The use of tumor dynamics and new lesions to predict survival with multivariate joint frailty models.

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Abstract: The RECIST criteria are used as standard guidelines for the clinical evaluation of cancer treatments. The assessment is based on the anatomical tumor burden: change in the sum of the longest diameters (SLD) of target lesions and evolution of non-target lesions (NTL): appearance of new lesions (NL) and unequivocal progression of NTL determined before treatment. Despite indisputable advantages of this standard tool, RECIST are subject to some limitations such as categorization of continuous tumor size or negligence of its longitudinal trajectory. In particular, it is of interest to capture the tendency of a short-term decrease and a long-term re-growth of tumor size that is often present under an advanced cancer treatment and model it simultaneously with time to event for NTL and OS. This complex analysis is achievable using multivariate joint frailty models for longitudinal and survival data. We propose a new joint model for a longitudinal biomarker (SLD) and two types of survival data. In the model, the tumor size trajectory is described using a mechanistic model that accounts for the natural growth and treatment induced decline with resistance to drug effect. We perform a simulation study to validate the proposed method and apply the model to a real dataset of a phase III clinical trial for metastatic colorectal cancer. In the results of the analysis, we determine on which component: tumor size (in all the phases), NTL or death, the treatment acts mostly and compare this model with models that consider parametric functions for the SLD trajectory in terms of predictive abilities. The application of the proposed model contributes to the current discussion on clinical endpoints and, eventually, may participate in an improvement of care of patients with cancer.

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