The Impact of the Proportion of Cured and Length of Follow-up on Mixture Cure Models (MCMs): A Simulation Study

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INTRODUCTION

- In recent years, despite the increase of cancer cases, patients' prognosis has evolved, especially due to innovative treatments, such as immunotherapies, demonstrating efficiency in overall survival in cancers including melanoma and lung cancer. [1] [2]
  - In survival analysis, this improvement in survival results in a plateau at the tail of the Kaplan-Meier (KM) curve, which highlights that some patients can now be considered statistically cured.
  - This plateau can not be well-captured by standard parametric models.
- Mixture Cure Models (MCMs), developed in the 1950s, allow for patients not experiencing progression or death due to cancer to be included. [3]
- However, the context of application in which these models perform best is not clearly defined yet.

OBJECTIVE

This study aimed at understanding how the proportion of cured patients and data maturity impact MCMs performance, through a simulation study.

METHODS

Simulation study

- 1,000 simulations composed of 400 individuals including either 100 cured and 300 uncured patients or 200 cured and 200 uncured patients were generated the following way:
- Uncured patients were simulated with R survsim package [4] using censoring (Exponential) and time-to-event (Weibull) distributions from literature having a median survival time around 11 months, [5]
- Cured patients were generated using Guyot's algorithm using US lifetables [6] and merged with uncured patients,
- Four scenarios were generated, varying cured proportion (25% or 50%) and length of follow-up (13 or 33 months).

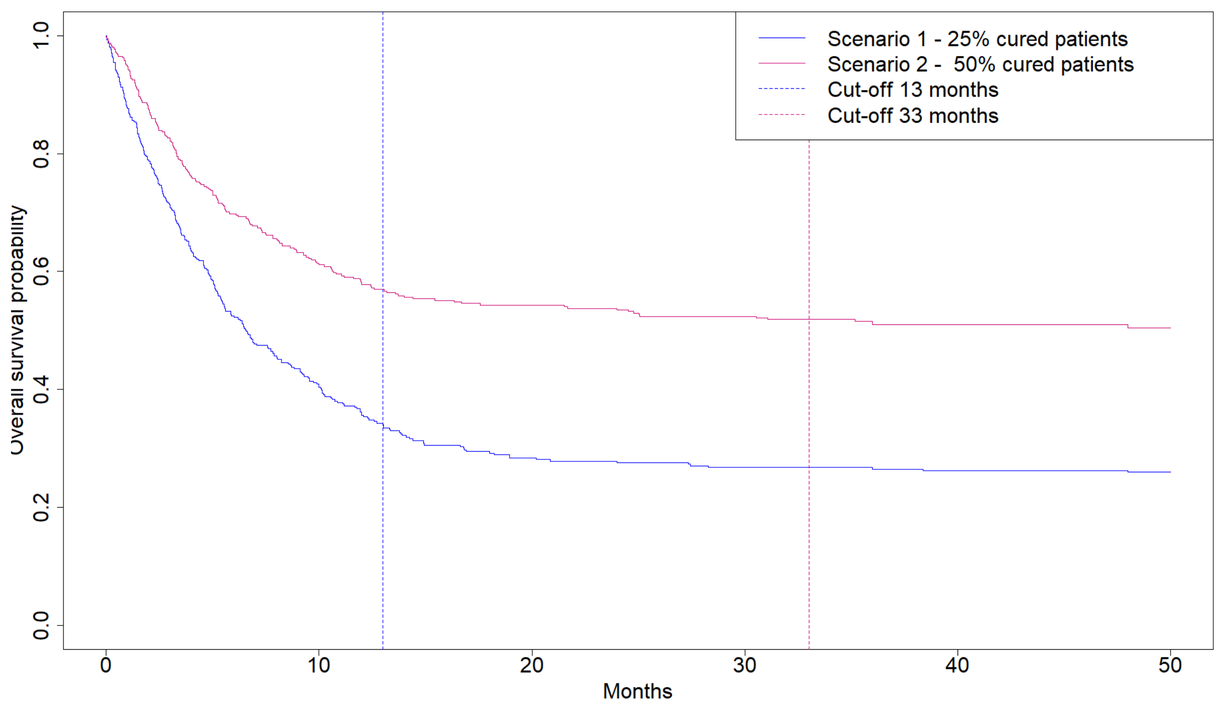
MCMs

- MCMs were applied to the 1,000 simulations of each scenario with limited follow-up. In adjusted MCMs, survival is computed the following way:

$$S(t) = \pi + (1-\pi) \times S\_u(t),$$

- Where π corresponds to the probability for an individual to be cured and S_u is the survival function of the uncured patients.

