

Can we really conclude that treatment delays are associated with poorer outcome in patients with colorectal cancer awaiting elective surgery?

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study

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Can we really conclude that treatment delays are associated with poorer outcome in patients with colorectal cancer awaiting elective surgery?

Dear Editor,

We read with great interest the systematic review by Whittaker et al. [1] published in *Colorectal Disease*. Their study aimed to explore the association between treatment delay (TD) and overall survival (OS) or disease-free survival (DFS) in patients undergoing elective surgery for colorectal cancer (CRC). The authors concluded that elective surgery for CRC should not be postponed for longer than 4 weeks. Although we endorse the importance of the aim of the study, we have some methodological concerns regarding this systematic review and meta-analysis.

Considering the wide heterogeneity in the definition of TD, it is questionable whether it is valid to perform a meta-analysis of the included studies. Although the end of the TD is generally clearly defined, the time point used as diagnosis, which is mostly taken as the starting point of TD, is defined less consistently. Definitions of diagnosis can vary from first investigation for defining malignancy to diagnosis confirmed by a multidisciplinary team meeting [2]. From experience in our own hospital, these time-points can be as far as 7–14 days apart. In some studies, such as that of Kucejko et al. [3], diagnosis was not specified at all. Heterogeneity in the definition of TD makes it questionable whether it is valid to pool hazard ratios from the included studies in a meta-analysis.

Besides our concern about the methodology, we believe that the conclusion is not sufficiently supported by the data presented. The authors state that elective surgery for CRC should not be postponed for longer than 4 weeks. This interval seems to be chosen arbitrarily, as this 4-week interval is not consistent with the intervals used in the included studies. For example, the study of Strous et al. [4] used

a cut-off point of >5 weeks. In addition, with regard to the inconsistencies in definition of diagnosis, it is unclear how this maximum TD of 4 weeks (or any TD) should be interpreted (i.e. 4 weeks starting when?).

The conclusion seems to be based on the association between TD and OS, while the association between TD and DFS is far more interesting with regard to treatment delays and preparation for surgery. It is well known that OS is influenced by many factors. Some studies show that frailer patients often have a longer TD, which might at least partially explain a possible association between a longer TD and OS [3]. As also acknowledged by the authors, not all included studies adjusted their analysis for patient factors associated with frailty [5]. As the main concern with longer treatment delays is tumour growth and risk for metastasis, DFS should be the main outcome of this systematic review.

We agree with the authors that TDs other than those that are needed for pretreatment work-up or optimization of health should be avoided in order to provide optimal care and minimize patient distress. However, especially in patients at high risk for complications, interventions aimed at reducing complications might be more instrumental than aiming for short treatment delays. Perhaps a shift in thinking from 'treatment delay' to 'optimization period' would allow for more individualized 'treatment intervals'.

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Reply to: Franssen, Ruud; Strous, Maud; Vogelaar, F Jeroen; Janssen-Heijnen, Maryska. Can we really conclude that treatment delays are associated with poorer outcome in patients with colorectal cancer awaiting elective surgery?

Dear Sir,

The authors of the original systematic review would like to thank Franssen et al. for their correspondence with regard to our recent work. The feedback and constructive criticism provided is greatly appreciated.

Given the lack of a recent meta-analysis on this topic [1] we attempted to quantify the delay from diagnosis to surgical treatment in elective colorectal cancer from the available literature. The evidence base available to the authors was of poor quality as acknowledged by the ROBINS-I score which declared three papers at serious risk of bias. The lack of uniformity in delay time at 4 weeks was acknowledged; however, it was the most reported interval and national guidelines recommend this interval. Thus, we felt it was the most appropriate approximation for a short delay interval.

As there is no consensus in the evidence base on the categorization of delay, we still believe future work should report the association between delay and mortality as a continuous variable. This will allow uniformity in statistical analyses so that future work can compare correlations directly.

We would like to highlight that a significant conclusion from this meta-analysis was the lack of consistency in the literature. From our work, a statistically significant correlation between delay and overall survival at 4 and 12 weeks justified a cautious recommendation for clinicians counselling patients. This is particularly prescient given the worldwide pandemic and current delays to surgical waiting times [2].

The categorization for 12 weeks was consistently reported in the cited studies. Therefore, a meta-analysis at this delay point was warranted and important to assess for patient safety. We do agree that even with this time interval the three studies adjusted for varying confounding variables. However, the error was reduced by using a random inverse model as suggested by the Cochrane Handbook [3].

We agree with the final point made by [4] that the interval between diagnosis and treatment could be an opportunity for optimization and should be utilized in the most efficient manner possible. Perhaps future research could address the optimum point for treatment delay and the benefits of prehabilitation. As highlighted by our results, the majority of studies did not describe the reason for