



Surgical approach to synchronous colorectal liver metastases: staged, combined, or reverse strategy

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Abstract: An increasing number of patients with colorectal cancer (CRC) are presenting with synchronous disease to the liver. The optimal surgical approach for this complex patient group is controversial, but ultimately depends on individual patient characteristics and institutional practices. Surgical strategies include the traditional staged approach, a combined colorectal and liver resection, or a liver-first reverse approach. In this review, the authors will provide an overview of each strategy, including case examples demonstrating the benefits of the more recently described liver-first approach, while arguing for individualized planning and multidisciplinary discussion for every patient.

Keywords: Synchronous colorectal liver metastases (SCRLM); liver-first reverse approach; multidisciplinary discussion

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Introduction

Colorectal cancer (CRC) is the third most common malignancy worldwide and as of 2018, it is the second leading cause of cancer death (1). The liver is the most common site of metastatic disease, with an estimated 15–25% of CRC patients presenting with synchronous colorectal liver metastases (SCRLM) (2,3). It is important to distinguish between synchronous disease, or liver metastases diagnosed prior to or at the time of diagnosis of CRC, and metachronous disease, or liver metastases diagnosed after resection of the primary tumor, given that recent literature suggests the incidence of SCRLM is increasing compared to metachronous (4-6). This is likely due to improvements in imaging technology allowing for earlier diagnosis. The definition of synchronous disease varies in the surgical literature in regards to the timing of liver disease diagnosis in relationship to the diagnosis of the primary tumor, ranging from 0 all the way to

12 months. In agreement with the international multidisciplinary consensus published in 2015, the authors suggest standardized definitions must be adopted. For the purpose of this paper, we will refer to patients presenting with imaging indicating a presence of both colorectal and liver disease (in the absence of other metastases) (6). Currently, synchronous disease is associated with a less favorable prognosis than metachronous disease (6,7).

For patients with colorectal liver metastases (CRLM), surgical resection is essential for long-term survival (8,9) and results in 5-year overall survival (OS) rates as high as 58% (9,10). However, the majority of patients who present with SCRLM have initially unresectable disease (6). Preoperative chemotherapy is used to treat the advanced stage, prevent further progression, and to improve patient selection for liver-directed surgical therapy. Thus, a thorough and multidisciplinary approach that includes early surgical consultation is imperative (6,11). In this review, the authors will discuss the treatment strategies for patients

presenting with SCRLM. These include: the traditional staged approach, the simultaneous combined approach, or the liver-first reverse approach.

A historical review: traditional staged approach to SCRLM

The traditional treatment algorithm for SCRLM is a staged approach that includes primary tumor resection, followed by systemic chemotherapy then resection of liver metastases for patients without progression of disease. The benefits of this approach are thought to include ensured treatment of the primary tumor (both to reduce the risk of new metastatic disease and to avoid the development of complications such as obstruction, perforation, or bleeding) and selection of patients with optimal tumor biology (often via extended pre-hepatectomy chemotherapy). Proponents of the traditional approach may also argue that the morbidity of simultaneous colorectal and liver resection is prohibitive (12).

A major concern with the traditional staged approach is that it ignores the fact that prognosis is driven by the metastatic disease. By definition, patients with SCRLM have systemic disease and by delaying both chemotherapy and liver resection, the risk of unresectability only increases. Should a patient experience a complication after resection of the primary tumor, such as anastomotic leak or wound infection, significant delays in treatment of the systemic disease can be incurred. Additional counterarguments are made against the need for upfront colorectal tumor treatment to avoid symptoms of obstruction, perforation, or bleeding. Retrospective studies comparing asymptomatic patients with SCRLM who did or did not undergo primary tumor resection have shown that the risk of developing such symptoms is negligible (13-16). A prospective, multicenter study using preoperative mFOLFOX6 with bevacizumab for patients with asymptomatic colon cancer and unresectable metastatic disease demonstrated acceptable rates of primary tumor-related complications (14%) (17). Further, as many as 30% of patients who do undergo elective colorectal resection will have a subsequent complication (15,18), suggesting that upfront resection of the primary tumor is more likely to cause complications than prevent them. Studies comparing groups with similar metastatic burden have found no difference in median survival based on patients who do or do not undergo colorectal resection for CRC in the setting of unresectable metastatic disease (15,18).