Figure 1: KM curves of the different scenarios, randomly-selected simulation



Model performance

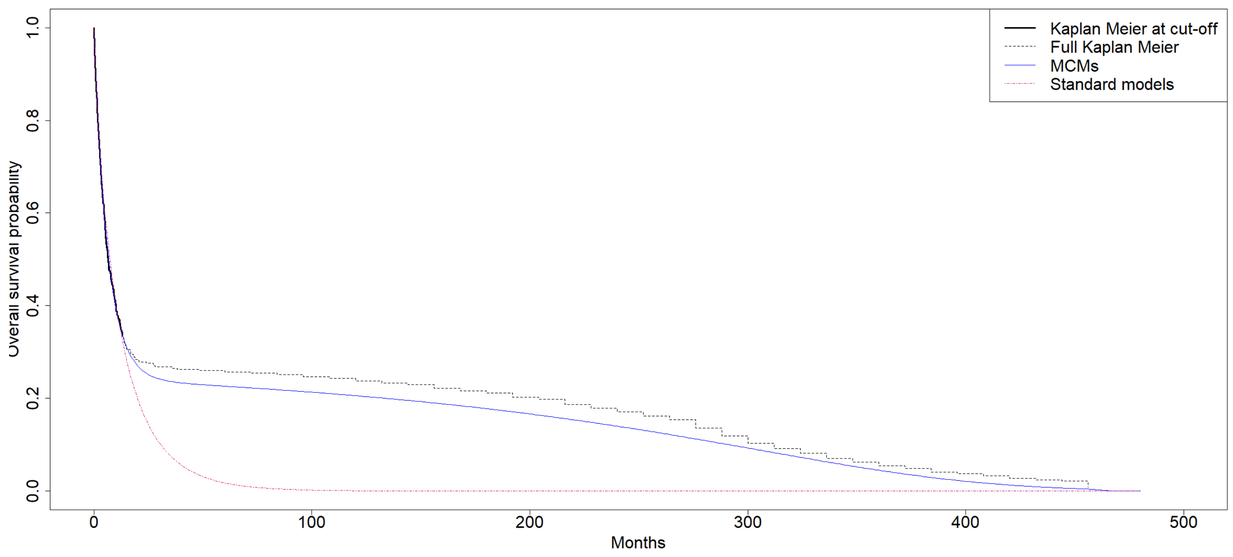
- Mean outcomes over the 1,000 simulations were computed for each scenario, including probability for a distribution to be the best based on AIC, the quadratic error, estimated cure rate, and mean survival.
- The probability for a distribution to generate abnormal values (misestimating the proportion of cured by at least 20% was also computed). The results are presented for one of the simulations in Figure 1.

RESULTS

Scenario with 25% cure fraction and 13 months follow-up

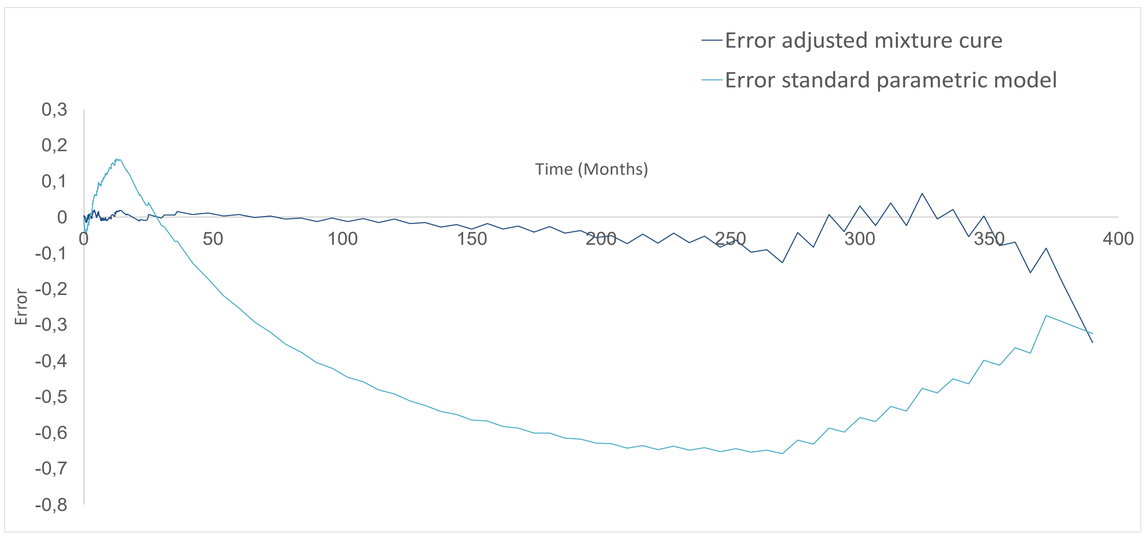
Figure 2 highlights that adjusted MCMs perform well in this case, compared to standard parametric models. The full KM curve is also presented in this figure, to understand how reliable the estimates are for each model type.

Figure 2: Extrapolations of KM data (Weibull distribution, 25% cure and 13 months follow-up)



In this scenario, cure rate was estimated on average between 22% and 26% for plausible MCMs, and mean survival at around 80 months versus 77 months in the simulated data.

Figure 3: Quadratic error (Weibull distribution, 25% cure and 13 months follow-up)



General conclusions on the fit of MCMs

- The following conclusions were highlighted in the analysis:
- Standard parametric models always underestimated the KM curve and are subject to important bias after cut-off.
- Adjusted MCMs provided the most reliable results, with limited bias and good average performance.
  - Adjusted MCMs were also associated with lower error in predictions than standard parametric models (Figure 3), which highlights that their estimates are more reliable when having a strong assumption of cured patients.

CONCLUSIONS

On average, the performance of plausible MCMs was not influenced by the proportion of cured patients nor the length of follow-up, as these models provided reliable estimates in both cases. However, the proportion of models associated with "implausible" estimates in terms of proportion of cured and mean survival was higher for data with a shorter follow-up. Overall, even if the plateau was not visible, MCMs were able to capture the shape of the KM after cut-off.
The use of these models must be justified by a strong clinical rationale.

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