Meta-analysis of time to event outcomes : common practices in oncology

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Time-to-event outcomes are the most common endpoints in meta-analyses (MA) of randomized clinical trials (RCT) in oncology. We will first report the results of a systematic review of the methods used in 70 published MAs in lung cancer treatment (Brignone et al, J Thorax Oncol 2007;2 (Suppl 4): S384) and then review the methods used for individual patient data (IPD) MAs.

In the lung cancer review, only 13% of the MA were based on individual patient data (IPD). The median (range) of the number of RCTs and patients were : 10 RCTs (6-22) and 2082 patients (807-4357) for IPD MA; 8 RCTs (2-37) and 1524 patients (173-7644) for summary data (SD) MA. In SD MA, treatment effects were estimated by combining the hazard ratios from RCTs in 39%, combining odds ratios at fixed time points in 41% and other methods in 20%. Fixed effect models alone, random effect alone, both fixed and random, and other methods were used in 51%, 23%, 23% and 3% respectively of SD MA; and 89 %, 0%, 11% and 0% in IPD MA. Overall, indirect comparisons between RCT groups, subgroup analysis and meta-regression were used respectively in 8%, 2% and 10% in SD MA; and 33%, 67% and 0% in IPD MA.

In the majority of IPD MAs the logrank test stratified by trial and the Peto one-step estimator is used, and less often the Cox model stratified by trial. Random effects model are not often applied, neither is adjustment on covariates. In our experience of IPD MAs, treatment effects estimated by random effect model or taking baseline covariates into account did not provide substantially different results as compared to fixed effect models. Tests of interaction or for trends are applied to compare groups of trials or groups of patients defined according to covariate categories. Hazard ratios within categories are based on analysis stratified by trial. We will present several methods to construct survival curves (Kaplan Meier method and survival curves based on the stratified hazard ratio value allowing for differential treatment effects in different time periods). In some cases, mortality is divided into cancer and non-cancer deaths by the method proposed by the Early Breast Cancer Trialist Collaborative Group.

In conclusion, IPD MA in oncology used straightforward survival methods and fixed effect models. The possibility to explore heterogeneity in detail and the size of the MA may explain this choice.

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