# Surgical Strategies for Synchronous Colorectal Liver Metastases in 156 Consecutive Patients: Classic, Combined or Reverse Strategy?

Antoine Brouquet, MD, Melinda M Mortenson, MD, Jean-Nicolas Vauthey, MD, FACS, Miguel A Rodriguez-Bigas, MD, FACS, Michael J Overman, MD, George J Chang, MD, FACS, Scott Kopetz, MD, Christopher Garrett, MD, Steven A Curley, MD, FACS, Eddie K Abdalla, MD, FACS

**BACKGROUND:** An increasing number of patients with synchronous colorectal liver metastases (CLM) are candidates for resection. The optimal treatment sequence in these patients has not been defined.

**STUDY DESIGN:** Data on 156 consecutive patients with synchronous resectable CLM and intact primary were reviewed. Surgical strategies were defined as combined (combined resection of primary and liver), classic (primary before liver), and reverse (liver before primary) after preoperative chemotherapy. Postoperative morbidity and mortality rates and overall survival were analyzed.

**RESULTS:** One hundred forty-two patients (83%) had resection of all disease. Seventy-two patients underwent classic, 43 combined, and 27 reverse strategies. Median numbers of CLMs per patient were 1 in the combined, 3 in the classic, and 4 in the reverse strategy group ($p = 0.01$ classic vs reverse; $p < 0.001$ reverse vs combined). Postoperative mortality rates in the combined, classic, and reverse strategies were 5%, 3%, and 0%, respectively ($p$ = NS), and postoperative cumulative morbidity rates were 47%, 51%, and 31%, respectively ($p$ = NS). Three-year and 5-year overall survival rates were, respectively, 65% and 55% in the combined, 58% and 48% in the classic, and 79% and 39% in the reverse strategy (NS). On multivariate analysis, liver tumor size >3 cm (hazard ratio [HR] 2.72, 95% CI 1.52 to 4.88) and cumulative postoperative morbidity (HR 1.8, 95% CI 1.03 to 3.19) were independently associated with overall survival after surgery.

**CONCLUSIONS:** The classic, combined, or reverse surgical strategies in patients with synchronous presentation of CLM are associated with similar outcomes. The reverse strategy can be considered as an alternative option in patients with advanced CLM and an asymptomatic primary. (J Am Coll Surg 2010;210:934–941. © 2010 by the American College of Surgeons)

Nearly 25% of patients with colorectal cancer have colorectal liver metastases (CLM) diagnosed at the same time the primary tumor is diagnosed (synchronous presentation). Surgical resection of all tumor sites is the only treatment that enables prolonged survival, but the synchronous presentation of CLM has been associated with poor outcomes.[1] Preoperative chemotherapy is widely used in these patients to provide early treatment of metastatic disease, to improve patient selection for surgical resection,[2,3] and to decrease the recurrence rate after surgery.[4]

The traditional surgical strategy for patients with resectable synchronous CLM includes resection of the primary tumor followed by chemotherapy and then liver resection. A combined strategy, with simultaneous resection of the primary and liver, has been used to avoid delaying surgical resection of metastatic disease. The main limitation of this strategy is that it can be offered only in selected patients with synchronous disease,[5-10] and it is associated with an increased risk of postoperative complications when major liver resection is combined with resection of the primary tumor.[11-13] Recently, a "reverse strategy," in which preoperative chemotherapy is followed by resection of the CLM and then by resection of the colorectal primary at a second

**Disclosure Information: Dr Vauthey is a speaker and receives honoraria from Sanofi-Aventis, Genentech, and Roche; Dr Rodriguez-Bigas is a speaker and receives honoraria from Genzyme and GSK/Adolor; and Dr Abdalla is on the speaker's bureau and receives honoraria from Sanofi-Aventis. All other authors have nothing to disclose.**

Received December 23, 2009; Revised February 6, 2010; Accepted February 10, 2010.

From the Departments of Surgical Oncology (Brouquet, Mortenson, Vauthey, Rodriguez-Bigas, Chang, Curley, Abdalla) and Gastrointestinal Medical Oncology (Overman, Kopetz, Garrett), The University of Texas MD Anderson Cancer Center, Houston, TX.

Correspondence address: Eddie K Abdalla, MD, Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 444, Houston, TX 77030. email: eabdalla@mdanderson.org.





ISSN 1072-7515/10/$36.00
doi:10.1016/j.jamcollsurg.2010.02.039

operation, has been proposed for patients with advanced synchronous CLM, and in particular, for patients in whom the primary is located in the rectum.[14] The rationale for the reverse strategy is 2-fold: primary-related complications (such as bleeding, obstruction, or perforation) are rare in patients with stage IV colorectal cancer receiving combination chemotherapy[15,16] and treatment of the metastatic disease is not delayed by local therapy for the primary tumor (surgery, and in the case of rectal cancer, radiotherapy or radiochemotherapy) or by complications of surgical treatment of the primary tumor. However, perioperative outcomes and oncologic results of patients treated using these different treatment strategies have not been compared.