An additional argument against the traditional approach lies in the advantage of early chemotherapy. Along with its survival benefits, early treatment with chemotherapy can translate to increased rates of resectability for unresectable CRLM. In 1996, Bismuth *et al.* reported a 16% conversion rate from unresectable to resectable metastatic liver disease with survival rates of 40% at 5 years (19). Since that time, experts agree that the use of preoperative chemotherapy is indicated for unresectable CRLM, leading to complete resection in 15–30% of patients (12,20). Thus, particularly in the setting of unresectable liver disease, delay in its initiation should be avoided. Recommended regimens include those used for advanced CRC, such as triplet therapy or doublets with bevacizumab or anti-EGFR therapy (21-23). While the issue of preoperative chemotherapy for initially resectable CRLM is more controversial, it is still recommended by most for synchronous disease (6). Results of a randomized controlled trial comparing perioperative FOLFOX (6 cycles before and 6 cycles after surgery) to surgery-only in initially resectable CRLM found improved progression-free survival with perioperative chemotherapy, although no significant difference in OS was shown with longer-term follow-up (24,25). These results do not directly translate to the SCRLM population, given only one-third of the patients presented with synchronous disease. However, given the high rates of recurrence for metastatic CRLM, there is rationale for perioperative chemotherapy in this disease, with mixed results shown in the literature (26-28). Based on the National Comprehensive Cancer Network (NCCN) guidelines, a total of six months perioperative treatment is preferred (29). Prolonged administration of chemotherapy should be avoided given the risk of chemotherapy-associated liver injury (30-32).

Combined approach to SCRLM

The combined approach to SCRLM involves complete surgical resection of liver metastases at the time of primary colorectal resection. This is most frequently preceded by preoperative systemic chemotherapy. Obvious benefits of the combined approach are efficient and early treatment of all disease with only one operation requiring general anesthesia. Most typically, patients selected for simultaneous resection have tumors that are easier to approach operatively: smaller or fewer liver tumors and right-sided colonic tumors. Aside from strict patient selection, downsides to approaching both the primary colorectal and liver disease in one operation are the

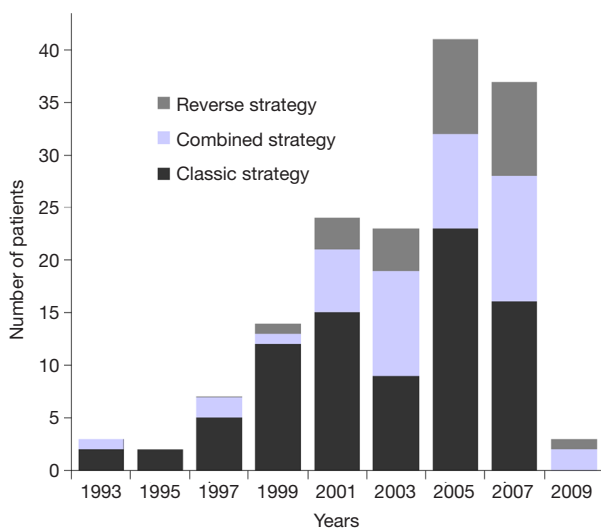


Figure 1 Patients operated on for synchronous liver metastases at MD Anderson Cancer Center over time. With permission from Brouquet *et al.* *J Am Coll Surg*, 2010.

prolonged operative time and potentially increased risk of perioperative morbidity. Particular attention to bleeding risk and intestinal perfusion preoperatively is essential in order to determine what types of cases can be performed simultaneously. In patients initially scheduled for combined resection, we make the intraoperative decision not to proceed with resection of the primary in cases of unanticipated difficult or protracted liver resection.

A number of early surgical series reported outcomes after using a combined approach to SCRLM (33-36). Some authors reported higher operative morbidity and mortality associated with simultaneous resection, leading them to recommend the traditional staged approach (33,34,37). In a study by Martin *et al.*, 134 patients who underwent combined resection of CRLM and a primary colorectal tumor were compared to 106 patients who underwent staged resections. Patients with right-sided colon tumors, and smaller and fewer liver metastases undergoing less extensive liver resection, were more likely to undergo a simultaneous approach. The combined group had fewer complications (49% *vs.* 67%, $P < 0.003$) and had a shorter median hospital length of stay (10 *vs.* 18 days, $P = 0.001$), with similarly low mortality rates (38). A large multicenter study by Reddy *et al.* included 327 patients requiring major liver resection for SCRLM. Patients who underwent simultaneous colorectal resection and major hepatectomy ($n = 36$) had higher rates of severe morbidity (36% *vs.* 15%,

$P < 0.05$) and mortality (8% *vs.* 1%, $P < 0.05$) compared to the staged approach ($n = 291$) (39). Therefore, the authors recommend that caution be exercised when considering a combined approach to SCRLM for cases requiring a major liver resection.

