

Treatment strategies for colorectal carcinoma with synchronous liver metastases: Which way to go?

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Abstract

AIM: To offer an up-to-date review of all available

treatment strategies for patients with synchronous colorectal liver metastases (CLM).

METHODS: A comprehensive literature search was performed to identify articles related to the management of patients with synchronous CLM. A search of the electronic databases PubMed, MEDLINE, and Google Scholar was conducted in September 2014. The following search terms were used: synchronous colorectal liver metastases, surgery, stage IV colorectal cancer, liver-first approach, and up-front hepatectomy. These terms were employed in various combinations to maximize the search. Only articles written in English were included. Particular attention was devoted to studies and review articles that were published within the last six years (2009-2014). Additional searches of the cited references from primary articles were performed to further improve the review. The full texts of all relevant articles were accessed by two independent reviewers.

RESULTS: Poor long-term outcomes of patients with synchronous CLM managed by a traditional treatment strategy have led to questions about the timing and sequence of possible therapeutic interventions. Thus, alternative paradigms called reverse strategies have been proposed. Presently, there are four treatment strategies available: (1) primary first approach (or traditional approach) comprises resection of the primary colorectal tumor followed by chemotherapy; subsequent liver resection is performed 3-6 mo after colorectal resection (provided that CLM are still resectable); (2) simultaneous resection of the primary colorectal tumor and CLM during a single operation presents intriguing options for a highly select group of patients, which can be associated with significant postoperative morbidity; (3) liver-first (or chemotherapy-first) approach comprises preoperative chemotherapy (3-6 cycles) followed by liver resection, adjuvant chemotherapy, and resection of the primary colorectal tumor (it is best suited for patients with

asymptomatic primary tumors and initially unresectable or marginally resectable CLM); and (4) up-front hepatectomy (or “true” liver-first approach) includes liver resection followed by adjuvant chemotherapy, colorectal resection, and adjuvant chemotherapy (strategy can be offered to patients with asymptomatic primary tumors and initially resectable CLM).

CONCLUSION: None of the aforementioned strategies appears inferior. It is necessary to establish individual treatment plans in multidisciplinary team meetings through careful appraisal of all strategies.

Key words: Colorectal cancer; Liver-first approach; Reverse strategy; Simultaneous resection; Up-front hepatectomy

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Core tip: There are four treatment strategies available for synchronous liver metastases of colorectal carcinoma (CLM): (1) primary first approach comprises resection of the primary colorectal tumor followed by chemotherapy and liver resection; (2) simultaneous resection of liver and colorectal primary tumor; (3) liver-first (or chemotherapy-first) approach comprises preoperative chemotherapy, liver resection, adjuvant chemotherapy, and resection of the primary colorectal tumor (best for asymptomatic primary tumors and initially unresectable or marginally resectable CLM); and (4) up-front hepatectomy (or “true” liver-first approach) includes liver resection followed by adjuvant chemotherapy and colorectal resection (for asymptomatic primary tumors and initially resectable CLM).

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INTRODUCTION

The liver is the most common site of colorectal cancer metastases. At the time of diagnosis, approximately 25% of patients have synchronous colorectal liver metastases (CLM)^[1]. These patients are thought to have less favorable cancer biology, and are less likely to become long-term survivors compared to patients with metachronous CLM^[2]. The endeavor to improve outcomes of patients with synchronous CLM led to questions about the timing and sequence of possible therapeutic interventions^[3,4]. Several alternative treatment strategies have been proposed, such as simultaneous resection, the liver-first approach, and an up-front hepatectomy approach.

A search of the scientific literature shows that

there is currently no complex review available that summarizes the pros and cons of all four possible treatment strategies with respect to the management of patients with synchronous CLM. Moreover, authors usually do not clearly distinguish the up-front hepatectomy from the liver-first approach, though several principal distinctions between both strategies are evident.

