

## Liver-first approach of colorectal cancer with synchronous hepatic metastases: A reverse strategy

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### Abstract

Recently, there has been a change in the strategy of how synchronous colorectal hepatic metastases are

attributed to the development of more valuable protocols of chemotherapy and radiotherapy for neoadjuvant treatment of colorectal neoplasms and their hepatic metastases. There is a consensus that patients with synchronous colorectal hepatic metastases have lower survival than those with metachronous colorectal hepatic metastases. Currently, controversy remains concerning the best approach is sequence in a patient with colorectal cancer and synchronous hepatic metastases resection. To obtain a better patient selection, the authors have suggested the initial realization of systemic chemotherapy in the circumstance of patients with colorectal tumor stage IV, since these patients have a systemic disease. The rationale behind this liver-first strategy is initially the control of synchronous hepatic metastases of colorectal carcinoma, which can optimize a potentially curative hepatic resection and longstanding survival. The liver-first strategy procedure is indicated for patients with colorectal hepatic metastases who require downstaging therapy to make a curative liver resection possible. Thus, the liver-first strategy is considered an option in cases of rectal carcinoma in the early stage and with limited or advanced synchronous colorectal hepatic metastases or in case of patients with asymptomatic colorectal carcinoma, but with extensive liver metastases. Patients undergoing systemic chemotherapy and with progression of neoplastic disease should not undergo hepatic resection, because it does not change the prognosis and may even make it worse. To date, there have been no randomized controlled trials on surgical approach of colorectal synchronous hepatic metastases, despite the relatively high number of available manuscripts on this subject. All of these published studies are observational, usually retrospective, and often non-comparative. The patient selection criteria for the liver-first strategy should be individualized, and the approach of these patients should be performed by a multidisciplinary team so its benefits will be fully realized.

**Key words:** Colorectal neoplasms; Neoplasm metastasis;

Liver neoplasms; Liver/surgery; Hepatectomy; Drug therapy; Survival; Prognosis

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**Core tip:** The liver-first approach or reverse strategy is a downstaging regimen, and it consists of systemic chemotherapy, chemoradiotherapy and/or biological agents, followed by resection of colorectal hepatic metastases prior to removal the primary colorectal tumor. It is a promising strategy in patients with synchronous colorectal liver metastases. The rationale behind this liver-first strategy is initially control of synchronous hepatic metastases of colorectal carcinoma, which can optimize the opportunity of a potentially curative liver resection and longstanding survival. The liver-first strategy can be applied for patients with early stage colorectal carcinoma and synchronous hepatic metastases. Extensive or locally advanced rectal carcinoma with limited or advanced synchronous hepatic metastases and asymptomatic colonic carcinoma with extensive synchronous hepatic metastases may be submitted to the liver-first strategy.

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## TEXT

Colorectal cancer remains the fourth most common malignancy in the United States, being the third most common cancer in both men and women<sup>[1]</sup>. Approximately 15% to 25% of these patients present with colorectal synchronous hepatic metastases detected either before or during operation<sup>[2]</sup>. There is a consensus that patients with synchronous colorectal hepatic metastases have lower survival than those with hepatic colorectal metachronous metastases<sup>[3]</sup>, and so this finding is considered a poor prognosis predictor<sup>[4]</sup>. However, the presence of synchronous colorectal hepatic metastases does not exclude the potential of long-standing survival and the opportunity of cure<sup>[5]</sup>.

It is agreed in the medical literature that surgical resection is considered the only curative option for patients with colorectal carcinoma and synchronous hepatic metastases<sup>[6]</sup>. Currently, combinations of three treatment regimens have been implemented in the treatment of colorectal synchronous hepatic metastases: preliminary resection of the colorectal tumor; concurrent resection of colorectal tumor and synchronous hepatic metastases; and the liver-first strategy, wherein resection of synchronous hepatic colorectal metastases precedes the resection of the primary colorectal tumor<sup>[5,6]</sup>.

The conventional surgical strategy for patients with

resectable synchronous colorectal hepatic metastases includes resection of the colorectal carcinoma, followed by chemotherapy, and eventually synchronous hepatic metastases resection<sup>[6]</sup>. The basis for this traditional approach is that the colorectal tumor is considered the common cause of symptoms and metastases<sup>[6,7]</sup>.

