Assessment of proportional hazards assumption: restricted mean difference as a potential alternative to the hazard ratio for the analysis of time-to-event endpoint on aggregate data

Background: Log-rank test and proportional hazard (PH) Cox model are the most common techniques used for analysing survival time data. Despite the hazards need to be proportional, rarely PH assumption is assessed and it is not uncommon to observe survival curve convergences and crossings in medical research. When individual patient data are not available, no wide available method to test the validity of PH assumption exists.
Methods: In this work we conducted a systematic review of phase II/III clinical trials in patients with advanced non-small cell lung cancer (NSCLC) and illustrated how to estimate the logarithm of the hazard ratio and its variance from the published Kaplan-Meier (KM) curves. We also proposed the use of fixed-effect meta-regression as a tool to test the PH assumption. When PH assumption is not met the use of Restricted Mean Survival Time (RMST) difference might be a powerful alternative to the HR.
Results: A total of 115 trials were identified; only 4 (3%) out of 115 studies reported whether PH assumption was met or not. 58 (50%) out of 115 studies reported the number of patient at risk at least at three different time-points and were then included in the analysis. For 12 (19%) out of 62 treatment comparisons PH assumption was violated. The type of treatment comparison resulted to be significantly associated with the violation of the PH assumption. No discrepancy was observed between the RMST results and the conclusions drawn by authors based on Cox model results.
Conclusions: Meta-regression seems a promising method to assess the proportionality of the hazards, but it needs to be further investigated by comparing the conclusion obtained with individual patient data and the conclusion obtained from aggregate data. The use of RMST should be considered more in trial design especially when a comparison between conventional therapy and biologics or tyrosine-kinase inhibitors is to be made.

Keywords: Survival analysis, Proportional hazards assumption, Restricted Mean Survival Time, Meta-regression, Non-Small-Cell Lung Cancer