Improving the routinely used analysis method for survival time data in cancer clinical trials: illustration of issues and development of an alternative method

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Abstract

In cancer clinical trials where time-to-event outcome is the primary endpoint, almost routinely, the logrank test is prespecified as the primary test and the hazard ratio (HR) is used to quantify treatment effect. The methods for the logrank test and the estimation of the HR provide coherent results in terms of statistical significance, which is desirable property for treatment decision making from the reported results of the clinical trials. Statistical theory also supports that the logrank test offers the most power so long as the ratio of the two hazard functions is constant [i.e., proportional hazards (PH)], and it is a valid test even in non-PH. However, from clinical perspective, the lack of robustness and clinical interpretability of the estimation of the HR is not negligible as it is essential for investigators of clinical trials to provide a magnitude of the treatment effect that is helpful for treatment decision making. Also, the violation of the PH assumption has been seen in quite a few clinical trials in cancer, where the logrank test is not optimal anymore. Given these, the current routine practice using the logrank test for comparison and the HR for summarizing the magnitude of the treatment effect may be sub-optimal. The overarching goal of my research is improving routinely used test/estimation method. Specifically, in this thesis, we illustrate one of the issues of HR estimation when the PH assumption does not hold. We also develop and propose a novel test/estimation approach based on the difference in restricted mean survival time which has been extensively discussed in recent cancer clinical journals as an alternative summary measure to the HR. We conclude that the proposed approach is a useful analysis method for survival time data in cancer clinical trials from both of the statistical and clinical perspectives.