The aim of this study was to compare indications, perioperative results, and oncologic outcomes in patients with a synchronous presentation of a colorectal primary tumor and CLM, according to these different surgical strategies. In addition, we sought to determine predictive factors of survival in patients with synchronous CLM.

## METHODS

### Patients

Between December1992 and May 2009, data on 156 consecutive patients who underwent surgical resection at 1 institution, for synchronous CLM with an intact primary, were collected prospectively. Patients were required to have had a preoperative diagnosis of synchronous CLM. Patients who had incidental discovery of synchronous CLM during operations for their primary tumors were excluded. Patients who underwent resection of their primary tumors at another institution were not included in this study. The study was approved by the Institutional Review Board of MD Anderson Cancer Center.

### Preoperative assessment and preoperative treatment

Because synchronous disease has been found to be associated with poor prognosis, the consensus approach at our institution is to consider preoperative chemotherapy in patients with synchronous CLM before any surgical treatment when the primary tumor is asymptomatic. Surgical resection was planned as soon as the disease was considered resectable or in the case of clearly resectable disease, typically after 3 to 5 cycles of preoperative chemotherapy. During preoperative chemotherapy, assessments of the tumor by radiographic imaging were conducted every 3 to 4 cycles. Treatment strategy decisions were made during case presentations at a multidisciplinary conference that included medical oncologists, radiation oncologists, hepatobiliary surgeons, colorectal surgeons, and radiologists. In general, decision-making was based on the location and the extent of the primary tumor, the need for preoperative radiotherapy in rectal primaries, the extent of the metastatic disease in the liver, the presence of extrahepatic disease, and the response to preoperative chemotherapy on imaging.

Surgical treatment strategies were defined as classic (resection of colorectal primary tumor at 1 operation, followed at an interval by a second operation for liver resection), combined (combined colorectal and liver resections at a single operation), and reverse (liver resection first, followed by colorectal primary tumor resection at a second operation). All patients with bilateral CLM who underwent 2-stage liver resection had their primaries resected either before the 2-stage liver resection or at the same time as the minor first liver resection, so these patients were included with those who underwent a classic strategy for the purpose of this analysis. For staged strategies, ie, classic and reverse strategies, interval chemotherapy could be administered. In patients who underwent classic strategy, chemotherapy was administered between resection of the primary and resection of CLM in the majority of patients. In patients who underwent reverse strategy, chemotherapy was administered before liver resection in the majority of the cases and chemoradiation for rectal primary could be administered between liver resection and the proctectomy. In patients who underwent combined strategy, chemotherapy was administered before operation.

### Surgical procedure

Liver resections were performed only with curative intent, ie, if all tumor deposits could be safely resected. Radiofrequency ablation was used in a small minority of patients for small tumors in selected patients in combination with liver resection, when a complete resection with staged resections and portal vein embolization were not otherwise possible.[17] During laparotomy, the peritoneal cavity was inspected in order to rule out extrahepatic spread. Palpation and intraoperative ultrasonography were carried out to better define the location of the metastases in the liver and their relationship with portal pedicles and hepatic veins in all patients. Parenchymal transection was performed using a cavitron ultrasonic surgical aspirator and hemostasis was achieved using saline-linked cautery and clips for vessels >3 to 6 mm.[18] Major hepatectomy was defined as liver resection including 3 or more contiguous liver segments.

### Perioperative results

Postoperative morbidity, 30-day, and 90-day mortality rates were evaluated.[19,20] Postoperative complications were graded using the Dindo classification.[21] Major postoperative complications were defined as complications graded 3 or more in the Dindo classification (requiring a surgical or

endoscopic or radiologic procedure). Cumulative overall postoperative morbidity and mortality rates were defined as the ratio of patients with postoperative complications and the ratio of postoperative death, respectively, after the primary tumor and/or resection of CLM. Cumulative complication rates per patient were reported in the patients who underwent multiple operations to enable comparison between groups.

### Postoperative period and long-term outcomes

Overall and disease-free survival rates were calculated from the time of final resection of all disease, ie, surgery date for combined resection, liver surgery date for classic, and date of last surgery for the staged resection and primary surgery date for reverse strategy.

