Reviewer’s report

Title: Individual Patient Data Network Meta-Analysis using either Restricted Mean Survival Time Difference or Hazard Ratios: is there a difference? A case study on locoregionally advanced nasopharyngeal carcinomas

Version: 0 Date: 05 Apr 2018

Reviewer: Raphaël Porcher

Reviewer's report:

The manuscript illustrates the impact of using restricted mean survival differences (rmstD) instead of hazard ratios (HR) in a network meta-analysis (NMA). The methodology presented is sound, the study well conducted, and the manuscript presents the first example of the use of rmstD for NMA, at least to my knowledge.

Major comments

1. Locoregional control was used as a secondary outcome, which adds the complexity of competing risks. In the analysis, distant failures as first events were treated as censored observations, which if fine to estimate HR: it resorts on computing a cause-specific hazard ratio. But the corresponding Kaplan-Meier estimator is biased for the probability of locoregional failure, because those with distant failure are considered as if they were still at similar risk of locoregional failure as patients who remained under follow-up. As a result, it is unclear what the area under the Kaplan-Meier curve estimates, as well as what lies under the definition of a RMST in that case. Extensions of RMST to competing risks exist (even in a recent BMC Medical Research Methodology paper by Calkins et al.) The authors acknowledge that competing risks were not considered, but this should at least be discussed. Likely, if there were only very few distant failures as first events, the impact of ignoring competing risks is negligible. But if not, then more appropriate analyses should be considered.

2. Two time horizon t* are used, 10 years for the primary analysis (with extrapolation if the last event occurred before 10 years) and 5 years as a sensitivity analysis. For HR analysis, however, the available follow-up was likely used. So for comparison both treatment effect measures are not exactly treated the same. For instance, HRs for follow-up restricted to 5 years could also be used, and could lead to different results, especially when hazards are not proportional. This issue could also be discussed further.

3. The figure 1 is informative, but is not specific to the NMA. I would add a second panel with the p-scores for all treatments with HR and rmstD (or put the figure 1 as supplementary material and replace it by my suggestion).
4. RmstD is not insensitive to non-proportional hazards (NPH), though it does not require such an assumption. In fact, if survival curves cross, for instance, the choice of the time horizon $t^*$ may be critical, and a treatment may offer a positive benefit in RMST at shorter follow-up times, but a negative one if $t^*$ was set at a longer time. This may be acknowledged, especially when discussing NPH for HR estimation.

Minor comments

1. Secondary outcome could be listed in the methods part of the Abstract, since they are (briefly) alluded to in the results.

2. In the table 1, the term "trial comparison" is unclear. Do the author mean trial? Also, the second column should give the treatment comparison (currently last column). This would facilitate reading. I would also put the p-value for PH testing just after the confidence interval (CI and not IC) for the HR, since it directly related to that measure of treatment effect.

3. "Significance change" could be changed to "change in significance". Similarly, page 11, "but changed the significance" would better be "but changed in significance".

4. The percentages given close to the curves on supplementary figure 2 are slightly misleading, except if one is really deep in the paper. Indeed, cumulative event rates could easily be mixed up with cumulative incidence, especially when the y-axis label also states "Cumulative event rate". I would suggest removing them except if this point is clarified and described more clearly than currently done.

5. Still on this issue, page 16, it seems that Supplementary figure 2 should be referred to instead of Supplementary figure 4 in the sentence "The cumulative event rates at 10 years were 94.8%, 96.6% and 99.0% respectively for OS, PFS and LRC (Supplementary Figure 4)."
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