Influence of the number of tumor size measurements on model-derived tumor size metrics and prediction of survival

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Background

- The tumor size ratio (TSR), time-to-tumor growth (TTG) and tumor growth rate (KG) are frequently suggested predictors of overall survival (OS) for different types of tumors[1,2].
- It should be acknowledged that all available measurements are typically used to estimate these metrics for an individual patient.
- However, it is unclear how many measurements are needed to adequately forecast the metrics and OS hazard.

Objectives

- This study aims to investigate how the number of available tumor size measurements may influence the accuracy of predicting the true tumor size metrics for an individual patient, which in turn could influence the metrics' value in predicting the hazard of death.

Conclusions

- This simulation study demonstrates that TSRw6 is a more promising metric than TTG or KG for early prediction of treatment outcome for an individual patient due to higher accuracies.
- Fewer measurements are needed for adequate estimation of TSRw6 compared to TTG or KG and hence for predicting OS, in line with its lower shrinkage [6].
- In addition to baseline and a week6 measurement, a week12 measurement appears beneficial for estimating an individual's TSRw6.
- TTG and KG metrics accuracy were questionable even after using 96 week follow up information.
- Similar results were identified in tumor metrics' predictability of survival. The TSRw6 metric was identified as a predictor of OS with higher accuracy compared to TTG and KG metrics.
- The study results infer that to predict KG or TTG metric accurately, the clinical study design may need to include few tumor measurements after disease progression and/or before treatment initiation.

Methods

Tumor size 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 [3].
- The tumor sizes at zero (baseline), and at 6, 12, 18, 24, 36, 48, 60, 72, 84, and 96 weeks were simulated for 1000 subjects, (1)assuming none of the subjects were dropped out during first two years of study and (2) where observations following an observation of 20% increase from tumor nadir were censored as disease progression[4].

Overall survival (OS) data

- The survival data was also simulated using the published parameter values[3].
- The different tumor metrics, calculated using different tumor size follow up data were used for prediction of the survival.

Evaluation of accuracy

- The 'true' TSR at week 6 (TSRw6), TTG and KG were derived from the simulated individual profiles (no residual error).
- The prospective evaluation function in PsN[5] was applied to investigate the accuracy of the predicted metrics and the OS estimation, based on the original model without re-estimation of parameters (Bayesian forecasting), were affected by a successive increase in the number of simulated tumor size observations (with residuals).
- The accuracy of the predicted tumor metric was calculated from the 'true' metric.
- Similarly, the accuracy in predicting 'true' hazard of death was calculated with or without re-estimating OS.
- During dropout model accuracy calculations and in plots, the tumor metric's accuracy using last available observation data was carried forwarded until end of study.

Simulations and model evaluations were performed using NONMEM version 7.3.

Results

Accuracy of Tumor metrics

Accuracy of TSRw6 prediction [Figures: A and B]:

- When only baseline and w6 measurements were used in the predictions of TSRw6, 70% of individuals had <10% deviation from 'true' TSRw6 with a shrinkage of 32%.
- By adding a w12 measurement, 78% (Fig. A) or 77% (Fig. B) of population had accurate TSRw6 prediction with low shrinkage (<16%).
- There was limited improvement in individuals´ predictions by adding observations after w18.

Accuracy of TTG prediction [Figures: C and D]:

- The accuracy of TTG predictions was in general low and associated with very high shrinkage (>80%).
- As expected, the accuracy improved as the number of measurements increased; from 32% to 69% of population having adequately predicted TTG (Fig. C).
- In the scenario with dropout (Fig. D), even after using up to 96weeks data, only 55% of the population had TTG imprecision within ±30%.

Accuracy of KG prediction [Figures: E and F]:

- The percentage of individuals with <10% deviation from 'true' KG improved from 41% (2 observations) to 77% when all 11 observations were used and there was no dropout.
- However, in the dropout scenario (Fig. F), the accuracy of KG was little affected by additional tumor measurement data and the accurately predicted proportion remained around 50%.