### Statistical analysis

Quantitative and qualitative variables were expressed as mean ± SD, median (range), and frequency. Overall and disease-free survivals were calculated using the Kaplan Meier method and compared using the log rank test. To detect factors associated with survival in patients with colorectal cancer and synchronous colorectal CLM, univariate analysis was used to examine the relationship between the survival and the following variables: age, gender, location of the primary tumor, node status of the primary tumor, multiple CLM, the size of CLM at the time of diagnosis $> 3$ cm, bilateral CLM, CEA plasma level $> 5$ ng/dL, the type of first line chemotherapy, duration of preoperative chemotherapy $> 12$ weeks, preoperative bevacizumab therapy, preoperative cetuximab therapy, preoperative multiple lines of chemotherapy, radiologic response to preoperative chemotherapy, surgical strategy, and occurrence of postoperative complications (cumulative). All variables associated with survival with $p \leq 0.1$ in a univariate proportional hazard model were subsequently entered into a Cox multivariate regression model with backward elimination. Values of $p < 0.05$ were considered statistically significant. Comparisons between groups were analyzed with the chi-square or Fischer exact test for proportions, the Mann-Whitney U test for medians, and the Student's *t*- test for means, as appropriate. Statistical analysis was performed using the statistical software package SPSS version 17.2 (SPSS).

## RESULTS

### Evolution of the number of cases over the last decade and patient characteristics

Among patients selected for surgery, an increase in the number of patients undergoing resection of synchronous CLM was observed with the sequential introduction of the combined and the reverse strategies over the last decade (Fig. 1). Patient characteristics are summarized in Table 1. Fifty-two percent of patients were treated for rectal cancer with synchronous CLM. Of these 81 patients, 66 (81%) were treated by chemoradiation. The majority (122 of 156, 78%) of patients received 5-fluorouracil in combination with either oxaliplatin or irinotecan, and only 21 (13%) were treated with a second-line chemotherapy. Biologic targeted agents (bevacizumab and/or cetuximab) were used preoperatively in 78 (50%) of patients. An objective radiographic tumor response after preoperative chemotherapy (complete or partial response) was observed in 67 (43%) of the patients. At the time of last follow-up, 142 patients had undergone resection of the primary tumor and liver metastases: 43 patients underwent combined, 72 classic and 27 a reverse strategy. In the classic group, 29 patients (40%) did not receive any treatment before resection of the primary tumor.

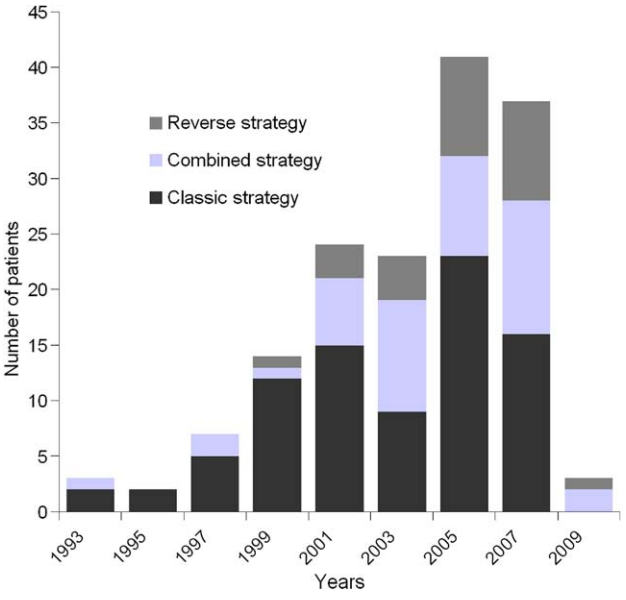


**Figure 1.** Patients operated on for synchronous liver metastases at MD Anderson Cancer Center over time.

### Comparison of preoperative characteristics in the different treatment strategy groups

Comparisons of preoperative characteristics of patients who underwent combined, classic, or reverse resection are detailed in Table 1. A significantly greater proportion of patients (19 patients, 70%) had a rectal primary in the reverse strategy group as compared with the other 2 groups (53 patients, 46%, $p = 0.02$). At the time of diagnosis, patients had a median of 2 CLMs in the combined resection group and 3 CLMs in the staged resection groups (classic + reverse) ($p < 0.01$). Eleven (11%) patients received 6 cycles or more of preoperative chemotherapy in

**Table 1.** Preoperative Characteristics of 156 Patients with Synchronous Colorectal Liver Metastases and 142 Patients Who Completed Combined, Classic, or Reverse Strategy