There are the following arguments in favor of an initial colorectal cancer resection: in patients with complications due to tumor (obstruction, bleeding, or perforation) and who require emergency surgery to control these complications, the interval time period between the colorectal resection and hepatic resection of synchronous metastases may exclude liver resection because in patients undergoing systematic chemotherapy, occult metastatic disease may become detectable<sup>[7,8]</sup>. Furthermore, in patients with symptomatic colorectal carcinoma, the liver-first strategy is not suitable<sup>[2]</sup>.

Consequently, patients with disease progression and unresectable disease should not undergo hepatic resection, avoiding the perioperative morbidity and mortality of hepatic surgery without benefit to the patient<sup>[8]</sup>. Furthermore, in patients with a locally advanced primary tumor there is a risk of complication while on chemotherapy<sup>[9]</sup>. So the preferred alternative is surgery of the colorectal tumor first to avoid complications related to this tumor and the need for emergency surgery with a high risk of stoma creation<sup>[9]</sup>.

On the other hand, there are arguments for not performing a preliminary colorectal resection in patients with colorectal carcinoma and synchronous colorectal hepatic metastases: the response of preoperative chemotherapy with oxaliplatin-and/or irinotecan-based regimens in colorectal cancer is correlated with a significantly corresponding response of colorectal hepatic metastases.

However, colorectal cancer resection in patients with hepatic metastases was related with a significantly higher postoperative mortality when compared with colorectal cancer resection in patients without liver metastases; the complications of leaving intact the colorectal cancer are not as high and can be overestimated; disease progression between the timing of the colorectal and hepatic surgeries may render the colorectal hepatic metastases unresectable, particularly when there are postoperative complications after colorectal cancer resection, preventing systemic chemotherapy and resection of colorectal hepatic metastases; and the main determinant of the patient's survival is the presence of systemic metastases, and the treatment of colorectal hepatic metastases should be the initial priority<sup>[7]</sup>.

In some cases, in particular with patients with colonic carcinoma, the approach should be neo-adjuvant therapy following the simultaneous resection approach. The traditional approach should be considered in patients with limited synchronous disease who do not require downstaging.

In the synchronous strategy, the hepatic metastases and colorectal tumor are resected simultaneously<sup>[6]</sup> with

the benefit of removing the entire identifiable tumor during a single procedure. Furthermore, experimental and preliminary clinical data indicated an increase in vascularization of metastatic disease after removing the colorectal carcinoma, and this event could enhance outgrowth of liver metastases<sup>[9]</sup>. This strategy has an important limitation, because it can be offered only in selected patients with synchronous disease<sup>[10]</sup>, and this approach is associated with high rates of postoperative complications in the case of hepatic resection of advanced colorectal hepatic metastases<sup>[7]</sup>.

The simultaneous resection of colorectal tumor and synchronous hepatic metastases is usually associated with good outcomes, shorter hospital stay, and reduced cost. However, simultaneous resection is accepted to be not appropriate for patients requiring major hepatic resection, elderly patients, and patients with locally advanced rectal cancer<sup>[11]</sup>.

de Haas *et al.*<sup>[12]</sup> studied 228 patients submitted to hepatectomy for synchronous colorectal hepatic metastases, 55 (24.1%) with a simultaneous colorectal resection and 173 (75.9%) with delayed hepatectomy. They observed disadvantages of the simultaneous strategy of complex hepatic resection associated with colorectal resection. The morbidity is not negligible, and there is some evidence that this combined strategy impacted negatively on free survival progression.

Actually, the incidence of colorectal carcinoma recurrence is higher in patients treated by the simultaneous strategy, but the three-year overall survival rates did not differ significantly concerning the surgical approach<sup>[2,3,6,7]</sup>. Furthermore, progression-free survival is significantly better when delayed hepatic surgery is performed<sup>[12]</sup>. In simultaneous strategy patients, it was observed that the morbidity rate persisted lower and the recurrence rate stayed higher, and the progression-free survival was significantly lower<sup>[12]</sup>.

Chemotherapy to colorectal cancer has considerably improved with the introduction of new cytotoxic agents (oxaliplatin, irinotecan) and targeted therapies (bevacizumab, cetuximab, panitumumab)<sup>[2]</sup>. The underlying principle for the utilization of preoperative chemotherapy in these patients is to provide early treatment of metastatic disease, to decrease the recurrence rate after surgery, to assess tumor biology, to better select patients for an aggressive surgical procedure, to avoid unnecessary surgery in patients with fast-progressing disease, to test chemosensitivity of the tumor, and to tailor postoperative treatment<sup>[10]</sup>. Tumors responding to systemic chemotherapy may reflect biologically less aggressive metastases<sup>[5]</sup>.

