Innovative Methods for the identification of Predictive Biomarker Signatures in Oncology

Abstract: We present a procedure based on a set of newly developed statistical methods, for the identification and evaluation of complex multivariate predictors of treatment effect. The procedure is implemented on data collected from two clinical studies AVADO and AVEREL. Both are prospective, randomized clinical trials designed to evaluate the efficacy of bevacizumab on patients with HER2-negative (AVADO) and HER2-positive (AVEREL) metastatic breast cancer. The objective of the analysis is to identify a subgroup of patients who may receive the largest benefit from bevacizumab using a panel of 10 biomarkers measured at baseline. To this end, we first develop a classification rule, based on an estimated individual scoring system, using data from the AVADO study only. In this stage several methods for estimate the individualized treatment effect are discussed and the optimal classification rule is selected via the cross-validation. We then separate the patients in the AVEREL study into the patient group with promising treatment benefit and the patient group without, based on this rule. In the group with promising treatment benefit, the estimated hazard ratio of bevacizumab versus placebo for progression-free survival is 0.687 (95% CI, 0.462-1.024, p=0.065), while in the not-promising group the hazard ratio is 1.152 (95% CI, 0.526-2.524, p=0.723). Many reports have discussed the potential of VEGF-A as a predictor of treatment response for bevacizumab. If we simply use the median of VEGF-A to divide the patients of the AVEREL study, then the HR becomes 0.711 (95% CI 0.435-1.163, p=0.174) in the promising group and 0.828 (95% CI 0.496-1.380, p=0.468) in the not-promising group. In conclusion, our constructed scoring system successfully identifies a subgroup of patients who may benefit from bevacizumab and the positive treatment effect within the subgroup can be verified on an independent study. The constructed scoring system performs better than VEGF-A alone in the test data. The proposed procedure has the potential of broad applications in other settings aiming for the development of personalized medicine.