| Characteristic | Patients (n = 156) | Combined (n = 43) | Classic (n = 72)* | Reverse (n = 27) | p Value† | p Value‡ | p Value§ |
|---|---|---|---|---|---|---|---|
| Median age, y (range) | 55 (25–81) | 58 (31–77) | 56 (25–81) | 48 (25–78) | NS | 0.02 | 0.02 |
| Gender (M/F) | 86/70 | 23/20 | 44/28 | 10/17 | NS | 0.03 | NS |
| Mean body mass index (± SD), kg/m$^2$ | 28 ± 5 | 28 ± 5 | 28 ± 5 | 28 ± 5 | NS | NS | NS |
| Primary tumor | | | | | | | |
| Location (colon/rectum) | 75/81 | 25/18 | 37/35 | 8/19 | NS | 0.05 | 0.02 |
| Node positive primary, n (%) | 96 (61) | 27 (63) | 52 (72) | 6 (59) | NS | NS | NS |
| Liver metastases at time of diagnosis | | | | | | | |
| Median (range), n | 3 (1–10) | 2 (1–10) | 3 (1–10) | 3 (1- 10) | <0.01 | NS | <0.01 |
| Median maximum tumor diameter, cm (range) | 3 (1–16) | 2 (1–12) | 3 (1–16) | 4 (2–11) | 0 0.01 | NS | <0.01 |
| Bilateral distribution, n (%) | 83 (53) | 13 (30) | 43 (60) | 17 (63) | 0.002 | NS | <0.01 |
| Median CEA plasma level, ng/mL (range) | 9 (1–42,173) | 4 (1–42,173) | 9 (1–5,743) | 34 (1–7,500) | 0.03 | NS | <0.01 |
| First line chemotherapy before completed resection | | | | | | | |
| FU-based, n (%) | 34 (22) | 10 (23) | 22 (31) | 1 (4) | NS | <0.01 | 0.03 |
| Oxaliplatin-based, n (%) | 89 (57) | 25 (58) | 31 (43) | 20 (74) | NS | <0.01 | NS |
| Irinotecan-based (%) | 33 (21) | 8 (19) | 19 (26) | 6 (22) | NS | NS | NS |
| Median number of cycles, n (range) | 6 (0–36) | 4 (0–14) | 8 (2–36) | 7 (3–20) | 0.02 | NS | NS |
| Second line chemotherapy, n (%) | 21 (13) | 1 (2) | 13 (18) | 2 (7) | 0.02 | NS | NS |
| Preoperative chemotherapy > 12 wk, n (%) | 80 (5) | 11 (26) | 44 (61) | 15 (55) | <0.01 | NS | 0.02 |
| Bevacizumab, n (%) | 69 (44) | 17 (40) | 19 (26) | 21 (78) | NS | <0.01 | <0.01 |
| Interval chemotherapy between stages of resection, n (%) | — | — | 50 (69) | 16 (59) | — | NS | — |
| Preoperative portal vein embolization (%) | 12 (8) | 2 (5) | 6 (8) | 3 (11) | NS | NS | NS |
| Objective radiologic response, n (%) | 67 (43) | 15 (34) | 39 (54) | 9 (33) | NS | NS | NS |

*Eleven patients had a 2-stage hepatectomy with resection of metastases in the future liver remnant combined with the resection of the primary tumor during the first stage.
†Combined versus classic.
‡Classic versus reverse.
§Combined versus reverse.
CEA, carcinoembryonic antigen.

the combined resection group and 59 (59%) patients received 6 cycles or more of preoperative chemotherapy in the staged resection groups (classic + reverse) ($p < 0.001$). Preoperative bevacizumab was administered in 21 (78%) patients in the reverse strategy group and 36 patients (31%) in the combined and classic groups ($p < 0.001$).

### Feasibility of the reverse strategy

Among 41 patients who underwent a reverse strategy, 14 did not have resection of the primary tumor. Of these 14 patients, 9 (64%) had a rectal primary tumor. Causes for no resection of the primary tumor were metastatic disease progression in 9 patients (64%), complete response of primary tumor in 2 patients, postoperative death after liver resection in 1 patient, progression of primary tumor in 1 patient, and loss of follow-up in 1 patient.

Symptoms related to the primary tumor occurred in 2 patients considered for a reverse strategy (2 of 41, 5%). These 2 patients underwent colostomy, including 1 attempt at treatment by dilatation and stent insertion complicated by perforation. In both patients, the colonoscope could not be advanced beyond a circumferential tumor at the time of the initial colonoscopy. Seven of the 14 patients who did not have resection of the primary tumor were dead at the last follow-up. Causes of death in these 7 patients were metastatic disease progression in 5 patients (82%), myocardial infarction in 1 patient, and postoperative complication after liver surgery in 1 patient. No patient died from events related to progression of the primary tumor or events related to the primary tumor still in place.

