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The use of a non-inferiority analysis to establish a safe timeframe for prehabilitation



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We read, with great interest, the article “Impact of therapeutic delay in colorectal cancer on overall survival and cancer recurrence – is there a safe timeframe for prehabilitation” by Strous et al., published online [1]. We believe that the research question in this study, whether it is safe to postpone surgery to facilitate optimization of the patient prior to surgery, is of great importance with the established fact that preoperative smoke cessation improves outcome, and the growing hope for improved postoperative recovery with preoperative physical activity interventions, at the same time as the shortening of lead times in several countries. However, we think that the question whether surgery could be safely postponed for a few weeks should be investigated with a non-inferiority analysis. That is, rather than testing the null hypothesis of no difference in survival between early and late initiation of surgery (i.e. verifying superiority of early initiation), we should seek to establish whether there is a clinically relevant deterioration in survival due to delayed surgery (inferior) or not (non-inferior). The non-inferiority limit chosen should hence reflect the loss in survival we are willing to accept to allow room for prehabilitation (that could in turn potentially improve survival). For illustration we performed a sample size calculation for a non-inferiority design. Accepting a 10% relative increase in mortality (non-inferiority limit

of 1.10 for the hazard ratio), assuming a true ratio of one, a 5-year mortality rate of 20% and a 5% significance level, then 13 600 patients are needed to achieve 80% power to declare therapeutic delay being non-inferior. With a limit of 1.20, the hazard ratio observed in this study, 3700 patients are needed. Based on the observed hazard ratio of 1.20 (95%CI: 0.88; 1.64) and a p-value of 0.249 in overall survival among 790 patients the authors conclude that delay does not lead to poorer survival.

We fear that, from a non-inferiority perspective, this study doesn't fully support the conclusion “prolonged treatment delay does not lead to poorer overall or cancer-free survival in patients with primary colorectal cancer who underwent curative surgical treatment”.

Reference

- [1] Strous MTA, et al. Impact of therapeutic delay in colorectal cancer on overall survival and cancer recurrence - is there a safe timeframe for prehabilitation? *Eur J Surg Oncol* 2019. <https://doi.org/10.1016/j.ejso.2019.07.009>.

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