

LETTERS TO THE EDITOR

Time-Dependent Bias of Tumor Growth Rate and Time to Tumor Regrowth

HB Mistry

To the Editor:

In a recent study by Han *et al.*¹ the authors highlight that a tumor growth inhibition metric termed time-to-tumor-growth (TTG) derived from imaging time-series data is a strong predictor of survival. The authors demonstrate the strength of TTG's correlation to survival using Kaplan-Meier curves in **Figure 2** of their article. Indeed, the relationship seems incredibly strong, maybe too good to be true. Perhaps it could well be as we now explain. One of the key forms of bias when using covariates that are time-dependent, which TTG and, in fact, any model-derived metrics are, is time-dependent (immortal time) bias.² In basic terms, this form of bias relates to the failure to account for the time taken to estimate a time-dependent covariate when performing a survival analysis. The Kaplan-Meier's plotted in **Figure 2** of Han *et al.*¹ assume that TTG is known at the beginning of the study; which is clearly not true. TTG can only be calculated once a certain amount of time-series data has been collected. Therefore, the Kaplan-Meier curves in **Figure 2** are incredibly misleading and biased. The article by Suissa² suggests options as to how to handle time-dependent covariates. One simple option could be to adjust the survival time to account for the time needed to estimate TTG.

By accounting for the time taken to estimate TTG, the authors would have an unbiased view on the relationship between TTG and survival. We encourage the authors to show this figure such that readers can see what the unbiased relationship looks like; unlike the biased one published. It must be stressed that this form of bias has been rife in survival analysis³ with the co-authors of Han *et al.*¹ publishing similar results in another journal.⁴ We implore people using such metrics to consider approaches that account for correcting time-dependent bias or at least state why it does not apply to their analysis.

1. Han, K. *et al.* Simulations to predict clinical trial outcome of bevacizumab plus chemotherapy vs. chemotherapy alone in patients with first-line gastric cancer and elevated plasma VEGF-A. *CPT Pharmacometrics Syst. Pharmacol.* 5, 352–358 (2016).
2. Suissa, S. Immortal time bias in pharmaco-epidemiology. *Am. J. Epidemiol.* 167, 492–499 (2008).
3. van Walraven, C., Davis, D., Forster, A.J. & Wells, G.A. Time-dependent bias was common in survival analyses published in leading clinical journals. *J. Clin. Epidemiol.* 57, 672–682 (2004).
4. Claret, L. *et al.* Evaluation of tumor-size response metrics to predict overall survival in Western and Chinese patients with first-line metastatic colorectal cancer. *J. Clin. Oncol.* 31, 2110–2114 (2013).

© 2016 ASCPT.