### Postoperative morbidity and mortality

Intraoperative characteristics and postoperative outcomes of patients who underwent combined, classic, and reverse strategies are compared in Table 2. Major liver resection was performed in 24 patients (89%) in the reverse strategy

**Table 2.** Postoperative Outcomes of 142 Patients Who Completed Combined, Classic, or Reverse Strategy for Synchronous Liver Metastases

| Outcomes | Combined (n = 43) | Classic (n = 72)* | Reverse (n = 27) | p Value† | p Value‡ | p Value§ |
|---|---|---|---|---|---|---|
| Margin status for resection of primary, n (%) | | | | | | |
| R0 | 41 (95) | 68 (94) | 25 (93) | NS | NS | NS |
| R1 | 2 (5) | 4 (6) | 2 (7) | | | |
| Resected liver metastases | | | | | | |
| Median number, n (range) | 1 (1–9) | 3 (1–15) | 4 (1–11) | <0.01 | NS | <0.01 |
| Median maximum tumor diameter, cm (range) | 2 (0.5–10) | 2 (1–12) | 4 (1–8) | NS | <0.01 | 0.02 |
| Type of liver resection | | | | | | |
| ≥3 liver segments, n (%) | 15 (35) | 48 (66) | 24 (89) | <0.01 | 0.04 | <0.01 |
| Radiofrequency ablation | 4 (9) | 24 (33) | 5 (19) | 0.02 | NS | NS |
| Margin status for resection of liver metastases, n (%) | | | | | | |
| R0 | 40 (93) | 62 (86) | 23 (85) | NS | NS | NS |
| R1 | 3 (7) | 9 (13) | 4 (15) | | | |
| Unknown | 0 | 1 (1) | 0 | | | |
| Median cumulative estimated blood loss, mL (range) | 300 (50–3,000) | 600 (100–3,300) | 500 (200–2,200) | <0.01 | NS | <0.01 |
| Blood transfusion requirement, n (%) | 7 (16) | 9 (13) | 2 (7) | NS | NS | NS |
| 30-day postoperative mortality, n (%) | 2 (5) | 2 (3) | 0 | NS | NS | NS |
| 90-day postoperative mortality, n (%) | 2 (5) | 2 (3) | 1 (4) | NS | NS | NS |
| Overall postoperative morbidity, n (%) | 20 (47) | 37 (51) | 10 (37) | NS | NS | NS |
| Cumulative major postoperative complication, n (%)‖ | 8 (19) | 12 (17) | 2 (7) | NS | NS | NS |
| Adjuvant chemotherapy | 33 (77) | 46 (64) | 21 (78) | NS | NS | NS |

*Eleven patients had a 2-stage hepatectomy with resection of metastases in the future liver remnant combined with the resection of the primary tumor during the first stage.
†Combined versus classic.
‡Classic versus reverse.
§Combined versus reverse.
CEA, carcinoembryonic antigen.
‖Major postoperative complications were defined as complications requiring reoperation, endoscopic or radiologic procedure.
R0, surgical margin ≥ 1 mm; R1, no margin or surgical margin <1 mm.

group and 63 (55%) in the 2 other groups ($p < 0.001$). Median cumulative blood loss was 300 mL in patients undergoing combined and 600 mL in patients undergoing staged resection (classic + reverse) ($p < 0.01$). Overall cumulative 30- and 90-day postoperative mortality rates were 4 of 142 (2.8%) and 5 of 142 (3.5%), respectively. Cumulative postoperative morbidity rate was 67 of 142 (47%). Twenty-two patients (15%) developed major postoperative complications and required either drainage of postoperative intra-abdominal fluid collection or reoperation. Cumulative postoperative morbidity and mortality rates were not statistically different between the groups.

## Survival and recurrence

Median follow-up from the date of completion of the treatment strategy was 25.1 months in the 142 patients who underwent resection of all disease (range 1 to 159 months). Overall median survival for the entire population who underwent a completed strategy was 64 months (95% CI 37 to 92 months); 3- and 5-year overall survival rates were 63% and 50%, respectively. Median survival rates were 95 months (95% CI 1 to 190 months) in the combined resection group, 55 months (95% CI 28 to 82 months) in the classic resection group, and 50 months (95% CI 22 to 78 months) in the reverse resection group ($p = 0.389$) (Fig. 2). Three- and 5-year overall survival rates were, respectively, 65% and 55% in the combined resection group, 58% and 48% in the classic resection group, and 79% and 39% in the reverse resection group. Overall, 93 patients (65%) developed recurrences: 23 in the combined resection group, 51 in the classic resection group, and 19 in the reverse strategy group (NS). Median disease-free survivals for patients who underwent a completed treatment strategy were 11 months in the combined (95% CI 6 to 16