Furthermore, response to chemotherapy is now widely recognized as a major prognostic factor in patients undergoing resection of colorectal hepatic metastases<sup>[2]</sup>. The finding of tumor progression of colorectal hepatic metastases in preoperative patients under systemic chemotherapy is associated with a poor outcome, independently carrying out a curative intent surgery<sup>[13]</sup>.

Taking into account the proposition that the liver metastases represent the most common cause of a patient's death, Mentha *et al.*<sup>[14]</sup> described the liver-first strategy with systemic chemotherapy followed by hepatic resection of synchronous hepatic metastases and subsequent colorectal cancer resection. In this strategy, after the period of systemic chemotherapy, the colorectal liver metastases are resected before the colorectal tumor, usually after a period of downstaging chemotherapy or radio chemotherapy. This procedure was first recommended for rectal carcinoma patients with synchronous hepatic metastases, because these patients habitually required chemoradiotherapy previous to their colorectal carcinoma resection<sup>[2,11]</sup>.

The liver-first strategy may represent one treatment option for patients with locally early/advanced stage rectal cancer and limited/extensive synchronous hepatic metastases. Actually, this approach should be called "chemotherapy-first" and not "liver-first" because the first approach is systemic chemotherapy that does not impair negatively on resection of the rectal carcinoma and synchronous hepatic metastases, and may downstage previously liver metastases believed unresectable<sup>[5]</sup>. Beside with these effects on synchronous colorectal hepatic metastases, the chemotherapy could downstage the primary rectal tumor. Patients with no obstructive colonic cancer with wide liver disease that necessitates downstaging may benefit from the liver-first approach<sup>[11,15]</sup>.

The logical for the liver-first approach is represented by the following: major complications are uncommon in patients with stage IV colorectal cancer beneath chemotherapy; hepatectomy before the resection of colorectal carcinoma permits control of the liver metastases, making curative hepatic resection possible; subsequent resection of the primary tumor may prevent loss of primary tumor-induced inhibition of the metastases; and treatment of the metastatic disease is not postponed by radio-chemotherapy of the rectal tumor or by complications of surgical treatment of the colorectal carcinoma<sup>[2,10,11,16]</sup>. Moreover, this strategy provides a period of time that permits occult extrahepatic metastases existing to be detected<sup>[12,17]</sup>.

The fact that systemic chemotherapy treats both diseases is an important advantage of the reverse strategy in patients with locally advanced colorectal carcinoma and synchronous hepatic metastases<sup>[5,18]</sup>. Mild colonic obstruction, pain, bleeding, and mucous discharge usually resolve after few a cycles of systemic chemotherapy<sup>[5]</sup>. Another advantage of the liver-first strategy is the concept that systemic metastatic disease originates from the liver's metastatic disease<sup>[6,19]</sup>.

The failure to complete the liver-first approach is characterized by disease development in the liver or primary tumor, death from other comorbidities while expecting primary surgery, and morbidity and mortality succeeding liver resection<sup>[11]</sup>. When we apply the liver-first approach, there is a real jeopardy that an primarily

resectable colorectal tumor may become progressive and unresectable due to perforation or invasion into nearby structures, despite the fact that this event during induction chemotherapy is sporadic<sup>[11,15]</sup>.

However, currently, the surgical pattern sequence for patients with synchronous colorectal liver metastases still remains controversial<sup>[20]</sup>. The traditional approach is staged by the limited risk of progression of colorectal liver metastases during treatment of the primary colorectal tumor. No less important is that the combined approach is only suitable for patients with not advanced or even limited metastatic liver disease. In patients with advanced metastatic disease requiring major liver resection or bilateral liver resection, chemotherapy is started first, and the reverse approach can be proposed in case of a suitable response to chemotherapy<sup>[8,20]</sup>.