Liver-first approach to SCRLM

More recently, the liver-first or reverse strategy has been proposed to treat SCRLM. In this treatment algorithm, preoperative chemotherapy is administered prior to hepatectomy and followed by resection of the colorectal primary at a later date. Initially proposed in 2006, Mentha *et al.* described the feasibility of this approach and impressive survival outcomes in 20 patients with advanced disease (40). The approach proved particularly well-suited for rectal cancers, with 7/8 patients with rectal tumors receiving a full course of pelvic radiotherapy shortly after hepatectomy but prior to rectal surgery. A notable advantage of this strategy, as well as the combined strategy, is that the delay in addressing the systemic disease that drives OS is avoided. Whether this is with initial locoregional therapy of a primary rectal tumor or surgical resection, both can result in significant delays in initiation of systemic chemotherapy. Critics of the reverse approach argue that failure to treat the primary colorectal tumor will lead to complications such as bleeding, obstruction, or perforation. However, as previously mentioned, rates of primary tumor-related complications in asymptomatic patients treated with chemotherapy are quite low (13-16).

Brouquet *et al.* compared the three strategies for managing SCRLM, analyzing 72 staged, 43 simultaneous, and 27 reverse approach cases (3). In this study out of a single, large comprehensive cancer center, not only did the number of patients undergoing treatment for SCRLM increase over time, but there was also a shift in the preferred surgical strategy, with more patients undergoing combined or reverse approaches in more recent years (*Figure 1*). Patients who underwent the combined approach were less likely to receive six or more cycles of preoperative chemotherapy ($P < 0.001$). Those who underwent the reverse approach were much more likely to receive preoperative bevacizumab (78%) compared to the staged and combined groups (31%; $P < 0.001$). Patients treated with the reverse approach were also more likely to have a rectal primary tumor and a higher number of CRLMs resected (median of 4). Among 41 patients intended for the reverse strategy, 14 (34%) did not have resection of the primary tumor for

reasons such as: progression of metastatic disease (64%), complete response of a rectal primary tumor (14%), and postoperative death after liver resection, progression of primary tumor, or loss of follow-up in one patient each. Two of the 41 patients (5%) had symptoms from their primary tumor requiring colostomy. The mortality and cumulative morbidity rates between each of the three strategies were comparable. Survival rates also did not significantly differ. Multivariable analysis showed that greater tumor size (>3 cm) and cumulative postoperative morbidity were independently associated with survival.

Recommendations for approaching SCRLM

Preoperative considerations & strategies for complex cases

Patients with SCRLM are not always candidates for upfront surgical resection given the overall burden of disease (6). As previously mentioned, preoperative chemotherapy can improve resectability in many cases (12,19,20). Imaging characteristics such as tumor size [based on traditional Response Evaluation Criteria in Solid Tumors (RECIST) criteria] and tumor morphology should be used to determine response to preoperative therapy (6). Morphologic response of tumor attenuation, degree of enhancement, and borders on computed tomography (CT) imaging has been shown to correlate with pathologic response and survival outcomes in patients receiving preoperative chemotherapy regimens containing bevacizumab (41). Follow-up studies suggest that morphologic response may be superior to RECIST criteria for assessing pathologic tumor response in CRLM regardless of the preoperative regimen (42,43). In addition to tumor-specific characteristics, it is also important to assess for signs of steatosis and portal hypertension on preoperative imaging. Approximately 10% of patients receiving preoperative chemotherapy for CRLM develop sinusoidal obstruction syndrome and up to 20% develop steatosis (30,44). Liver injury varies depending on the type and duration of chemotherapy (45).

In cases of insufficient future liver remnant (FLR), strategies such as portal vein embolization (PVE) can be effective. During PVE, the portal venous system draining the affected liver (planned for resection) is embolized in order to induce hypertrophy of the non-embolized liver and reduce the risk of post-hepatectomy liver failure (45). The two-stage approach to hepatectomy can be used, often in conjunction with PVE, as a sequential treatment strategy in cases of bilateral CRLM. Currently, the most commonly

employed strategy is as follows: first-stage liver resection intended to “clear” the less-involved hemi-liver, followed by PVE within 2–5 weeks of the first stage, and second stage hepatectomy after another 5–8 weeks (46). In some cases, combined colorectal tumor resection can be performed at the time of one of the two liver resections. This two-stage approach to CRLM has been shown to be safe and effective, with completion rates ranging from 60–90% (46–50). Associated liver partition and portal vein ligation for staged hepatectomy (ALPPS) is an additional strategy that has been used in setting of advanced bilateral CRLM. Currently there is no data evaluating the appropriate sequencing for the management of SCRLM in association with ALPPS.