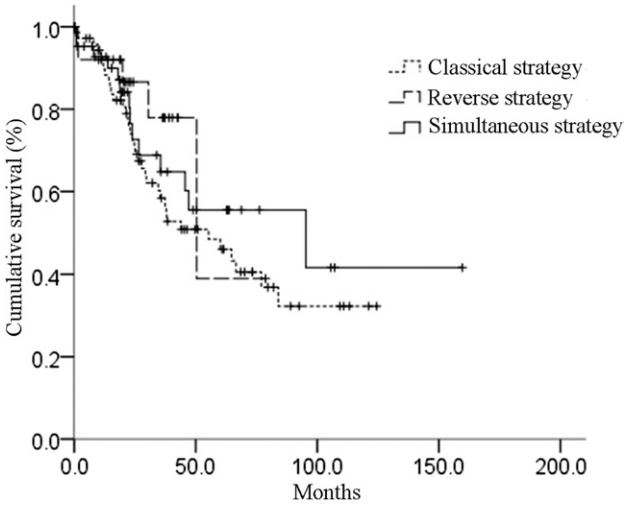


**Figure 2.** Overall survival of 142 patients treated for synchronous colorectal liver metastases, log rank test p = 0.389.

months), 11 months in the classic (95% CI 8 to 14 months), and 11 months in the reverse resection group (95% CI 4 to 18 months; NS).

### Factors associated with survival in patients with synchronous CLM

Univariate analysis showed that maximum liver tumor size > 3 cm at the time of diagnosis (p = 0.08), and the need for a second line of preoperative chemotherapy (p = 0.01), were associated with survival in patients operated on for synchronous CLM. On multivariate analysis, only liver tumor size > 3 cm (hazard ratio [HR] 2.72, 95% CI 1.52 to 4.88) and overall cumulative postoperative morbidity were independent factors associated with survival after surgery (HR 1.81, 95% CI 1.03 to 3.19).

## DISCUSSION

To our knowledge, this study is the first to evaluate the 3 different surgical strategies used for treatment of patients with synchronous CLM with an intact primary. In patients whose surgical treatment was complete, postoperative and oncologic outcomes were similar despite more extensive disease in patients undergoing the reverse strategy. In recent years, the reverse strategy contributed to the expansion of the resectability in patients with advanced synchronous CLM.

In determining the proper surgical strategy for a given patient with synchronous CLM, a number of factors must be considered. In the classic strategy, the risk for progression of CLM while the patient is treated for the primary tumor is a concern. In some patients, CLMs become unresectable during this interval. In the subset of patients with primary rectal cancer, the delay until the resection of the CLM that results from preoperative chemoradiation and primary rectal resection is frequently greater than 3 months.[22] The systemic effectiveness of the chemotherapy delivered during chemoradiation is unknown. To overcome the limitations of the classic strategy, the combined strategy has been used in selected patients with synchronous CLM.[7,9,10] However, it can be offered only in 18% to 56% of patients.[5,6,8] The major limitation of this strategy is that extensive resections including major or extended hepatectomy are associated with increased mortality and severe morbidity rates up to 8% and 36%, respectively, when combined with resection of the primary tumor.[11-13]

For these reasons, Mentha and colleagues[14] proposed the reverse strategy in a prospective series of 20 patients with advanced synchronous CLM and a primary tumor in place treated with a preoperative combination of fluorouracil, oxalitplatin, and irinotecan. This study demonstrated the feasibility and safety of this strategy with morbidity and mortality rates of 19% and 0%, respectively, and a 3-year overall survival of 83%.[14] In our study, the reverse strategy was associated with postoperative morbidity and mortality rates of 31% and 4%, respectively, and a 3-year survival rate of 79%. With similar morbidity, mortality, and overall survival rates between the different strategies, our study indicates that a reverse strategy in patients with advanced synchronous CLM may be an appropriate option for the surgical sequencing of this complex group of patients.

The reverse strategy was initially proposed for patients with synchronous colorectal liver metastases from rectal cancer.[14] We showed in this study that the reverse strategy can be considered in patients with advanced synchronous colon or rectal liver metastases, and it helps to increase the resectability in patients initially not deemed suitable for surgery, as indicated in Figure 1. Patients most likely to be considered for the reverse approach are those with advanced liver metastases in whom a delay off chemotherapy allowing hepatic progression would preclude otherwise curative surgery. Among patients with asymptomatic rectal primary tumors, long durations off effective systemic treatment may occur as a result of preoperative chemoradiation, problems related to diverting ileostomy (including poor tolerance to chemotherapy with dehydration), or complications of rectal resection. Although a lesser problem with colon primary tumors, complications of the primary tumor operation can delay systemic treatment for the liver and allow progression. In contrast, when the liver is addressed first, a period of time off treatment is rarely a major problem with regard to the primary tumor.

In some patients with advanced bilobar disease, all liver metastases cannot be resected during the same surgical pro-

cedure because of the risk of postoperative liver failure. In such cases, we have previously reported[23] a 2-stage liver surgery with preoperative chemotherapy. With regard to patients with intact primary tumors and bilateral metastases, this approach combines minor hepatectomy (generally clearance of the future liver remnant of metastases) with colorectal resection. When indicated based on volumetry,[24] portal vein embolization is performed before second stage major liver resection to remove remaining disease. In this study, 11 patients underwent complete resection of extensive disease using this strategy. We consider this strategy as an alternate option in patients with advanced synchronous disease with bilobar lesions.