The aim of the present paper is to offer an up-to-date review of all four available strategies for the treatment of patients with colorectal cancer and synchronous CLM. This article summarizes the current data concerning the rationale, benefits, and potential drawbacks of the particular strategies (primary-first, simultaneous approach, liver-first approach, and up-front hepatectomy).

MATERIALS AND METHODS

A comprehensive literature search was performed to identify articles related to therapeutic strategies for patients with colorectal cancer and simultaneous CLM. The search combined the following terms: synchronous colorectal liver metastases, surgery, stage IV colorectal cancer, liver-first approach, and up-front hepatectomy. Sources included MEDLINE, PubMed, and Google Scholar databases. Particular attention was devoted to studies and review articles that were published within the last six years (2009-2014).

RESULTS

Current treatment strategies

Although there have been significant improvements in the management of stage IV colorectal cancer in the last few decades, only radical surgical resection of both the primary tumor and CLM can offer long-term survival for patients presenting with CLM^[1,5,6]. Surgery is performed with the intent to achieve minimal intraoperative blood loss and low postoperative morbidity and mortality, because these factors have been shown to compromise not only short-term results, but also long-term outcomes^[7-9].

The management of patients with colorectal cancer and synchronous CLM is multimodal and comprises surgery, chemotherapy, and radiotherapy. Multimodality and the need for surgery at the two different sites (colorectal primary tumor and CLM) enable various sequences and timing for therapeutic modalities. Poor long-term outcomes of the traditional treatment strategy (primary-first approach) led to the proposal of alternative paradigms for patient management, called reverse strategies. Presently, four therapeutic strategies are available: the primary-first approach, simultaneous resection, a liver-first approach, and up-front hepatectomy.

Primary-first approach

The primary first approach, often referred to as

the “classical” or “traditional” approach, includes resection of the primary colorectal tumor followed by chemotherapy (plus radiotherapy for rectal primaries). Liver resection is performed 3-6 mo after colorectal resection (provided CLM are still resectable).

The rationale for the primary-first approach is twofold: colorectal primary tumors are thought to be a likely source of subsequent metastases and also the source of symptoms. The main advantage of the strategy is that it avoids potential complications from the primary tumor and decreases the risk of potential progression of the primary tumor during liver surgery or initial chemotherapy^[3,4]. Conversely, the main drawback of the primary-first approach is the progression of CLM beyond resectability during the primary tumor resection (especially in patients with postoperative complications after colorectal resection)^[3].

Because of frequent CLM progression beyond resectability, only few patients benefit from the traditional strategy. In 2012, analysis based on the LiverMetSurvey revealed that < 30% of patients underwent the complete treatment plan of primary-first strategy (from primary tumor resection to liver resection)^[10]. Conversely, reverse strategy enables completion of the treatment plan in almost 80% of patients^[3,11].

Simultaneous resection

Simultaneous resection of colorectal primary and synchronous CLM presents an intriguing option for many surgeons. The simultaneous resection can be employed with or without preoperative chemotherapy; adjuvant chemotherapy is applied after the surgery (plus radiotherapy for rectal primaries).

The strategy of simultaneous resection had been proposed in the effort to avoid delaying surgical resection of metastatic liver disease^[12]. The main advantage of this strategy is the removal of all macroscopic cancer during a single operation followed by systemic chemotherapy with minimal delay. Conversely, the main disadvantage of this strategy is that it is associated with significantly increased postoperative morbidity and possibly mortality^[12-14]. Increased risk of infectious liver complications (due to bacterial contamination from intestinal resection), increased risk of anastomotic complications (due to impaired liver function), and limited extent of feasible liver resection have been reported^[13,14]. There is also some evidence that simultaneous resection may have a negative effect on progression-free survival^[15].

Several studies have demonstrated that reasonable postoperative morbidity and mortality can be achieved if colorectal resection is combined with minor hepatectomy. In recent series of simultaneous resections, postoperative morbidity in the range of 5% to 48% was reported when minor hepatectomies were performed, and from 33% to 55% when major

hepatectomies were performed simultaneously with colorectal resection^[13-16]. Perioperative mortality of \leq 5% was noted, but a higher number can be expected when major hepatectomies are performed.

