



Operating Characteristics of Tumor Kinetic Response Assessments in Early Phase Oncology Trials

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Summary: While the RECIST criteria have been a valuable tool in standardizing anticancer treatment response assessment, they do not take into account the tumor growth rate prior to treatment intervention, which can be highly heterogeneous, particularly in phase 1 all-comers trials. We describe methodology whereby additional pre-study scans can be used to estimate each patient's pre-treatment growth rate and therefore treatment benefit, defined to be the observed deflection from that initial rate. We show that this methodology outperforms RECIST percent change from baseline in terms of accuracy of estimation of antitumor effect, even when RECIST percent change from baseline is enhanced to account for 'placebo' tumor growth rates. We therefore anticipate that this kinetic based measure of antitumor effect will enable more precise dose, exposure, and biomarker vs. response relationships, leading to more informed decisions in early oncology development.

Objectives: To investigate and compare the operating characteristics of kinetic-based methods for quantifying antitumor effects of investigational anticancer agents, in particular the Change From Baseline (CFB) method and the Pre-treatment Tumor Kinetics (PTK) method which requires an additional pre-baseline tumor burden assessment [1-2].

Methods: Simulated data was generated from a ($N=10^5$) virtual patient population having log-normally distributed (exponential) tumor growth rates (TGRs), with median (mTGR) and %CV (cvTGR) of TGR tested over ranges encompassing clinically observed values [1,3,4]. Normalized growth rate inhibition $GRI = (\text{growth-kill})/\text{growth}$ were uniformly distributed from -1 to 1, resulting in simulated RECIST response frequencies similar to those observed in early phase oncology trials. Exponential tumor burden measurement error (8.5%) as fitted from a recent scan-to-scan variability study [5] was also simulated. For each virtual patient, the CFB estimate of GRI_{CFB} was calculated via log linear regression to assessments at -1 (baseline), 8 and 16 weeks after start of treatment. The PTK estimate GRI_{PTK} for each patient was calculated via piecewise log linear regression to assessments at -8 (pre-study), -1 (baseline), 8 and 16 weeks after start of treatment. Accuracy of each method for a given (mTGR, cvTGR) parameter set was defined as the fraction of GRI estimates falling within an arbitrary tolerance (± 0.1) of the true GRI values.

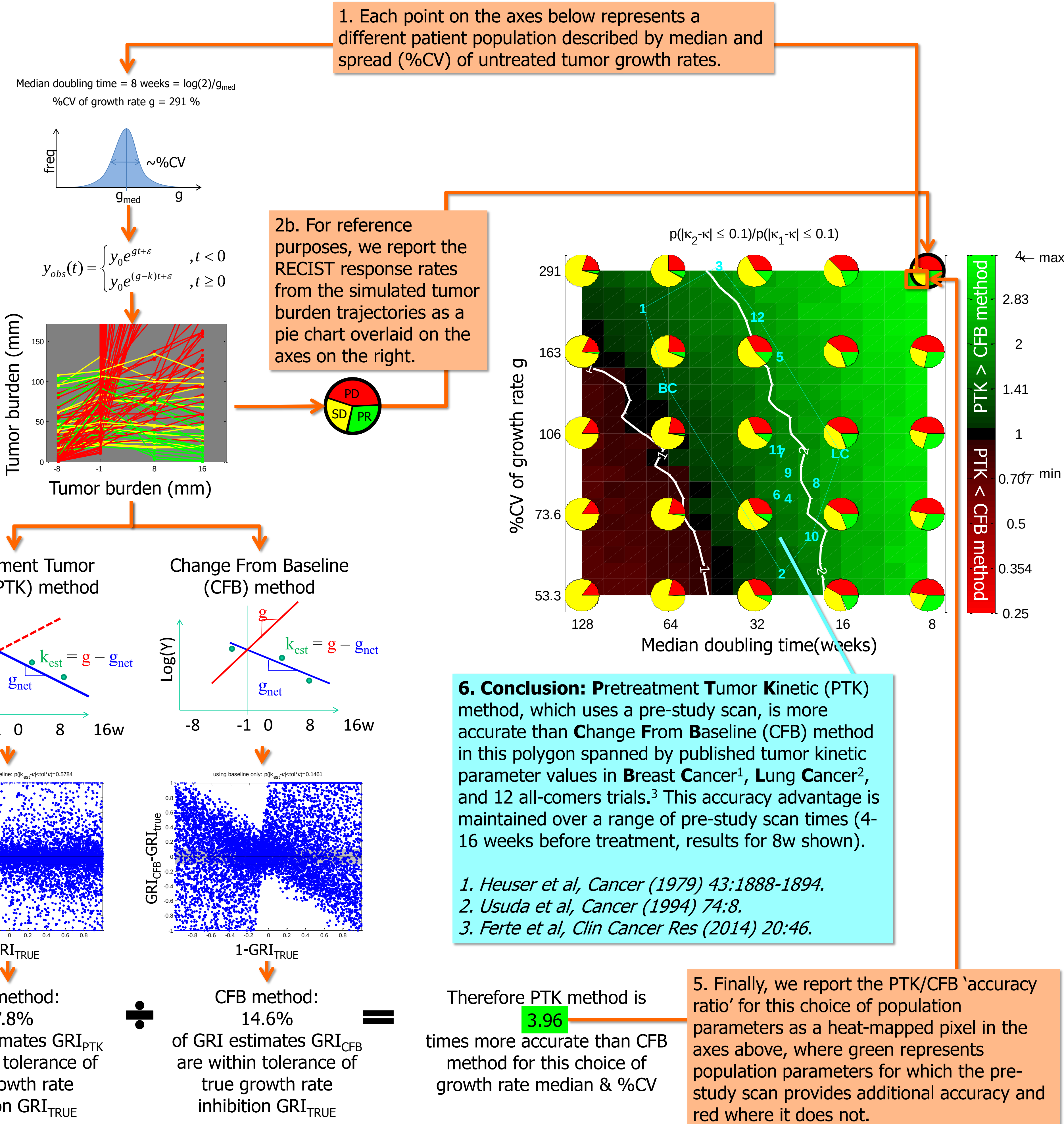
2. Next, we draw 10000 patients from each population distribution and simulate their tumor burden time courses, including ~8.5% random measurement error and assuming $g_{treated}/g$ uniformly distributed between -1 and 1 to generate RECIST response rates typical of targeted ph1 monotherapy trials.