Preoperative molecular and pathologic tumor assessment

While achieving a negative surgical margin should remain the goal of CRLM resection (with at least 1 mm clearance), recent investigations have emphasized the importance of pathologic response to preoperative therapy and molecular tumor biology (6). While complete pathologic response is rare, pathologic assessment for tumor response to preoperative chemotherapy is essential for guiding further therapy and understanding prognosis (51,52). In addition, RAS mutation has been shown to be associated with worse survival outcomes after resection of CRLM (53–55). A meta-analysis of studies analyzing the prognostic impact of KRAS by Brudevik *et al.* found a mutation rate of 28% and a negative association with OS (hazard ratio 2.24, 95% confidence interval: 1.76–2.85) (56). BRAF V600E mutation, although more rare, is also associated with poor OS (57–59). Tumor biology and pathologic assessment should be incorporated into multidisciplinary discussions whenever possible.

An individualized approach

Ultimately, comparing the staged, combined, and reverse strategies to SCRLM is based on retrospective surgical series with inherent selection bias as patients are chosen for each approach based on individual characteristics. Similarly, improvements in technology and perioperative care limit direct comparison of an open-incision staged approach performed ten years ago to a simultaneous, often minimally-invasive, approach to SCRLM today. Undoubtedly, the patients undergoing these operations will have differences in their presentation, tumor biology, and metastatic burden of disease. Institutions and disciplines also have varying opinions regarding best practices. Without a randomized

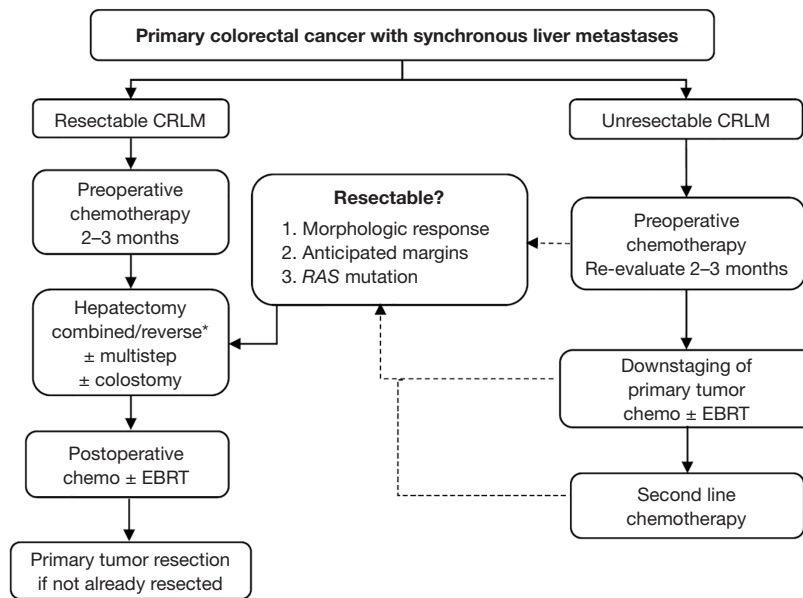


Figure 2 Structured approach to synchronous colorectal liver metastases (SCRLM). *, this is provided there is no obstruction as determined by preoperative colonoscopy as described in discussion section: “An Individualized Approach.” CRLM, colorectal liver metastases.

controlled trial, which would be impossible to perform given the large spectrum of patient presenting with SCRLM, the authors can only use experience and results of the published surgical literature to make recommendations. *Figure 2* shows a structured treatment algorithm used at our institution, which can be referenced when dealing with SCRLM. Importantly, an individualized approach must be used for every patient.