Simultaneous resection is best suited for highly select patients; many authors recommend considering simultaneous resection only if one of the intended surgical resections is minor. It is reasonable to perform rectal resection simultaneously only with minor hepatectomy (< 3 segments), or to perform major liver resection (\geq 3 segments) simultaneously with (right-sided) colon resection^[14,16,17]. However, major hepatectomies should be pursued only in very carefully selected patients by an experienced hepatobiliary team. A patient's general health status and comorbidities also have to be considered.

Liver-first (chemotherapy-first) approach

The reverse treatment strategy was first introduced by Mentha *et al.*^[3] in 2008. The liver first approach comprises initial preoperative chemotherapy (3-6 cycles) followed by liver resection and subsequent resection of the primary colorectal tumor. Chemotherapy (possibly with radiotherapy for rectal primaries) is administered between colorectal and liver resection.

The introduction of modern potent cytotoxic drugs (oxaliplatin-based and irinotecan-based) in combination with targeted agents (directed against epidermal growth factor receptor or vascular endothelial growth factor) resulted in improved tumor response rates (up to 60% of tumors) and prolonged survival of patients with colorectal cancer^[16,18]. Effectiveness of modern chemotherapy regimens (in adjuvant settings) led to the application of chemotherapy, also in neoadjuvant settings, for patients with colorectal carcinoma and synchronous CLM. It is believed that the prognosis of patients with stage IV colorectal cancer is determined mainly by the curability of CLM and not by the primary tumor or its potential complications^[3,4,14].

As a matter of fact, preoperative chemotherapy is the initial treatment modality during the liver-first approach, which is why the term “chemotherapy-first” is suggested to be more accurate for this strategy^[17]. The expression “chemotherapy-first” emphasizes the main rationale of the reverse strategy, which is to provide early systemic treatment to patients with stage IV colorectal cancer.

Benefits of the chemotherapy-first approach are: (1) early application of systemic treatment; (2) lowering the risk of CLM progression; and (3) the possibility of CLM downsizing or converting unresectable CLM to resectable.

As stage IV colorectal cancer presents as systemic disease, it seems reasonable to offer systemic chemotherapy as soon as possible after the diagnosis is established. Moreover, patients with synchronous CLM are supposed to have more aggressive tumors with less favorable cancer biology. By using preoperative

chemotherapy administration, effective systemic treatment is not delayed by colorectal surgery and its possible postoperative complications^[3,4,12].

The risk of CLM progression is significantly lower when the chemotherapy-first approach is employed, compared to the traditional strategy^[3,12,17]. Furthermore, preoperative chemotherapy offers the opportunity for initial disease control and CLM downsizing. Liver metastasis shrinkage after preoperative chemotherapy enables surgeons to perform more conservative liver surgery more often and to achieve R0 resection in more patients. Preoperative chemotherapy application also allows for the assessment of tumor response to chemotherapy. In theory, another possible advantage of preoperative chemotherapy is the elimination of micrometastatic disease and the eradication of dormant cancer cells^[17,19].

Fears of complications arising from unresected primary tumors (such as bleeding, obstruction, or perforation) in the course of initial chemotherapy and liver resection represent principal arguments against the reverse strategy. Nevertheless, primary tumor complications in patients with stage IV colorectal cancer are very rare according to several studies. The vast majority (> 90%) of patients with initially asymptomatic colorectal primary tumors and synchronous CLM who receive modern chemotherapy regimens never require surgical intervention because of primary tumor-related complications^[20]. Besides, Scheer *et al*^[21] demonstrated that primary tumor resection provided only minimal palliative benefit to these patients. This is why systemic chemotherapy regimens are advocated as initial treatment modalities for asymptomatic primary tumors with synchronous CLM. If the tumor does not respond to preoperative chemotherapy in patients with initially unresectable CLM, useless colorectal surgery can be avoided^[14,19].

