

Comparison of TGD-OS Models with a Long-Term Surviving Fraction

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Objectives

In certain oncology disease and treatment settings, some patients achieve long-term survival. In these cases, the survival function for the time to event can appear to have a non-zero asymptote. Two approaches using tumor growth and overall survival (TGD-OS) modeling that accommodate such a “cure fraction” are the mixture cure rate (CR) model [1] and the promotion time CR rate model [2]. The analysis objectives were to compare and contrast the assumptions, model fit, and long-term survival predictions of these two approaches.

Summary

The mixture CR model directly expresses the cure fraction as a function of baseline covariates but not time-varying predictors. In contrast, the promotion time CR model estimates fewer parameters and allows for baseline and time-varying predictors to influence the cure fraction, but the cure fraction has to be derived using numerical methods. Objective function values and visual predictive check (VPC) plots indicate both models fit the observed data equally well (Figure 2). However, the models yield different extrapolations to 5-year survival (Figure 3, Table 1). For example, for patients with programmed cell death ligand 1 (PDL-1) expression > 50%, the promotion CR model estimates a 5-year survival of 0.02 (.01, .05) and .29 (.19,.38) for chemotherapy and pembrolizumab, respectively, while the mixture CR model estimates are 0.09 (.04,.20) and .26 (.18,.34) respectively. The difference in treatments Δ (pembrolizumab-chemotherapy) for the mixture CR model is .17 (.03, .27), while for the promotion CR model it is .27 (.18, .36).

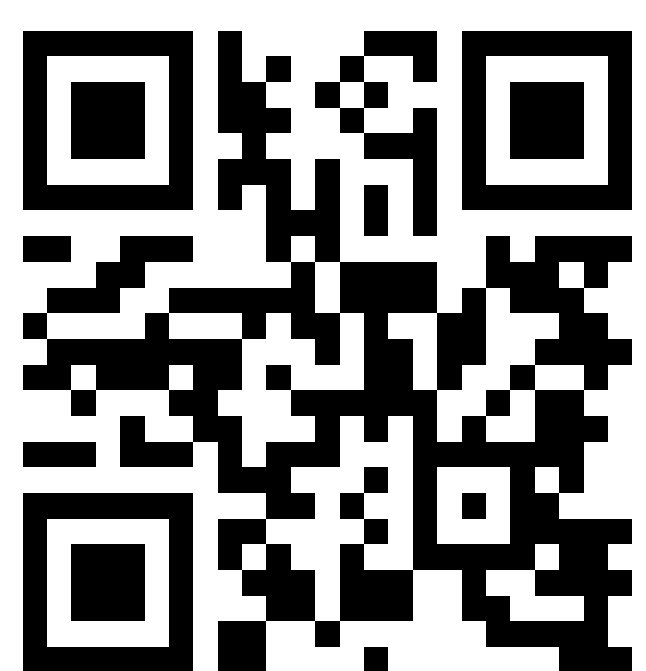
Comparisons of Promotion Time and Mixture CR Models

- Notable differences in the 5-year treatment Δ
- Promotion time CR model allows time-varying predictors to affect CR probability while mixture model does not (it can only incorporate baseline predictors)
- Mixture CR model makes a clear distinction between effects on cure fraction and hazard among subjects at risk for death but contains additional parameters

Conclusion

Mixture and promotion time CR models produce similar results over the observed time span yet yield different predictions of long-term survival. The promotion time CR model allows more flexibility in the key drivers of long-term OS.

QR Code



Results

Figure 1: Joint tumor growth - overall survival model.