There are three major preoperative issues to consider when first evaluating a patient with SCRLM. First, the extent of surgery will have a significant impact on choosing the appropriate strategy. For example, an abdominoperineal resection for rectal cancer may be combined with a wedge resection of the liver, but it would not be appropriate to combine it with a right hepatectomy. Second, the wide spectrum of patients and variability in presentation mandate specific considerations. Patient-specific risk factors need to be weighed when considering a combined approach. A higher-risk combined operation (such as a right colectomy and right hepatectomy) may be undertaken, permitting the patient is low-risk without major comorbidities and a normal body habitus. As mentioned, close collaboration with all surgeons and anesthesiologists involved in the operation is essential to discuss the sequence of resection (colon or liver first), specific perioperative needs (such as low central venous pressure for liver resection), or changes

in the risk of the operation than may preclude a planned combined procedure. The authors recommend starting with liver resection and continuing with the colon or rectal resection pending there are no intraoperative factors (i.e., bleeding or hypotension) that change the overall risk of the operation. This individualized strategy can be modified up to the date of the operation or even intraoperatively. Third, the “symptoms” from the colorectal primary do not define the strategy, but rather specific primary tumor factors should be assessed. This includes whether or not the tumor is anatomically obstructive. The authors’ institutional practice is that the reverse approach is contraindicated in patients in whom an adult colonoscope cannot traverse the tumor. In this scenario, either resection of the primary or colostomy should be performed first. Patients with anemia should be managed with transfusion and chemotherapy rather than upfront surgical resection for “symptomatic” disease. In cases of tumor perforation, surgical therapy must be first priority. However, in most patients presenting with SCRLM, chemotherapy should be administered first.

We present two cases of SCRLM to demonstrate the use of this treatment algorithm, highlighting the utility of the liver-first strategy in patients with a complex presentation. The first case is a patient who presented with an asymptomatic primary tumor of the sigmoid colon and two metastatic liver lesions in segments 4/8 and 6, with

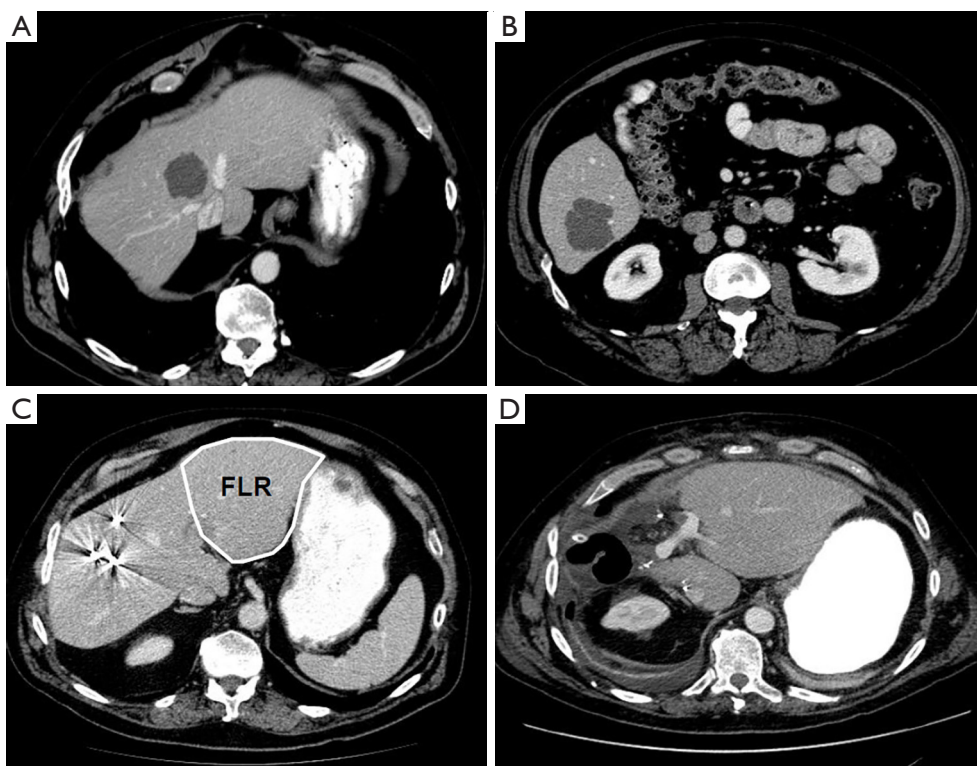


Figure 3 Computed tomography (CT) images from a patient with asymptomatic colon cancer and multiple synchronous liver metastases. (A,B) After preoperative chemotherapy with FOLFOX-6 + bevacizumab; (C) after portal vein embolization; (D) after extended right hepatectomy and prior to sigmoid colectomy.

the former encasing the middle hepatic vein (*Figure 3*). After multidisciplinary discussion, the patient received FOLFOX-6 with bevacizumab, which resulted in a type 1 morphologic response (sharp tumor-liver interface and resolution of the peripheral rim of enhancement) (41). The patient subsequently underwent right-sided PVE, which increased the FLR from 10% to 33% and allowed for an extended right hepatectomy to be safely performed. The patient underwent a sigmoid colectomy 7 weeks later. Here, using the reverse approach allowed for initial management of systemic disease with early preoperative chemotherapy and avoided delays in approaching the hepatic disease, while ensuring treatment of an asymptomatic primary tumor in a safe fashion.