Recently, an international multidisciplinary panel generated a consensus concerning the reverse strategy^[22]. The most important recommendations were as follows. First, the reverse strategy should be considered for all patients with predominant hepatic disease and asymptomatic primary tumor. Second, preoperative chemotherapy should be offered to patients with asymptomatic colorectal cancer and synchronous CLM (resectable, marginally resectable, and unresectable). Third, at least four courses of first-line chemotherapy should be given. Fourth, the use of doublet or triplex chemotherapy regimens combined with targeted therapy is recommended. Fifth, chemotherapy duration should be as short as possible and liver resection should be performed as soon as technically possible. Lastly, tumor response and patient reassessment should be performed 2 mo after starting chemotherapy.

In the last decade, many (> 400) papers focusing on liver-first strategy evaluation have been published. However, according to several recent systematic reviews^[4,17,23], scientific evidence for the justification

of the liver-first approach is very limited. For instance, there are no randomized controlled trials, and many papers have very limited scientific validity (such as reviews, case reports, letters, editorials, and abstracts). There are only four cohort retrospective studies reporting outcomes of a total of 121 patients with colorectal cancer and synchronous CLM managed by the liver-first approach^[4,17,23]. In these studies, postoperative morbidity was in the range of 11% to 37%; postoperative mortality was < 4%. Disease recurrence rates were 25%-70%; three-year survival rates varied in the range of 41% to 79%, and five-year survival rates were 31%-39%^[3,12,24,25]. The majority (66%-81%) of patients completed the entire liver-first strategy treatment plan (preoperative chemotherapy to colorectal resection). This is in contrast to < 30% of patients completing the primary-first strategy^[3,10,12,24,25].

The reverse strategy is best suited for patients with an asymptomatic primary tumors and advanced hepatic metastases^[4,16,17,22]. There is general agreement that patients with unresectable or borderline resectable CLM should be offered aggressive doublet or triplex chemotherapy regimen combined with targeted therapy as the initial treatment modality, followed by liver resection, if technically amenable. The optimal initial treatment strategy for patients with initially resectable synchronous CLM is debatable.

Up-front hepatectomy

Surgical resection represents the only treatment modality that can offer long-term survival to patients with synchronous resectable CLM. The limited evidence for preoperative (neoadjuvant) chemotherapy employment led to the proposal of an up-front hepatectomy strategy, which is in fact the "true" liver-first approach. The common sequence of up-front hepatectomy strategy comprises liver resection, adjuvant chemotherapy, colorectal resection, and adjuvant chemotherapy. The strategy was originally proposed by Grundmann *et al*^[26] in 2008 for patients with asymptomatic colorectal carcinoma and synchronous resectable CLM.

There are several benefits to preoperative chemotherapy administration for the treatment of resectable synchronous CLM: testing tumor chemoresponsiveness, elimination of micrometastatic disease (in theory), and the possibility of tumor shrinkage enabling more conservative liver surgery in some cases; the benefits were discussed in detail in the previous section^[11,14,19].

The main drawbacks of preoperative chemotherapy include liver toxicity, missing lesions, and risk of tumor progression. Chemotherapy induces pathologic changes in the liver parenchyma, which are dependent on the number of chemotherapy cycles (such as steatosis, chemotherapy-associated steatohepatitis, and sinusoidal obstruction syndrome). In addition, chemotherapy increases the risk of systemic toxicity, postoperative bleeding, and infection (by inducing neutropenia)^[19,27,28]. A recent meta-analysis demonstrated a high variability in the frequency of

chemotherapy-induced hepatotoxicity^[18]. Hepatic steatosis was detected after regimens with 5-fluorouracil in 6%-76% of patients, steatohepatitis was observed after irinotecan-based regimens in 3%-8% of patients, and sinusoidal obstruction syndrome was noted after oxaliplatin-based regimens in 5%-51% of patients^[18]. Chemotherapy-induced liver injury results in worse postoperative outcomes of subsequent liver resections. Increased postoperative morbidity has been demonstrated by several studies, though no impact on postoperative mortality was observed^[29-33]. Especially after extended surgical resection performance, preoperative chemotherapy may contribute to the development of liver failure.