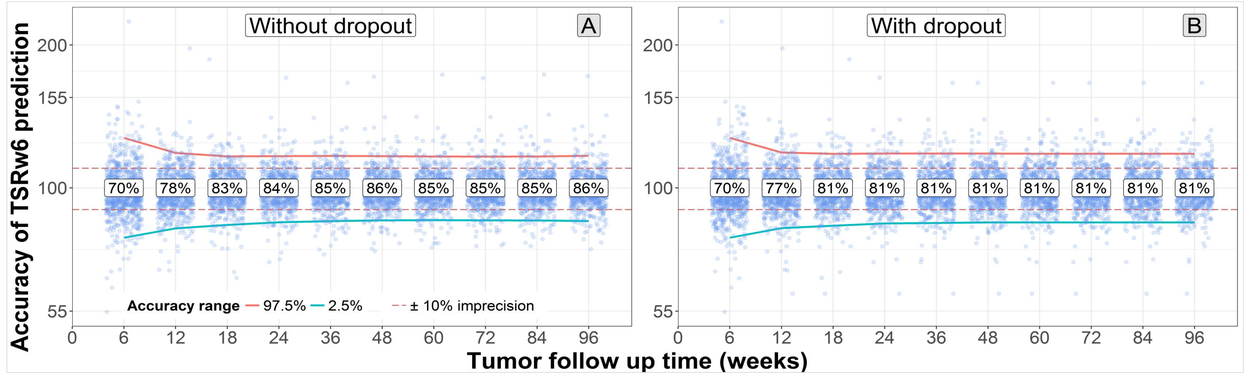
Accuracy of OS prediction

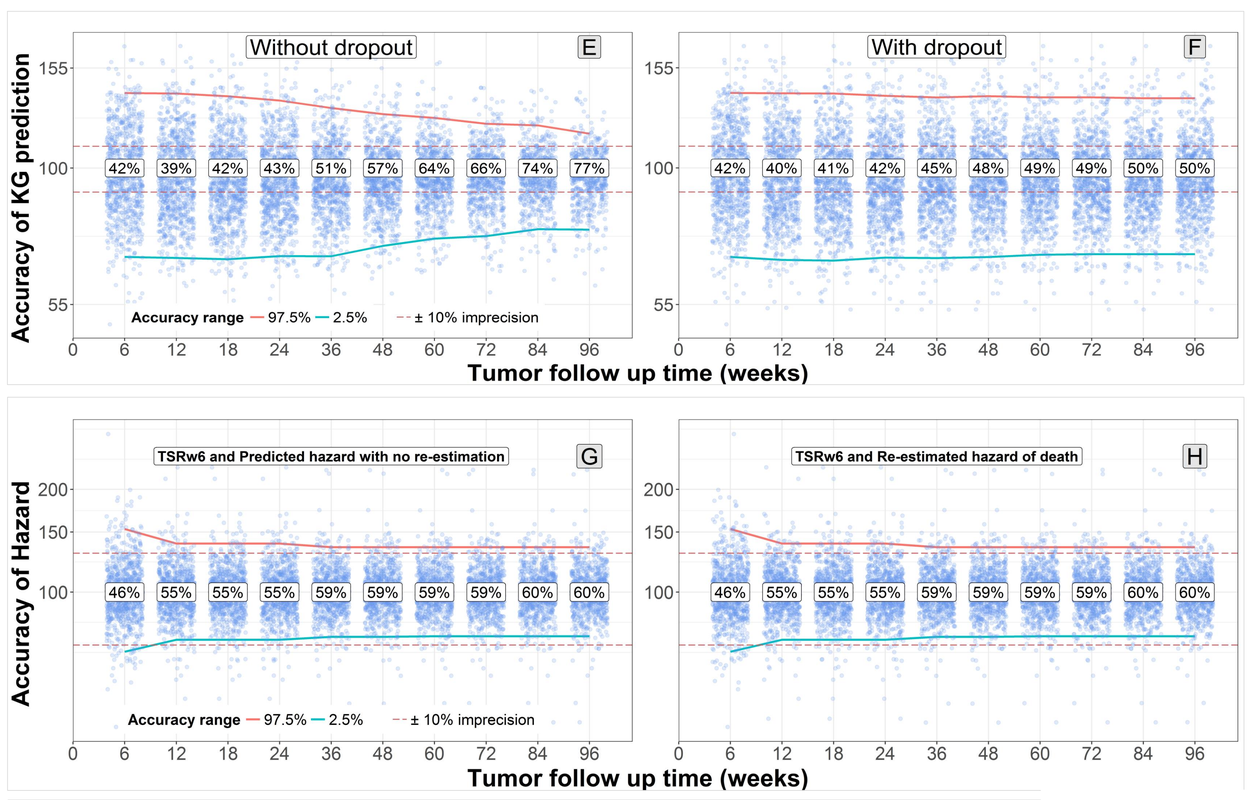
TSRw6 as a predictor of OS [Figures: G and H]:

- Based on the current study, to accurately predict the 'true' hazard of the population, the tumor size need to be followed for at least 36weeks.
- The individual accuracy of predicted hazard without re-estimation (Fig. G) and estimated hazard (Fig. H) of death using TSRw6 metrics as predictor were reasonably good.

TTG and KG as predictors of OS:

- Even after using 96weeks follow up data, the 'true' hazard of the population was not accurately estimated.
- About 50% of individuals had adequate accuracy in predicted hazard when KG or TTG were predictors of OS.
- When KG or TTG metrics was used to re-estimate of hazard of death, only 30% of individuals' hazard was estimated within ±10%.





References

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