM was estimated over the PFS and OS data of the trial separately. Non-informative priors were assumed, and treatment effects were applied to all three parameters of the log-logistic MCM. A log-logistic MCM was then fitted where individual cure rates were jointly estimated for PFS and OS, but separately for active and placebo arms. The shape and scale parameters of the log-logistic distribution were modelled separately for PFS and OS by treatment. In a separate analysis, the posterior PFS cure rates estimated with the log-logistic MCM were used as prior for the log-logistic MCM on OS data.[3]
- The cure rates, mean and incremental mean survival were compared for 1) fitting the MCM directly on the OS data; 2) jointly modelling PFS and OS; and 3) when using PFS cure as prior for OS cure.

Conclusions

- Jointly modelling PFS and OS cure rates or using PFS cure rates as a prior for OS cure rates in MCMs can inform immature OS predictions..
- The approach can easily be extended to other parametric distributions in MCM and non-MCM.

Key Results

- For PFS, the standard log-logistic MCM predicted cure rates of 0.14 [credible interval (CrI) 0.08; 0.20] and 0.33 [0.26; 0.39] for sunitinib and nivolumab + ipilimumab, respectively (Table 1).
- For OS, the standard log-logistic MCM predicted slightly different cure rates for sunitinib and nivolumab + ipilimumab with large CrIs (Table 1).
- The visual fit of all approaches to the OS data was good (Figure 2).
- Jointly modelling the cure rate of PFS and OS with a log-logistic MCM resulted in similar cure rates than the standard log-logistic MCM PFS cure rates (Table 1).
- Using the posterior PFS cure rates as prior for the log-logistic MCM on the OS data produced results similar to when the cure rate of PFS and OS was jointly modelled (Table 1).
- Both methods leveraging PFS cure data demonstrated significant incremental mean survival for the active treatment compared to placebo, whereas the standard approach showed insignificant results.