CLM that respond well to preoperative chemotherapy may no longer be visible on CT or during surgery. Tumor disappearance was noted in 2%-36% of patients after preoperative chemotherapy^[28]. Problematic identification of invisible lesions during surgery is associated with a higher risk of incomplete (non-radical) resection and disease early recurrence^[34]. Furthermore, lesion disappearance (on CT scans) does not mean complete pathologic response. Benoist *et al.*^[19] demonstrated that > 80% of invisible metastases (invisible lesions on CT scans after chemotherapy) contained viable tumor cells at the time of resection. When the "watch and see" policy is applied (after disappearance on imaging techniques), local recurrence was reported in 38%-74% of patients^[34,35].

The risk of tumor progression in the course of preoperative chemotherapy is another drawback of its routine use in the management of patients with initially resectable CLM. According to recent systematic reviews and meta-analyses, CLM progression (changing from resectable to unresectable disease) was observed in 7%-37% of patients undergoing preoperative chemotherapy. However, some authors suggest that disease progression during preoperative chemotherapy is a consequence of highly aggressive tumor biology and may in fact prevent unnecessary postoperative surgical morbidity and mortality^[36,37].

The European Colorectal Metastases Treatment Group in its Multidisciplinary International Consensus recommends preoperative chemotherapy for patients with initially resectable synchronous CLM^[22]. These recommendations are based mainly on the results of the EORTC 40983 trial, which are a slightly misleading. The EORTC trial evaluated outcomes of 364 patients with resectable CLM divided into two groups: (1) patients managed with three cycles of preoperative FOLFOX, liver resection, and three cycles of postoperative FOLFOX; and (2) patients undergoing liver resection alone without chemotherapy. In other words, the EORTC trial unfortunately did not compare the effect of preoperative chemotherapy (patients in the FOLFOX group) with patients undergoing liver resection plus adjuvant chemotherapy (the FOLFOX group was only compared with patients undergoing surgery alone). In the FOLFOX group, there was

significantly longer progression-free survival at three years (35.4% vs 28.1%), but overall survival was not increased. Moreover, higher numbers of postoperative complications were recorded in the FOLFOX group compared to patients undergoing surgery alone (25% vs 16%)^[29].

In an effort to overcome the aforementioned handicap of the EORTC trial, several studies have been executed. For instance, Adam *et al.*^[38] compared 169 patients treated with preoperative chemotherapy with a retrospective group of 1302 patients who underwent surgery and adjuvant chemotherapy; postoperative complications were more frequent in the neoadjuvant group (37% vs 24%). No impact on survival or disease-free interval was found in the neoadjuvant group, but improved survival was found in patients treated with surgery and adjuvant chemotherapy. Reddy *et al.*^[39] published very similar results in favor of adjuvant chemotherapy. Additional studies (with several hundreds of patients) also showed no significant differences between the outcomes of patients receiving preoperative chemotherapy compared to those without preoperative chemotherapy^[40-42].

The aforementioned pros and cons of preoperative chemotherapy administration make it difficult to determine which strategy is the best option for patients with synchronous resectable CLM. The need for prospective randomized trials of neoadjuvant vs adjuvant chemotherapy is emphasized by all authors. However, recent systematic reviews and meta-analyses focusing on the preoperative chemotherapy evaluation concluded that "routine use of neoadjuvant chemotherapy for patients with clearly resectable lesions is not recommended due to a lack of benefit on survival"^[18]. Many authors share the same conviction and recommend performing up-front hepatectomy in patients with synchronous initially resectable CLM^[11,14,19,27,40,42-44].

