



## Comment on: simultaneous versus delayed resection for initially resectable synchronous colorectal cancer liver metastases

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We read with great interest the recently published article of Boudjema and collaborators (1). The authors evaluated the safety and efficacy of delayed resection (DR) versus simultaneous resection (SR) for patients with initially resectable synchronous colorectal cancer liver metastases (CRC-SLM). The aforementioned study (METASYNC) was the first randomized controlled trial comparing two resection strategies for CRC-SLM. In the literature, large retrospective studies didn't seem to favor one type of treatment, particularly when comparisons are based on a propensity match score (2).

In the paper, the authors suggested that patients with CRC-SLM could undergo SR. Their results underlined the absence of statistical significant difference of postoperative complications between the two groups of treatment, together with a 2-year overall survival that tended to be prolonged after SR, and a percentage of R1 resection higher in the DR group (but not statistically significant). The percentage of digestive complications was higher in the SR group, but without statistical significance.

We believe that certain aspects are open to further discussion and analysis. First of all, the small sample size that doesn't yield a great statistical power, despite a long period of inclusion (over 10 years). On average, two patients were eligible and a single patient was randomized per year and per center (10 centers out of 10 years of inclusion), which seems little for high volume centers. Was the screening exhaustive? Taking into account the heterogeneity of the population according to the stage of

the initial CRC tumor, primitive localization, use and type of perioperative chemotherapy treatment tumor biology, 85 patients is a small number. Moreover, it would have been informative to do an intention-to-treat analysis. Resection margins have been cited in the article in favor of SR, but evidences about colorectal liver metastases (CRLM) suggest that R1 resection could have no prognostic value per se but reflect a more severe disease (3). Most of all, nowadays oncological issues in CRLM surgery cannot adequately be discussed and addressed without an analysis of the biology of the tumor, in particular *RAF/RAS* mutational status and response to perioperative chemotherapy (4-6). Since the study didn't consider all the aforementioned factors, overall survival (OS) differences reported in the study between SR and DR may be related more to the stage and biology of the tumor, rather than to the technique used. It is a pity that the database was updated in December 2017 and not more recently in order to have a better follow-up for a more precise and perhaps significant difference in OS and disease-free survival (DFS) since the publication has just taken place in 2020. Nevertheless, between the two groups compared, the number of rectal cancers was higher in the DRs (21 vs. 12), as well as the number of patients with three or more liver metastases was double in the DRs (18 vs. 9). These data must be considered when interpreting the results: for example, liver tumor number [as well as tumor volume (7) that in the study is not reported] are well known prognostic factors in patients with synchronous metastases (8), and would have been interesting data to

have. Part of the reasons for the difference in OS, as well as the higher rate of R1 resections, may be attributable also to hepatic progression of metastases. But previous studies show that patients with more numerous liver lesions, as well as patients with rectal cancer, are usually referred to liver first strategy, while in the paper in question they go more frequently to DR, which conceptually is exactly the opposite (2). How do you explain this tendency and how do you think this can be related to your results?

Since the METASYNC study began in 2006, the evolution of the management of perioperative chemotherapy with EORTC Intergroup Trial 40983 published in 2008 (9), interval chemotherapy and surgical techniques may also have played a role in confounding surgical and oncological outcomes, as well as the too long interval before performing liver surgery (higher than 12-week in the DR group). Due importance must be given to this type of considerations when you try to draw conclusions from the difference in OS or DFS between the two groups.

Furthermore, the lower number of rectal surgeries in SRs can have a considerable impact also on postoperative short-term complications, given the greater technical difficulty of the intervention. Early digestive complications are already higher in SRs (28.2% *vs.* 13%), but this difference could still increase if the subgroup of rectal resections is considered. This could lead the therapeutic choice towards a different strategy, in our opinion, considering that postoperative morbidity is the only outcome statistically different between the two groups. In order to give a correct judgment on surgical outcomes and their impact, especially in oncological patients, it would also have been important here to take into account an assessment of the quality of life, where chemotherapy must be weighed up on one hand and postoperative complications on the other.

In conclusion, the study is of great importance but robust conclusions that favor one particular treatment cannot be drawn. The strategies of simultaneous and delayed surgeries should not be mutually exclusive but rather proposed to different types of patients. In particular, patients with single or few liver lesions, could benefit more from SR, while patients with numerous liver lesions or a technically difficultly resectable rectal cancer could be directed to other strategies. Further prospective studies that have a shorter duration and a greater focus on perioperative therapy, tumor biology and patient-related factors are needed.

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