At our institution, the consensus for treatment of patients with resectable synchronous CLM is to consider preoperative chemotherapy if the primary tumor is asymptomatic. This concept is supported by a recent report by Poultsides and associates[15] indicating that the primary tumor can be left in place without the need for resection in patients with stage IV disease who received palliative systemic chemotherapy for advanced unresectable metastatic disease. In their study, among 233 patients with advanced stage IV colorectal cancer, only 26 patients (11%) had symptoms related to the primary, which was similar to the 15% rate seen in the subset of patients with rectal primaries left in place. In our study, among the 41 patients presenting with primary tumors initially left in place in the setting of a reverse strategy, 2 (5%) developed primary tumor-related complications. One of these patients had a perforation after an attempt at stent insertion, and the delay related to the treatment of the perforation could have contributed to disease progression in this patient. The reverse strategy should not be considered in patients with an initially circumferential obstructive tumor. However, in most patients this strategy is appropriate because it establishes early control of stage IV disease systemically and in the liver[4, 25] and it is also associated with an effective response in the primary tumor.[26]

Univariate analysis showed that tumor size, need for a second line of preoperative chemotherapy, and occurrence of postoperative complications were associated with outcomes. Only tumor size and cumulative postoperative morbidity were independent predictive factors of worse outcomes on multivariate analysis. The influence of postoperative complications on oncologic results after resection of CLM has already been reported.[27-29] Although the rate of postoperative complications was similar after the different surgical strategies, it underlines the importance of prioritizing treatment of the most problematic component of the patient's disease, and the choice of a treatment strategy designed to enable the lowest possible complication rate. The postoperative morbidity rate should no longer be considered a secondary endpoint for treatment because it directly affects outcomes; patients with major complications either do not proceed to completion resection or never recover sufficiently to receive planned completion chemotherapy. Tumor size and need for second-line chemotherapy before operation to achieve tumor response reflect the severity of the patient's underlying disease. The recurrence rate of 65% among patients with a synchronous diagnosis of CLM suggests that despite resection, additional disease exists, defining a population of interest to target with systemic chemotherapy.

The primary limitations of this study are that it is a retrospective analysis of selected patients at a single institution and the analysis could be underpowered. Feasibility of the classic strategy cannot be provided because of referral selection bias for liver surgery. In addition, comparison of feasibility between strategies is not appropriate because of differences in disease extent between groups. However, the purpose of the study was to evaluate the treatment strategies used for patients with synchronous presentation of colorectal liver metastases with primary tumor in place whether a classic, combined, or reverse approach was used. Disease extent influences the choice and sequence of treatments, yet despite different disease extent, outcomes are good with all approaches. Because each strategy has its benefit, placing the priority on safety and on disease site (primary or liver), which poses the greatest problem, in our practice, the different strategies rarely compete. The common difficulty that arises regardless of treatment strategy is systemic disease recurrence after surgery, which emphasizes the need for better patient selection.[3] Despite these limitations, these findings expand on the premise that a reverse strategy could be a safe alternative for patients with advanced synchronous CLM.

In conclusion, the classic, combined, and reverse strategies are associated with similar outcomes. The reverse strategy should be considered as an alternative option for treatment of advanced CLM in patients with an asymptomatic primary tumor in place. In these patients, surgical treatment of the metastatic disease is prioritized first, with treatment of the primary tumor second. The outcomes for patients treated with the reverse strategy and more extensive disease are similar to outcomes of patients treated with classic or combined resection with lesser disease extent.

## Author Contributions

Study conception and design: Abdalla, Vauthey, Curley, Rodriguez-Bigas

Acquisition of data: Abdalla, Mortenson, Brouquet

Analysis and interpretation of data: Abdalla, Mortenson, Brouquet, Vauthey

Drafting of manuscript: Abdalla, Brouquet, Vauthey

Critical revision: Abdalla, Mortenson, Brouquet, Vauthey, Rodriguez-Bigas, Chang, Overman, Kopetz, Garrett, Curley