DISCUSSION

Proposal of a decision strategy

With regard to current published data and according to all aforementioned benefits and drawbacks of particular strategies, we propose the following decision treatment scheme for patients with synchronous CLM.

Patients with colorectal cancer and synchronous CLM should undergo careful clinical examination focused on determining a patient's performance status, comorbidities, and tumor stage. It is necessary to establish an individual treatment plan for each patient in a multidisciplinary team meeting that includes experienced colorectal and hepatobiliary surgeons.

The traditional strategy (primary-first approach) is best suited for patients with symptomatic primary tumors and synchronous CLM. Assessment of the simultaneous approach execution should be conducted in patients with limited CLM extent, especially when

one of the intended surgical resections is minor (minor hepatectomy or right-sided colon resection). Patients with unresectable or marginally resectable CLM should be offered the chemotherapy-first approach. The administration of a duplex or triplex chemotherapy regimen combined with targeted therapy is recommended. Evaluation of tumor response and patient reassessment is advised after two months, followed by liver resection if technically amendable. Patients with initially resectable CLM should be offered up-front hepatectomy as a first-line treatment strategy.

The management of patients with colorectal cancer and synchronous CLM is complex and multiple factors must be considered (such as location and extent of primary tumor and CLM, presence of symptoms, patient's general health status, and comorbidities). None of the aforementioned treatment strategies (primary-first, simultaneous resection, chemotherapy-first, or up-front hepatectomy) appears inferior to the others^[23]. However, the optimal treatment strategy is still unclear because of limited available evidence^[4,17,23]. It is necessary to establish an individual treatment plan for each patient with synchronous CLM in multidisciplinary team meetings through careful appraisal of all strategies with the aim of avoiding unnecessary surgical complications and to achieve long-term cures.

COMMENTS

Background

Although there have been significant improvements in the management of stage IV colorectal cancer in the last few decades, only radical surgical resection of both the primary tumor and liver metastases can offer long-term survival. The management of patients with colorectal cancer and synchronous colorectal liver metastases (CLM) is multimodal, comprising surgery, chemotherapy, and radiotherapy. Multimodality and the need for surgery at the two different sites (primary colorectal tumor and CLM) enable various sequences and timing for therapeutic modalities.

Research frontiers

A search of the scientific literature shows there is currently no complex review available that summarizes the pros and cons of all four possible treatment strategies with respect to the management of patients with synchronous CLM. Moreover, authors usually do not clearly distinguish the up-front hepatectomy from the liver-first approach, although several principal distinctions between both strategies are evident.

Innovations and breakthroughs

In this paper, the authors offer a comprehensive review of all four different therapeutic strategies that are currently available for patients with synchronous CLM: primary-first approach, simultaneous resection, liver-first approach, and up-front hepatectomy. Authors summarize up-to-date data on the rationale, benefits, and potential drawbacks of the particular strategies. Based on the available published data, authors propose a decision scheme (between particular strategies) for patients with synchronous CLM.

Applications

The present review offers comprehensive insight into current treatment options available for patients with synchronous CLM. The proposed decision scheme may work as a helpful tool for multidisciplinary teams when establishing a treatment plan for particular patients.

Terminology

Primary-first approach comprises resection of colorectal primary followed by chemotherapy and subsequent liver resection. Simultaneous resection is resection of the primary colorectal tumor and CLM during a single

operation. Liver-first (or chemotherapy-first) approach comprises preoperative chemotherapy (3-6 cycles) followed by liver resection, adjuvant chemotherapy, and resection of the primary colorectal tumor. Up-front hepatectomy (or "true" liver-first approach) includes liver resection followed by adjuvant chemotherapy, colorectal resection, and adjuvant chemotherapy.

Peer-review

The topic of this review is important, and the publication is well written and readable. The discussion is well organized as findings correspond with the literature.

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