Accuracy in estimation of true hazard in simultaneous and sequential estimation approaches of tumor size and overall survival (OS) modeling

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Background

- Frequently suggested tumor metrics of predicting overall survival (OS) in different tumor types are tumor-size time course (TSt), tumor size ratio at e.g. 6 weeks (TSRw6), time-to-tumor growth (TTG), and the tumor growth rate constant (KG) [1,2].
- In addition to the accuracy of these tumor metrics, the estimation approach used for connecting tumor metrics to OS might also influence the estimated hazard (HZ) of death, in a similar way as when models of PK are connected to PD models [3].
- To evaluate if the treatment is suitable for a patient, it would be of interest to predict the risk (hazard) of death based on early response.

Objectives

- This study aims to investigate how sequential and simultaneous estimation approaches, as well as the number of tumor size measurements based on available models and their parameters, influence the accuracy of estimated HZ of death for an individual patient.

Conclusions

- The analysis method has little influence on accuracy of estimated HZ; in the scenarios investigated here, the PPP&D approach appears preferable since it had shorter runtimes compared to SIM and slightly better results than IPP.
- Among the investigated tumor metrics as a predictor of survival the accuracy of re-estimated hazard was TSW6 > TSt > TTG/KG.
- With fewer tumor measurements, TSRw6 found to be best candidate of those investigated as predictor of OS with good metric[4,7] and HZ accuracy while longer follow up (at least until tumor dropout) are needed to obtain better accuracy[7] of KG, TTG & TSt metrics and estimated HZ.
- TSt or derivate of the TSt may be best when the intervention is changing during the treatment period.

Results

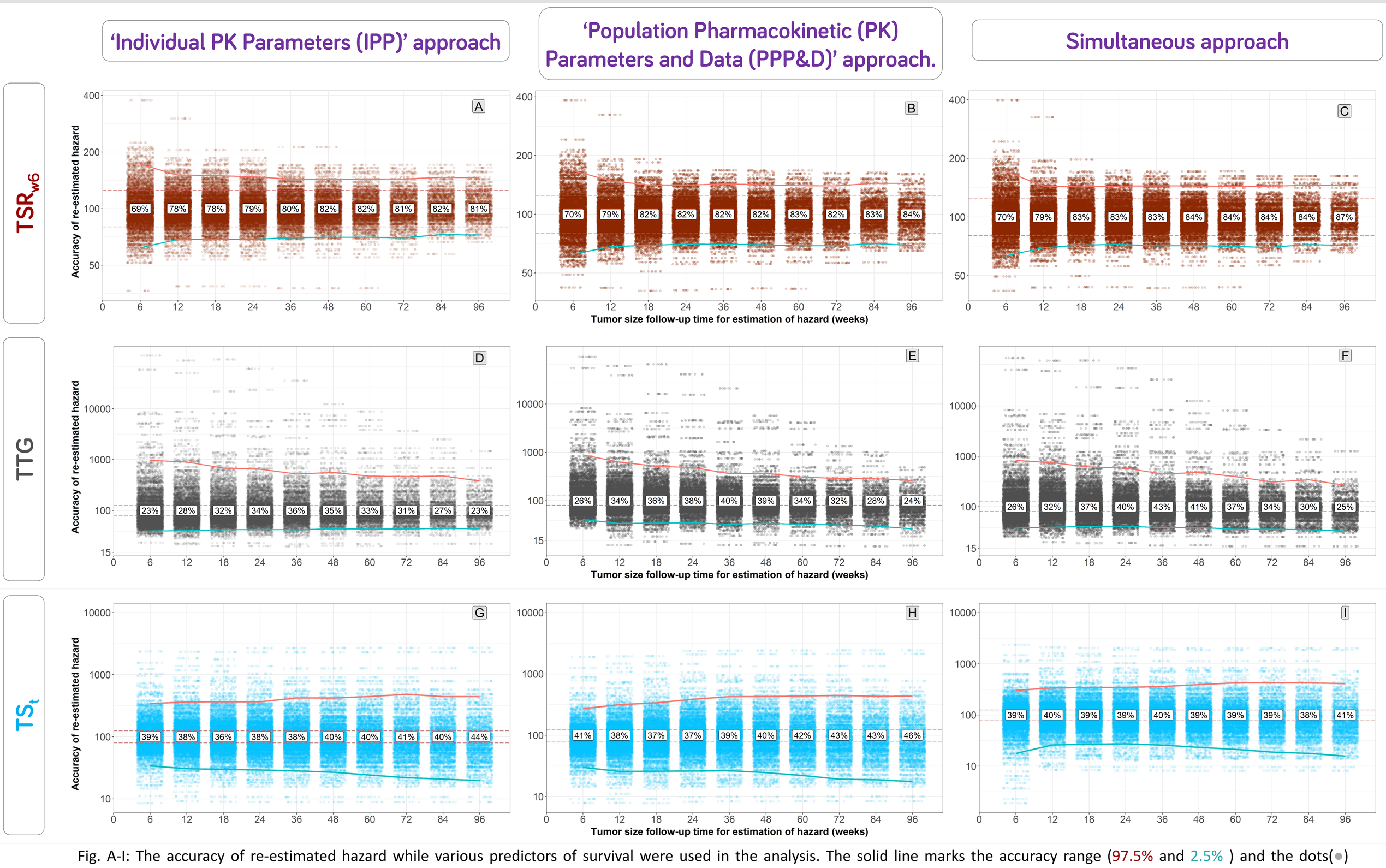

Fig. A-I: The accuracy of re-estimated hazard while various predictors of survival were used in the analysis. The solid line marks the accuracy range (97.5% and 2.5%) and the dots(●) represents the individual accuracy of re-estimated hazard. The different amount of percentages in the boxes indicate the percentage of the population with accuracy of 80-125% of time.

Methods

Tumor size and OS data

- Longitudinal tumor size data were simulated using a simplified tumor growth inhibition model (TGI) and previously published tumor growth/response parameters for bevacizumab plus chemotherapy in colorectal cancer [5]. Dropout from tumor measurements was considered and forced at 20% increase from the tumor nadir.
- The survival data was also simulated using Weibull function and the published parameter values[5]. The different tumor metrics, calculated using different tumor size follow up data were used for prediction of the survival.

Estimation approaches

- **Sequential**: (a)The Empirical Bayes estimates were derived from the simulated individual tumor size data. and the prospective evaluation function in PsN[6]. The individuals' tumor model parameters were applied in the derivation of tumor metrics and the estimation of HZ, similar to 'Individual PK Parameters (**IPP**)' approach.
  - (b)Alternatively, the tumor data and the population tumor parameters were used in the derivation of the tumor metrics and the estimation of the HZ, similar to 'Population Pharmacokinetic (PK) Parameters and Data (**PPP&D**)' approach.
- **Simultaneous (SIM)**: Tumor parameters and OS parameters were estimated simultaneously using a joint model.

Evaluation of estimation approaches

- In all scenarios, the influence of the number of tumor size observations in estimation of HZ was investigated.
- The accuracy of the estimated HZ was calculated as percentage deviation from the 'true' HZ.
- The acceptable accuracy was set to 80-125% of the 'true' HZ.
- Simulations and model evaluations were performed using NONMEM version 7.3.

References

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