The second case is a patient presenting with symptoms of obstruction from a primary rectal tumor and synchronous multiple, bilobar metastases (*Figure 4*). While some may argue this is a patient who should undergo a traditional staged approach, his treatment sequence included a combined first-stage left partial hepatectomy

and colostomy. He underwent PVE after 3 weeks and second-stage extended right hepatectomy. After receiving postoperative chemotherapy and external beam radiation therapy, proctectomy was performed. The patient is alive without recurrence 6 years later.

Conclusions

Patients presenting with CRC and synchronous disease of the liver are a complex group, given the high burden of disease and the variability in presentation. Therefore, the authors recommend a multidisciplinary discussion for all patients with SCRLM. The three recognized surgical strategies for SCRLM include the traditional staged approach, combined approach, and liver-first reverse approach. In recent years, the combined and reverse approaches are being used more often and the authors recommend the use of the traditional staged strategy only for those patients with a primary tumor causing obstruction. Most patients with SCRLM should initially be treated with

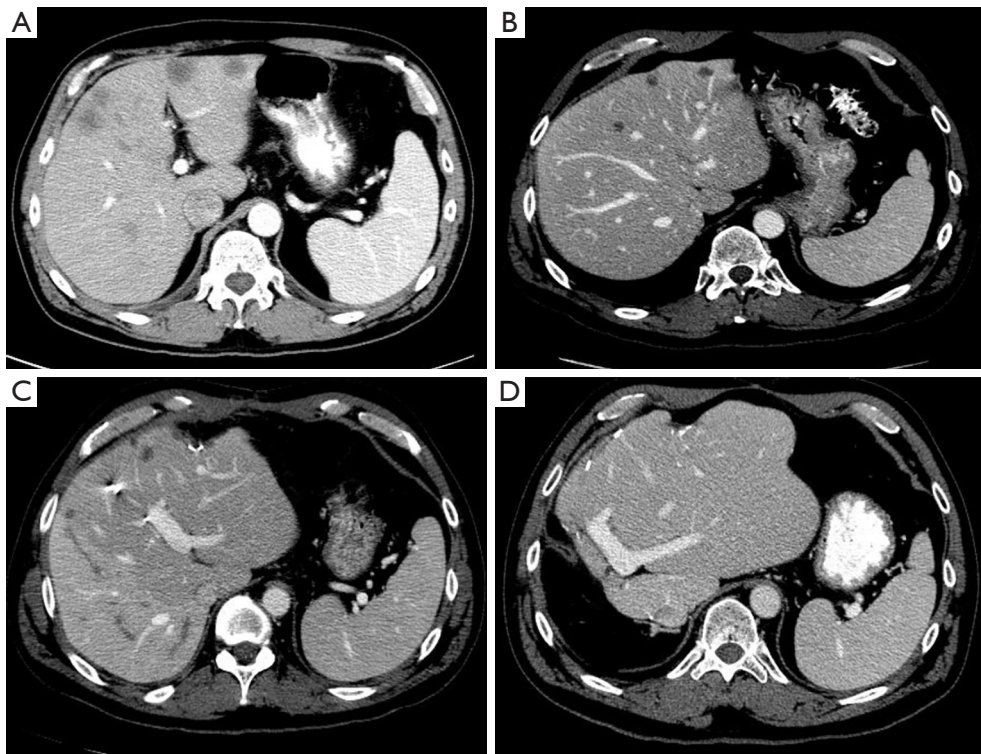


Figure 4 Computed tomography (CT) images from a patient with an obstructive rectal cancer and multiple, bilobar synchronous liver metastases. (A) Pre-treatment CT showing multiple bilobar liver metastases; (B) post-chemotherapy type I morphologic response; (C) after partial left hepatectomy, colostomy, and subsequent right-sided portal vein embolization; (D) after extended right hepatectomy and prior to management of rectal tumor.

preoperative chemotherapy. Importantly, an individualized approach must be taken for all SCRLM patients.

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Footnote

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appropriately investigated and resolved.

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