## REFERENCES


1. Nordlinger B, Guiguet M, Vaillant JC, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Francaise de Chirurgie. Cancer 1996;77:1254–1262.
2. Allen PJ, Kemeny N, Jarnagin W, et al. Importance of response to neoadjuvant chemotherapy in patients undergoing resection of synchronous colorectal liver metastases. J Gastrointest Surg 2003;7:109–117.
3. Chun YS, Vauthey JN, Boonsirikamchai P, et al. Association of computed tomography morphologic criteria with pathologic response and survival in patients treated with bevacizumab for colorectal liver metastases. JAMA 2009;302:2338–2344.
4. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet 2008;371:1007–1016.
5. Martin R, Paty P, Fong Y, et al. Simultaneous liver and colorectal resections are safe for synchronous colorectal liver metastasis. J Am Coll Surg 2003;197:233–241.
6. Lyass S, Zamir G, Matot I, et al. Combined colon and hepatic resection for synchronous colorectal liver metastases. J Surg Oncol 2001;78:17–21.
7. Vogt P, Raab R, Ringe B, et al. Resection of synchronous liver metastases from colorectal cancer. World J Surg 1991;15:62–67.
8. Weber JC, Bachellier P, Oussoultzoglou E, et al. Simultaneous resection of colorectal primary tumour and synchronous liver metastases. Br J Surg 2003;90:956–962.
9. de Santibanes E, Lassalle FB, McCormack L, et al. Simultaneous colorectal and hepatic resections for colorectal cancer: postoperative and longterm outcomes. J Am Coll Surg 2002;195:196–202.
10. Capussotti L, Ferrero A, Vigano L, et al. Major liver resections synchronous with colorectal surgery. Ann Surg Oncol 2007;14:195–201.
11. Reddy SK, Pawlik TM, Zorzi D, et al. Simultaneous resections of colorectal cancer and synchronous liver metastases: a multi-institutional analysis. Ann Surg Oncol 2007;14:3481–3491.
12. Tanaka K, Shimada H, Matsuo K, et al. Outcome after simultaneous colorectal and hepatic resection for colorectal cancer with synchronous metastases. Surgery 2004;136:650–659.
13. Bolton JS, Fuhrman GM. Survival after resection of multiple bilobar hepatic metastases from colorectal carcinoma. Ann Surg 2000;231:743–751.
14. Mentha G, Majno PE, Andres A, et al. Neoadjuvant chemotherapy and resection of advanced synchronous liver metastases before treatment of the colorectal primary. Br J Surg 2006;93:872–878.
15. Poultsides GA, Servais EL, Saltz LB, et al. Outcome of primary tumor in patients with synchronous stage IV colorectal cancer receiving combination chemotherapy without surgery as initial treatment. J Clin Oncol 2009;27:3379–3384.
16. Benoist S, Pautrat K, Mitry E, et al. Treatment strategy for patients with colorectal cancer and synchronous irresectable liver metastases. Br J Surg 2005;92:1155–1160.
17. Aloia TA, Vauthey JN, Loyer EM, et al. Solitary colorectal liver metastasis: resection determines outcome. Arch Surg 2006:460–467.
18. Aloia TA, Zorzi D, Abdalla EK, Vauthey JN. Two-surgeon technique for hepatic parenchymal transection of the noncirrhotic liver using saline-linked cautery and ultrasonic dissection. Ann Surg 2005;242:172–177.
19. Mullen JT, Ribero D, Reddy SK, et al. Hepatic insufficiency and mortality in 1,059 noncirrhotic patients undergoing major hepatectomy. J Am Coll Surg 2007;204:854–862.
20. Kishi Y, Abdalla EK, Chun YS, et al. Three hundred and one consecutive extended right hepatectomies: evaluation of outcome based on systematic liver volumetry. Ann Surg 2009. [Epub ahead of print]
21. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–213.
22. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006;355:1114–1123.
23. Chun YS, Vauthey JN, Ribero D, et al. Systemic chemotherapy and two-stage hepatectomy for extensive bilateral colorectal liver metastases: perioperative safety and survival. J Gastrointest Surg 2007;11:1498–1504.
24. Abdalla EK, Adam R, Bilchik AJ, et al. Improving resectability of hepatic colorectal metastases: expert consensus statement. Ann Surg Oncol 2006;13:1271–1280.
25. Blazer DG 3rd, Kishi Y, Maru DM, et al. Pathologic response to preoperative chemotherapy: a new outcome end point after resection of hepatic colorectal metastases. J Clin Oncol 2008;26:5344–5351.
26. Karoui M, Koubaa W, Delbaldo C, et al. Chemotherapy has also an effect on primary tumor in colon carcinoma. Ann Surg Oncol 2008;15:3440–3446.
27. Schiesser M, Chen JW, Maddern GJ, et al. Perioperative morbidity affects long-term survival in patients following liver resection for colorectal metastases. J Gastrointest Surg 2008;12:1054–1060.
28. Laurent C, Leblanc F, Bretagnol F, et al. Long-term wound advantages of the laparoscopic approach in rectal cancer. Br J Surg 2008;95:903–908.
29. Ito H, Are C, Gonen M, et al. Effect of postoperative morbidity on long-term survival after hepatic resection for metastatic colorectal cancer. Ann Surg 2008;247:994–1002.