

Reverse approach: a new paradigm in the treatment of synchronous liver metastasis from colorectal cancer

Abordagem reversa: novo paradigma no tratamento da metástase hepática sincrônica de câncer colorretal

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About 25% of patients with colorectal cancer have liver metastasis at the diagnosis of the primary tumor. Complete tumor removal (primary + metastasis) is the most efficient way to provide long survival¹, but the synchronous presentation (liver metastasis) has been associated with worse prognosis². Several advances have been achieved in the treatment of metastatic colorectal cancer, amongst them the more efficient use of chemotherapy and the technological development, which has allowed for more complex liver surgery and less morbidity. The combination of these two treatment modalities (surgery plus chemotherapy) has been responsible for improved outcomes in cancer, and five-year survival for metastatic disease has achieved results deemed unimaginable before³. Despite all these advances, the prognosis of patients with synchronous disease is worse. Therefore, some strategies have been proposed in an attempt to optimize these results⁴, one of them would be a change in the treatment sequence, as proposed by Mentha et al.⁴. The traditional approach has been the primary tumor followed by chemotherapy and subsequent liver surgery. Mentha et al.⁴ proposed the so-called "Reverse Approach", which consists of treatment with systemic chemotherapy followed by liver resection and subsequent treatment of the primary lesion. These authors published in 2006⁴ a series of 20 cases of colorectal cancer with synchronous liver metastases treated with the "Reverse Approach", nine cases of primary adenocarcinoma of the colon and 11 of the rectum (all cases of non-obstructive tumors). Patients were initially treated with two to six cycles of chemotherapy consisting of oxaliplatin, irinotecan, 5-FU and leucovorin. Response to chemotherapy was evaluated after three cycles and additional cycles were indicated if surgical resection of liver disease was not yet possible. Fourteen patients (70%) had liver disease and 60% had bilobar lesions larger than 5 cm. Staged hepatectomy was necessary for treatment of the bilobar injuries and portal embolization was carried out in cases where the expected remnant liver volume was inadequate. The primary tumor resection was planned in three to eight weeks after liver surgery or after completion of radiotherapy in the cases of rectal cancer. Sixteen patients (80%) had liver surgery with

curative intent, whereas 20% (four patients) presented with liver disease progression, making resection impossible. Median survival achieved was 46 months and an overall survival at four years of 56%.

These results were surprisingly better than the results previously reported for synchronous metastatic disease with the same gravity score⁵. In addition to the likely benefit in terms of survival, some theoretical arguments support the adoption of this new strategy. First, the use of more potent chemotherapy (oxaliplatin, irinotecan) as an initial step allows for immediate treatment of systemic disease (liver metastasis), i.e., the more severe disease and responsible for more than two thirds of the causes of death in cancer patients. Moreover, the response rate around 70%, confirmed in previous studies^{6,7}, justifies the postponement of surgery and the use of the "Reverse Approach", particularly in subgroups of poor prognosis (synchronous metastatic liver disease, bilobar lesions, multiple metastases, etc.). Second, the initial use of chemotherapy allows selection of patients whose treatment will have curative intent (regardless of the number and size of metastases) and prevents subsequent aggressive treatment in poor responders, in whom only palliative treatment would be most beneficial. Third, among the responders the initial removal of all liver disease protects against re-growth of liver lesions while the primary lesion is treated. This is particularly relevant in cases in which complications related to the treatment of the primary lesion occur, delaying the initiation of chemotherapy. Finally, this strategy allowed the use of radiotherapy prior to rectal resection, being beneficial in terms of local control.

More recently, Brouquet et al.⁸ published the experience of the MD Anderson Cancer Center in the treatment of 156 consecutive cases of colorectal cancer with synchronous liver metastasis, comparing the classical approach (primary tumor treated before liver metastasis), the combined (combined resection the primary tumor and liver metastasis) and "reverse" (treatment of liver metastasis and then the primary treatment). These authors found similar oncological outcomes between the three strategies, and similar morbidity and mortality. The authors' conclusion is that the "Reverse Approach" should be considered an

alternative in cases of advanced synchronous metastatic colorectal disease and that the results of this approach in patients with more extensive disease are similar to the classical approach and the combined one used in less extensive disease.

Advances in chemotherapy and surgery in the treatment of metastatic colorectal cancer has been clear in recent years. Nevertheless, a particular subgroup (synchronous metastatic liver disease) still requires action in order to optimize results. It is possible that this new paradigm (change in sequence of treatment) leverage the effects of the classical approach. Thus, despite the rational of the "Reverse Approach" is quite logical and the results published so far are interesting, the need for prospective randomized studies to define the true role of this new strategy and validate its implementation in clinical practice is evident.

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