Underlying Data

Figure 1. Reconstructed[4] Kaplan-Meier Data PFS and OS

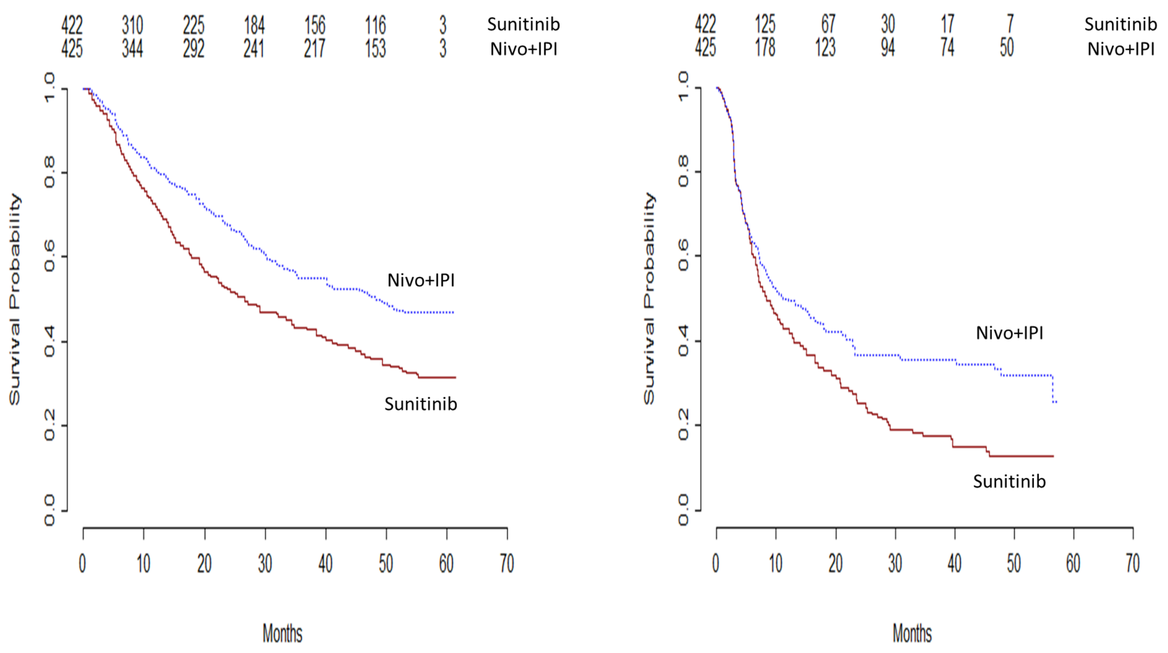
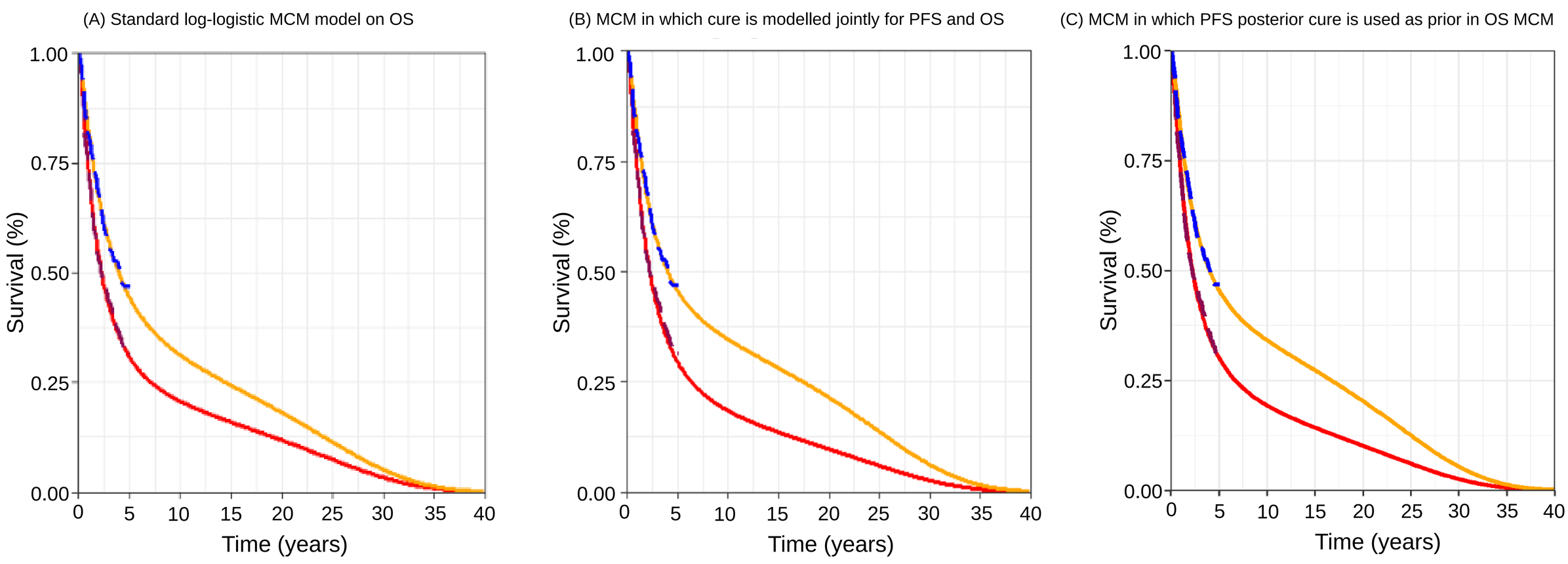


Table 1. Overview of cure rates, mean and incremental mean predicted life expectancy (standard approach and approaches leveraging PFS data)

	Sunitinib [CrI]	Nivolumab + ipilimumab [CrI]
Cure rates		
PFS	0.14 [0.08; 0.20]	0.33 [0.26; 0.39]
1) OS	0.16 [0.00; 0.27]	0.23 [0.00; 0.40]
2) Jointly modelling PFS and OS	0.12 [0.06; 0.19]	0.33 [0.27; 0.38]
3) PFS cure rate as prior for OS cure rate	0.14 [0.09; 0.20]	0.32 [0.21; 0.42]
Mean survival		
1) OS	6.36 [4.51; 7.94]	8.86 [6.38; 10.79]
2) Jointly modelling PFS and OS	5.84 [4.82; 6.82]	9.61 [8.69; 10.53]
3) PFS cure rate as prior for OS cure rate	5.96 [5.13; 6.87]	9.36 [8.00; 10.68]
Incremental mean survival		
1) OS	-	2.46 [-0.50; 5.17]
2) Jointly modelling PFS and OS	-	3.78 [2.43; 5.12]
3) PFS cure rate as prior for OS cure rate	-	3.38 [2.02; 4.75]

Abbreviations: CrI, credible interval; OS, overall survival; PFS, progression-free survival

Figure 2. Standard log-logistic MCM over OS (A) and jointly modelling PFS and OS (B) PFS posterior cure rate as prior for OS cure rate (C)



References

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