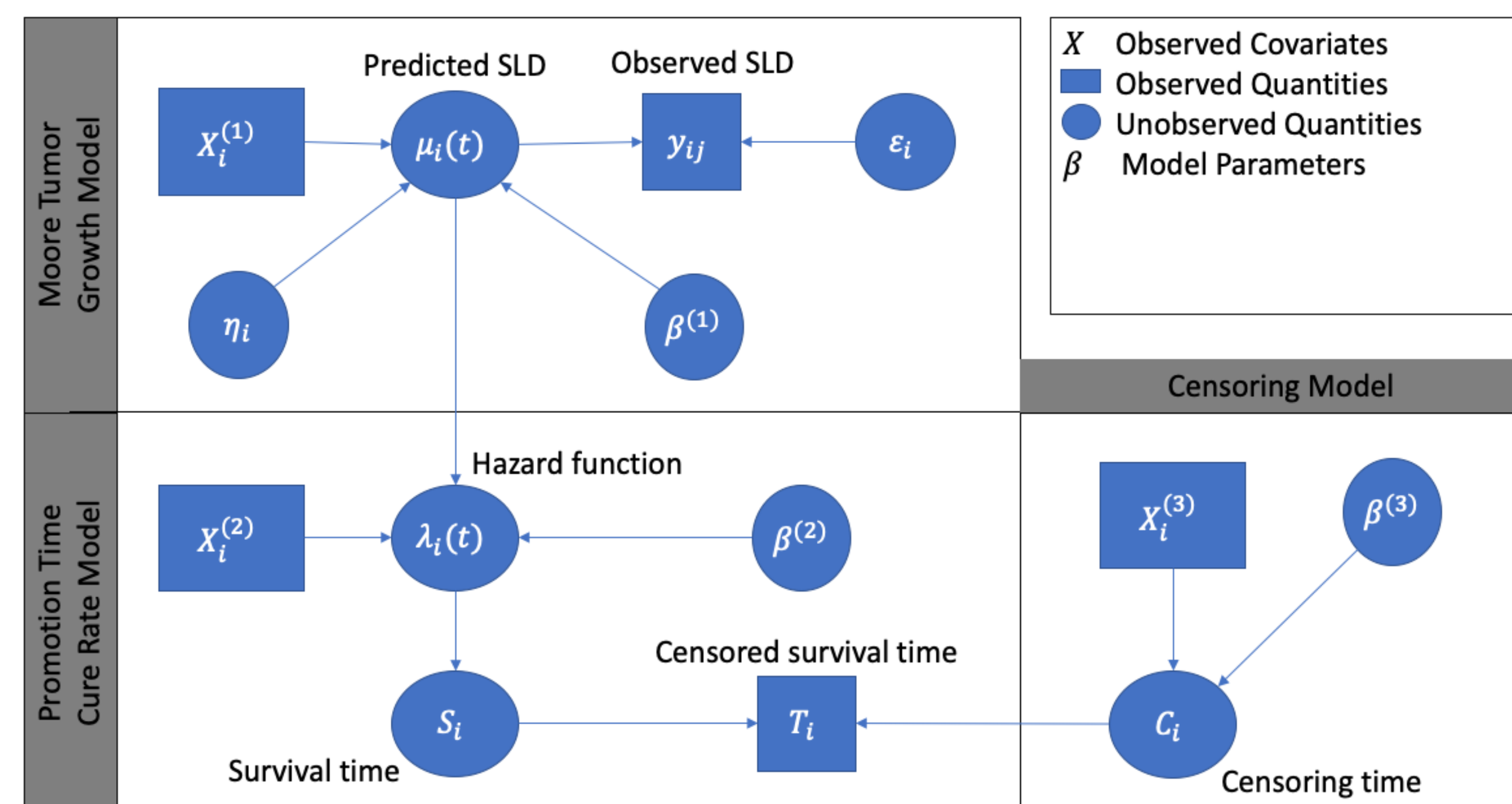


Figure 2: VPCs of patients with PDL-1 expression > 50%.

