Review of: "On The Need For Better Inform Results From Randomized Clinical Trials In Oncology"

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Potential competing interests: No potential competing interests to declare.

This is an important article, and I commend the authors for breaking down concepts like relative risk, absolute risk, and number needed to treat for the audience.

MAJOR COMMENTS

Some recommendations to improve this manuscript. The content is great, but I wonder if this paper would benefit from restructuring and reorganizing the manuscript.

- It is the opinion of this reviewer that a significant portion of the Discussion could be moved to the Introduction.
- The Introduction is brief, and the authors jump straight into NEJM cases. Here, they use terms like relative risk, absolute risk, or number needed to treat in the abstract. However, these terms are not defined for the reader. If the goal of this paper is to educate readers, many of whom may misunderstand or misapply these concepts, then it is the job of the authors to clearly explain the *why*.
- Another example is the first case example, where the authors state that "the [PFS] curves crossed, breaking the proportional hazards assumption," but then do not explain the context of why it is important to maintain the proportional hazard assumption in the first place.
- In all the cases, the authors calculate AR, RR, and NNT, but there is no explanation of what these terms mean in terms of the conclusions drawn from the NEJM articles and what the authors would do differently. Some examples for them to consider:

  - Case 2: The authors incorrectly state that the primary endpoint is PFS (it is actually disease-free survival). Furthermore, the overall survival data is not mature, and so while the mathematical calculations regarding AR and RR are welcome, they are misleading since the trial does not have mature OS data. At a minimum, the authors should have a statement that contextualizes their OS calculations.
  - Case 4: The authors correctly note that AR and RR reductions for PFS were significant, but not for OS. However, the authors miss an opportunity to provide context for these findings. For example, was there significant crossover in this study that abrogated the OS interpretation? Could there have been use of stereotactic radiosurgery for oligoprogressive lung lesions that could have influenced OS results?

- This is a critical concept that the authors mention and should be emphasized more throughout the manuscript – "Unfortunately, in this sample of 5 RCTs, only two (Tisotumab Vedotin and Dabrafenib/tTametinib) studies disclosed

the number of events in the curve figures, which makes it difficult for readers to calculate Relative and Absolute risks, despite these metrics being a must for RCTs according to the CONSORT statements."

MINOR COMMENTS

- In the discussion – recommend changing the following sentence "These concepts are nicely explained in **the following references"**[6][7][8]. The current formatting is awkward.
- Appreciate the humility, but the authors do need to apologize for their statistical background. Can delete this sentence "The authors of this work, though not expert statisticians, have endeavored to elucidate these complex concepts. However, it is possible that some nuanced details and potential pitfalls in the calculation and application of hazard ratios, relative risk, absolute risk, and number needed to treat in time-to-event analysis may have been overlooked [10][11]."