

Competing risks with time-to-event outcomes in an individual patient data meta-analysis

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Introduction and objective

The presence of a competing risk (CR) E2 in a time-to-event analysis of event E1 may render the use of conventional Kaplan-Meier estimates of cumulative event rates invalid if the times to occurrence of E1 and E2 are correlated (informative censoring). For instance, in cancer patients one may wish to assess the risk of occurrence of late treatment toxicities. Deaths due to cancer (or any causes other than the toxicity of interest) appear as a CR; the subsequent occurrence of toxicities, had the patient survived, can no longer be observed. The risk of cancer death may plausibly be correlated with the risk of toxicity.

Methods are available for the calculation of valid cumulative incidence (CI) rates as a function of time in the presence of competing risks [1-3] for a single group of cases. CI methods are widely employed for CR in cancer patients such as graft-versus-host disease, recurrence and death [2], or local and distant recurrence [3]. We propose two alternative methods for the calculation of competing risks cumulative incidence (CRCI) curves for each of the two treatment arms in a meta-analysis for which the individual patient survival times and event data are available. We applied these methods to a meta-analysis of second malignancy (SM) rates following treatment for Hodgkin's lymphoma (HL); competing risks are deaths from causes other than SM.

Materials and methods

Our first approach is based upon Peto's method for computation of odds ratios and time-to-event curves pooled over several trials [4,5]. Firstly, Peto's method is used to compute pooled event-free survival (EFS) odds ratios and cumulative rates for each treatment arm at regular timepoints based on the occurrence of the first event of either type (E1, E2). Secondly, Peto's method is applied to calculate pooled odds ratios for the event of interest (E1) at the same timepoints. Thirdly, the pooled EFS cumulative rates and the pooled E1 odds ratios are combined [1] to obtain cause-specific incidences, which are cumulated over time to give CRCI rates for event E1 in the presence of competing risk E2.

In our second approach, CRCI rates and their variances are calculated separately for each arm of each trial. Within-trial differences in CRCI rates between the arms are pooled over trials using the inverse variance weighting method. Finally, pooled differences are used to compute pooled CRCI rates in each arm.

The meta-analysis used for illustration was based upon individual patient data from 37 randomised trials comparing radiotherapy alone (RT), chemotherapy alone (CT) and combined chemo-radiotherapy (CRT) for untreated HL [6]. For each treatment comparison, CRCI curves for SM, with non-SM death as competing risk, were computed and compared qualitatively with the conventional Peto time-to-SM curves. A further analysis of SM risk focussed on the effect of first-line therapy only, and censored at HL recurrence. Accordingly, HL recurrence was here regarded as a CR in addition to non-SM death.

Results

Illustrative results from our first approach (Peto-based) for the comparison RT versus CRT comparing conventional Peto cumulative SM rates with Peto-computed CRCI rates are depicted in Fig. 1, separately for patients with early and advanced stage disease. CRCI rates were markedly lower than the equivalent conventional Peto rates. In advanced stage patients, the disparity is larger due to the higher rate of non-SM death. However, the results with and without consideration of CR agree qualitatively with respect to the ratio of event rates between treatment arms.

In the further analysis with censoring at HL recurrence, conventional cumulative SM rates were similar in both treatment arms, whereas CRCI rates were lower in the RT arm than in the CRT arm. This is a consequence of the higher HL recurrence rate after RT alone.

Results of the second approach applied to the same data will be presented at the meeting.

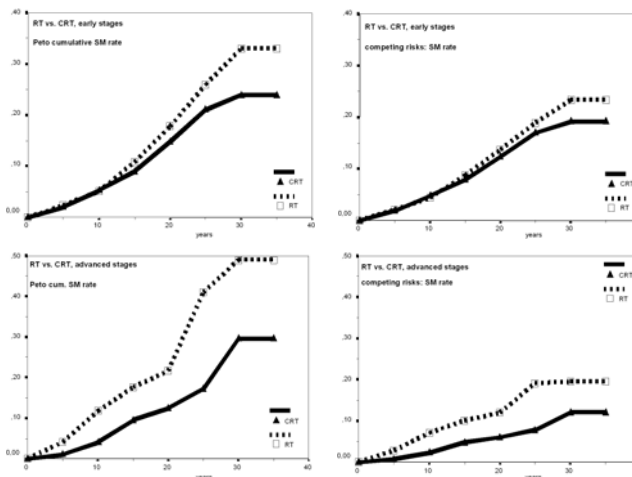


Fig. 1. Comparison of Peto methods with and without accounting for competing risks for the treatment comparison RT vs. CRT

Discussion

The first proposed method combines computed pooled event free survival rates with computed pooled cause-specific hazard ratios, the pooling in each case following Peto's method. Thus, a high degree of homogeneity of events rates among trials is assumed.

Our second approach for meta-analysis in the presence of competing risks has already been proposed [7]. With this method, the calculation of variances permits testing for overall differences in CI rates between treatment arms at the specific timepoints. Comparison of the results shown in Figure 1 with our second approach will be presented at the meeting. CRCI rates are usually lower than the comparable Kaplan-Meier or conventional Peto rates because the latter compute 'net' (or 'conditional') event rates based on the surviving proportion of cases not experiencing the competing risk, whereas CRCI rates are 'crude' (or 'marginal') rates based on the entire cohort. Progressive losses due to the competing risk reduce the CRCI rates. In particular for Hodgkin Lymphoma, the high cumulative second malignancy rates several decades after treatment often calculated using conventional Kaplan-Meier methods are based on a very small proportion of surviving patients, and the assumption of independence between SM and competing risks may be untenable. Competing risks methods provide a more tenable and realistic estimate. However, the dependence of CRCI rates on the occurrences of both the event of interest and the competing risk(s) must be considered when interpreting results.

Literatur

- [1] Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. New York, Wiley, 1980.
- [2] Pepe MS, Mori M. Kaplan-Meier, marginal or conditional probability curves in summarizing competing risks failure time data. *Statist Med* 1993; 12: 737-751.
- [3] Tai BC, Machin D, White I, GebSKI V. Competing risk analysis of patients with osteosarcoma: a comparison of four different approaches. *Statist Med* 2001; 20: 661-684.
- [4] Early Breast Cancer Trialists' Collaborative Group. Effects of adjuvant Tamoxifen and of cytotoxic therapy on mortality in early breast cancer. *N Engl J Med* 1988; 319: 1681-92.
- [5] Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic or immune therapy. *Lancet* 1992; 339: 1-15, 71-85.
- [6] Franklin JG, Paus MD, Pluetschow A, Specht L: Chemotherapy, radiotherapy and combined modality for Hodgkin's disease, with emphasis on second cancer risk (Cochrane review). In: *The Cochrane Library*, issue 4, 2005. John Wiley, Chichester, UK.
- [7] Hozo I, Djulbegovic B. Individual patient data meta-analysis (IPD-MA) in the presence of competing risks. *Cochrane Colloquium*, 2006, Melbourne, Australia, abstract O-06. <http://www.cochrane.org/colloquia/abstracts/melbourne/O-06.htm>