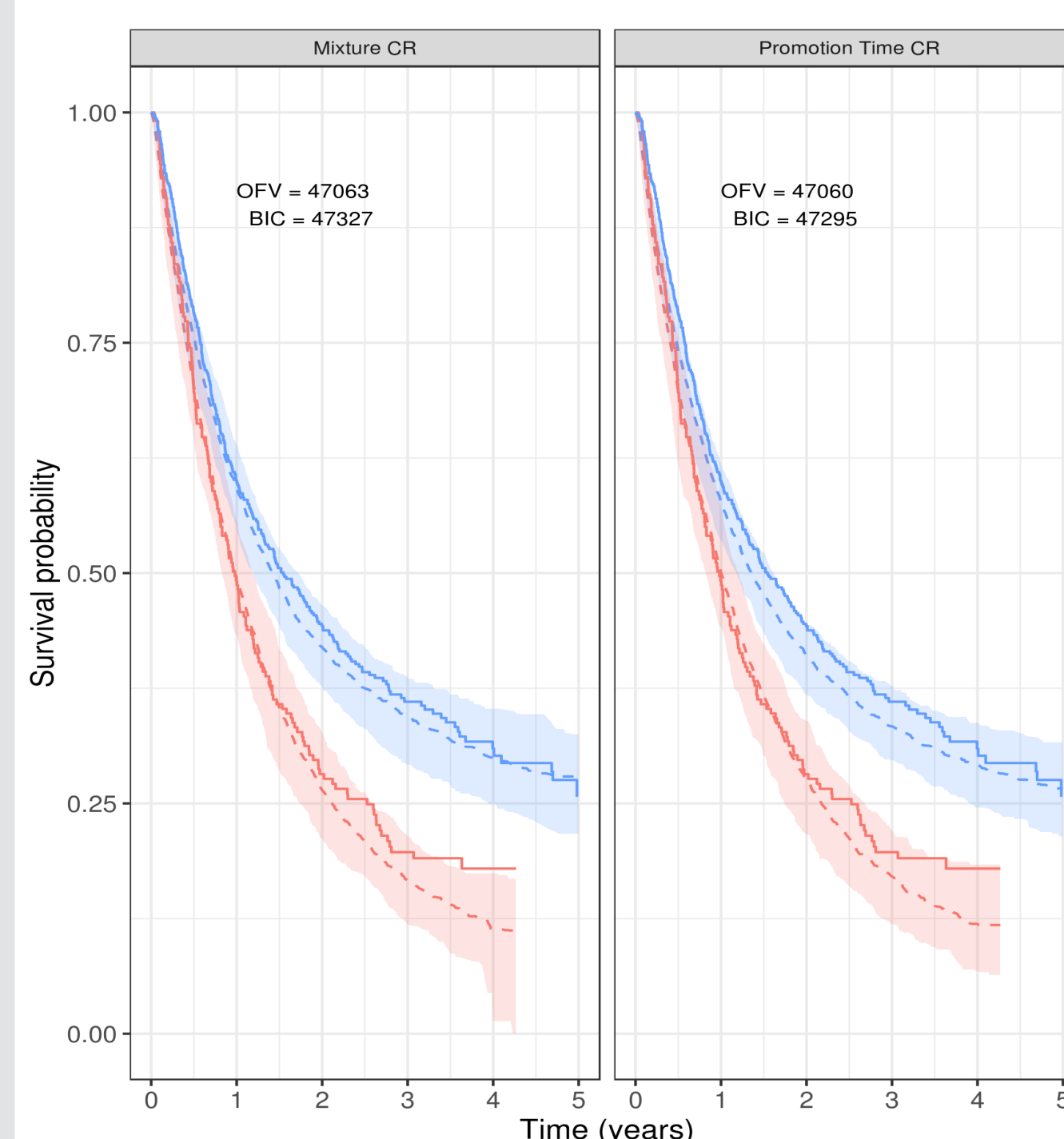


Figure 3: 5-year OS of patients with PDL-1 expression > 50%.