Brouquet *et al.*<sup>[10]</sup> retrospectively analyzed the outcomes of 156 patients with synchronous colorectal hepatic metastases managed by three different surgical approaches: traditional ( $n = 72$ ), combined ( $n = 43$ ), and the liver-first strategy ( $n = 27$ ). Patients treated with the liver-first approach had a significantly higher number and larger colorectal liver metastases than patients treated by the combined and traditional approaches. The authors reported that the postoperative mortality rates in the combined, classic, and reverse strategies were 5%, 3% and 0%, respectively, and the postoperative morbidity cumulative rates were 47%, 51% and 31%, respectively. The different surgical approaches did not exhibit different cumulative postoperative morbidity and mortality rates. There was no significant difference in 3-year and 5-year survival between the three groups, and the median disease-free survival was 11 mo in all three groups.

Andres *et al.*<sup>[21]</sup> achieved a survival analysis of the liver-first reversed approach of advanced synchronous colorectal hepatic metastases based on the LiverMetSurvey with patients submitted to resection of two or more colorectal liver metastases associated with irinotecan and/or oxaliplatin-based chemotherapy before liver surgery. The authors analyzed 787 patients: 729 submitted on resection of the colorectal carcinoma, and subsequent resection of colorectal hepatic metastases all (classical approach) and 58 patients submitted on reverse strategy, which consisted of colorectal hepatic metastases directed systemic chemotherapy, resection of all hepatic metastases, and the resection of the colorectal carcinoma with neoadjuvant radiotherapy for rectal cancer. Overall survival and disease-free survival at 5 years were similar in both groups of patients.

In a systematic review about the liver-first strategy, Jegatheeswaran *et al.*<sup>[6]</sup> evaluated 90 patients. They reported that disease progression during the procedure period occurred in 23 (19%) patients. de Rosa *et al.*<sup>[11]</sup> reported the outcomes of 82 patients with synchronous colorectal hepatic metastases after the liver-first strategy. The authors related low global morbidity and mortality rates, with a relapse rate from 25% to 70%

and an overall 5-year survival rate from 31% to 41%.

Lam *et al.*<sup>[7]</sup> reported a systematic review of the liver-first strategy in patients with colorectal carcinoma and synchronous colorectal hepatic metastases. One hundred and twelve (93%) patients underwent hepatic resection of colorectal liver metastases. Eighty-nine (74%) of the initial 121 patients underwent colorectal cancer resection. They observed a post-operative morbidity of 20% and a mortality of 1% after the hepatic resection. Moreover, they related postoperative morbidity and mortality after colorectal cancer resection of 50% and 6%, respectively. In this systematic review, the overall survival was 40 mo median (range 19 to 50 mo) with a recurrence rate of 52%.

Kelly *et al.*<sup>[22]</sup> described the network meta-analysis review comparing classical, combined, and liver-first approaches. These authors included 18 studies with 3605 patients in this review. Network meta-analysis and pair-wise meta-analysis of the 5-year overall survival showed no significant differences between the three surgical strategies: combined vs colorectal-first, liver-first vs colorectal-first, liver-first vs combined. In addition, network meta-analysis of the perioperative mortality among the three strategies was not significant. In a systematic review, Lykoudis *et al.*<sup>[2]</sup> suggested that the three surgical strategies have similar results.

Despite the relatively large number of published studies on surgical strategies to synchronous colorectal hepatic metastases, there are no randomized controlled trials. The greater part of published studies is observational, usually retrospective, or non-randomized comparative studies. The identification of subgroups that could benefit from a specific strategy is a cornerstone, because outcomes are equivalent in the different approaches in the treatment of synchronous colorectal hepatic metastases<sup>[23-27]</sup>.

Although the protocols used in the different studies are comparable, the liver-first strategy for patients with synchronous colorectal hepatic metastases is related with different survival results<sup>[6]</sup>. Furthermore, there is a necessity for a randomized clinical trial comparing different approaches. Factors previously considered contraindications for liver resection, such as number of metastases, synchronous metastases, and even the presence of extrahepatic disease, must not prevent the patient from having the opportunity of being treated with curative intention<sup>[16,28]</sup>. Indeed, nowadays it is accepted that even in the presence of poor prognostic factors, the possibility of long-standing survival and cure can be reached for patients with synchronous colorectal hepatic metastases<sup>[9,29,30]</sup>.

The liver-first approach has been demonstrated to be safe and successful and can be an alternative in patients with locally advanced colorectal carcinoma and synchronous hepatic metastases. This approach may allow a negligible number of patients to be submitted to curative resections for the synchronous colorectal hepatic metastases and may help avoid unnecessary



surgeries in patients with incurable metastatic disease.

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