3. For each patient, we estimate the study drug's antitumor Growth Rate Inhibition in two different ways:

- The **Pretreatment Tumor Kinetic method (PTK, left)** uses the patient's historical pre-study scan to estimate the 'placebo' growth rate g . This is the 'beyond RECIST' estimate.
- The **Change From Baseline method (CFB, right)** instead uses the median on-treatment growth rate of patients with progressive disease to estimate the 'placebo' growth rate g . This was intended to represent the best possible estimate obtainable without a pre-study scan.

In both methods, we estimate the net growth rate on treatment g_{net} and report the 'Growth Rate Inhibition' as $GRI = 1 - g_{net}/g$.

4. We then compare the PTK and CFB methods to address the key question: **what is the incremental benefit of obtaining a pre-study scan in addition to the baseline and on-treatment assessments we typically collect?** We do this by summarizing each method's accuracy as the percent of **growth rate inhibition (GRI)** estimates falling within a given tolerance of the true GRI originally used to simulate the tumor trajectories. For the particular case shown (8w doubling time, 291% CV), the PTK method, which uses the pre-study scan, is 57.8% accurate while the CFB method, which does not, is only 14.6% accurate.



Results: While the PTK method was not universally more accurate than the CFB method over all (mTGR, cvTGR) parameter values tested, it was consistently more accurate than CFB over the clinically observed ranges. Specifically, PTK advantage over CFB was most pronounced in populations with fast growing tumors and highly heterogeneous TGRs, while CFB was actually more accurate than PTK in populations with very slow growing tumors and relatively homogenous TGRs. Increasing the time span between the pre-study assessment and the start of treatment from 4 weeks to 16 weeks further increased the advantage of PTK over CFB.

Conclusions: While the PTK method outperforms the CFB method in all clinically feasible scenarios tested thus far, the absolute accuracy advantage of PTK over CFB varies from negligible to significant with increasing mTGR, cvTGR, and time between pre-study baseline scans. This anticipated accuracy advantage should be weighed against the minimal additional cost of reading the pre-study scan required for the PTK method.

References

- [1] Charles Ferte et al, "Tumor Growth Rate Is an Early Indicator of Antitumor Drug Activity in Phase I Clinical Trials," *Clin Cancer Res* January 1, 2014 20; 246.
- [2] Sylvie Retout et al, "A model-based approach to optimize detection of treatment effects in early oncology trials," *J Clin Oncol* 31, 2013 (suppl; abstr e13508).
- [3] Louis Heuser et al, "Growth Rates of Primary Breast Cancers," *Cancer* 43:1888- 1894, 1979.
- [4] Katsuo Usuda et al, "Tumor Doubling Time and Prognostic Assessment of Patients with Primary Lung Cancer," *CANCER* October 15, 1994, Volume 74, No. 8.
- [5] Geoffrey Oxnard et al, "Variability of Lung Tumor Measurements on Repeat Computed Tomography Scans Taken Within 15 Minutes," *J. Clinical Oncology*, Volume 29, No. 23, August 10 2011.