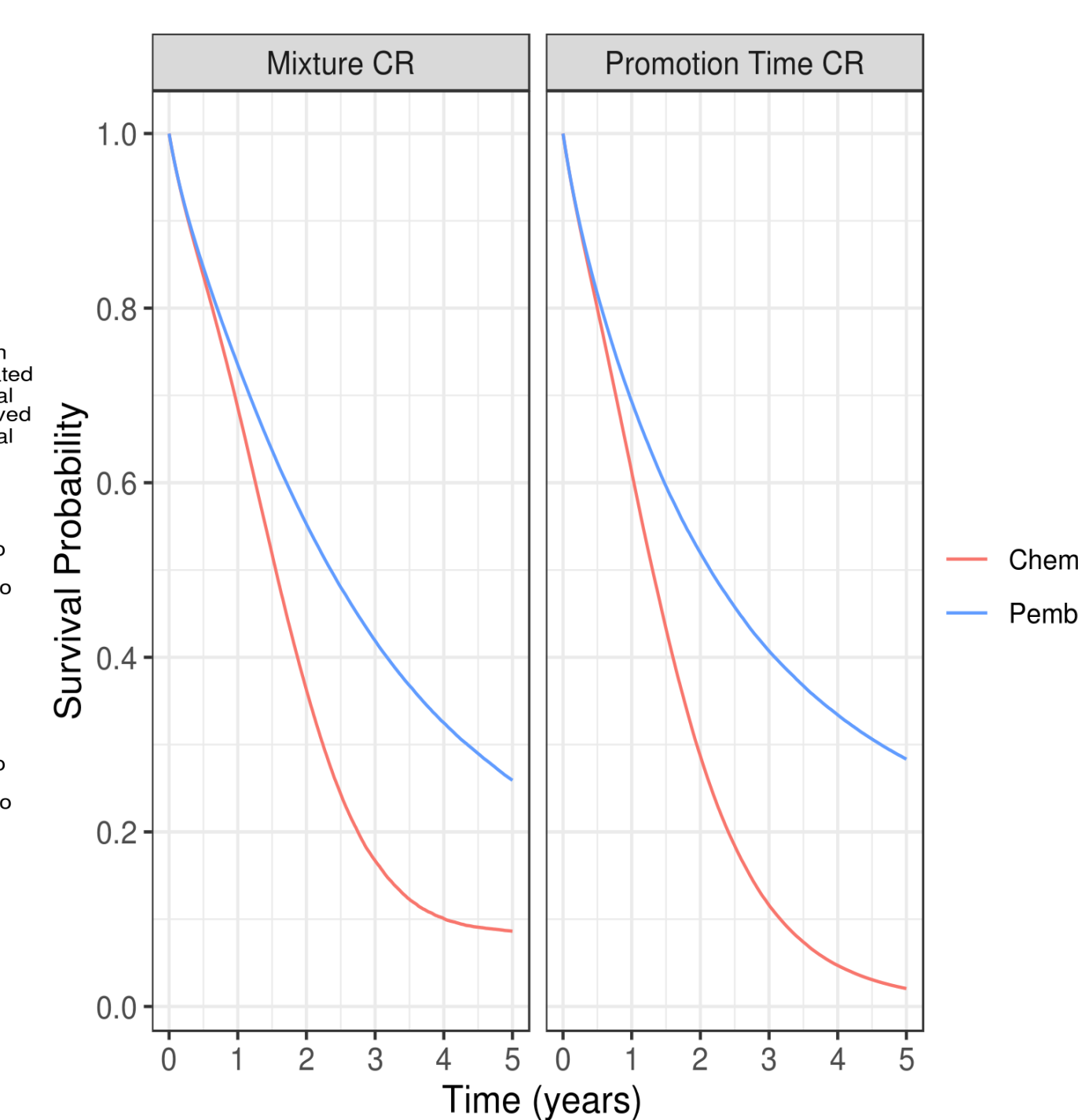


Table 1: Predictions and 95% confidence intervals of 5-year overall survival by CR model, treatment, and PDL-1 expression.

Treatment	PDL1 Status	Mixture CR Model	Promotion Time CR Model
Chemo	PDL-1 Weak	0.085 (0.045,0.21)	0.026 (0.0071,0.084)
Pembro	PDL-1 Weak	0.086 (0.038,0.19)	0.017 (0.0043,0.047)
Chemo	PDL-1 Strong	0.087 (0.043,0.2)	0.02 (0.0056,0.054)
Pembro	PDL-1 Strong	0.26 (0.18,0.34)	0.29 (0.19,0.38)
Pembro -Chemo	PDL-1 Weak	-0.0052 (-0.1,0.11)	0.00042 (-0.039,0.023)
Pembro -Chemo	PDL-1 Strong	0.17 (0.029,0.27)	0.27 (0.18,0.36)

Strong = PDL1 expression > 50%; weak = PDL1 expression < 50%

References

- [1] Law NJ, Taylor JM, Sandler H. The joint modeling of a longitudinal disease progression marker and the failure time process in the presence of cure. *Biostatistics*. 2002;3(4):547–563. doi:10.1093/biostatistics/3.4.547
- [2] Chen M-H, Ibrahim JG, Sinha D. A new Bayesian model for survival data with a surviving fraction. *J Am Stat Assoc*. 1999 Sep;94(447):746.

Methods

A joint model for tumor size and survival (Figure 1) using a promotion time CR framework was developed for patients with non small cell lung cancer treated with chemotherapy or pembrolizumab from three clinical studies. In this model the hazard function is given by:

$$h_i(t) = \lambda \alpha_i R T S_i(t)^\beta \exp(-\lambda t) \quad (1)$$

where $R T S(t)$ is the predicted tumor size relative to the baseline value, and α_i is a scale parameter which includes effects of subject-specific covariates. A key feature of this model is that when $R T S(t)$ is bounded or $R T S(t)$ is substituted by a tumor metric $g(t)$ which is $O(\exp(-t))$ then the limit of the cumulative hazard function is finite, which is a property required of a CR model (Figure 4).

The promotion time cure model was compared to a mixture CR model:

$$S_i(t) = p_i + (1 - p_i) S_{1i}(t) \quad (2)$$

where p_i is the probability of achieving long-term survival, and $S_{1i}(t)$ is an exponential survival function. The hazard of the mixture model, p_i , and α_i were modeled by baseline sum of longest diameters SLD, Eastern Cooperative Oncology Group (ECOG) status, and tumor histology.

For both CR models, the same structural tumor size model (Moore 2016) was used where the predicted tumor size $y_i(t)$ is equal to:

$$y_i(t) = y_0 5 T_{max,i} (1 - \exp^{-K_{grow,i} t}) + y_0 \exp^{-K_{dying,i} (t_i - \tilde{t}_i)} \quad (3)$$

The tumor parameters ($K_{dying,i}, K_{grow,i}, T_{max,i}$) were modeled by age, line of therapy, brain metastases, epidermal growth factor receptor gene mutation, tumor histology, and ECOG status. The parameter $T_{max,i}$ was parametrized such that $T_{max,i} \in (0, 1)$, which bounds $R T S_i(t)$, allowing for the CR condition to hold (Figure 4):

$$\Lambda_i(t) = \int_0^t h_i(u) du < \infty \iff \lim_{t \rightarrow \infty} S(t) > 0. \quad (4)$$

Figure 4: Cumulative hazard and survival functions of the promotion time CR model of a patient.

