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Clinical Outcomes of the Liver-First Approach in the Management of Synchronous Colorectal Liver Metastases: A Retrospective Study

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Abstract

Introduction Almost 25% of colorectal cancer (CRC) patients have synchronous colorectal liver metastasis (SCLM) coinciding with the disease diagnosis. Liver-first approach for the treatment of SCLM involves neoadjuvant chemotherapy, subsequent liver resection, and then primary tumor resection. This strategy is adopted as the prognosis of the disease depends mainly on the metastases, not the primary tumor. This study aims to evaluate the feasibility of the liver-first approach and clinical prognosis in managing SCLM.

Materials and Methods This retrospective study included 25 patients with SCLM from July 2015 to July 2020. All patients were subjected to a liver-first approach with an "intention-to-treat" approach. Follow-up was planned for at least 3 years. Data were collected from the hospital records and included survival rates and univariate analyses of the prognostic factors, such as gender, age, and number of chemotherapy cycles to evaluate their effect on the survival probability.

Results Nineteen patients completed the treatment paradigm. Long-term outcomes reported a median overall survival (OS) of 32 months. One-year and 3-year survival probabilities were 89.5% and 42.1%, respectively. The median disease-free survival was 13 months. The number of metastatic lesions, unilobar versus bilobar disease, and the frequency of administered chemotherapy cycles significantly affected survival ($p < 0.05$). Seven patients (36.84%) remained disease free (no recurrence) while 2 patients (10.53%) survived with recurrence. The overall mortality included 10 deaths (52.63%) due to recurrence.

Conclusion Synchronous colorectal liver metastasis treated with the liver-first approach achieved a notable overall advantage. However, the recurrence rate remained relatively high.

Keywords
- colorectal cancer
- synchronous colorectal liver metastasis (SCLM)
- liver-first approach

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Introduction

The third most frequent type of cancer in the world today is colorectal cancer. At the time of diagnosis, 20 to 25% of colorectal cancer patients have stage IV disease, of which 15 to 25% have synchronous colorectal liver metastasis (SCLM), and, in 70 to 80% of these instances, the metastasis is confined to the liver. Surgical excision is the only treatment that could potentially be curative for SCLM.[1]

A total of 15 to 20% of those with colorectal cancer who receive their initial diagnosis develop SCLM), which continues to be the main cause of death in individuals with colorectal diseases. Despite major advancements in colorectal cancer management techniques over the past few decades, metastatic disease is still challenging to cure and frequently regarded as incurable. However, surgical resection affords the highest chance for the survival of patients with colorectal liver metastases (CRLM); it can be curative, and it is still the gold standard.[2]

The availability of new systemic therapies has extended survival, and recent advancements in surgical management techniques have widened the eligibility requirements for resection.[3,4] Even with these advancements, metastatic illness continues to be the leading cause of mortality. However, metastatic illness does not preclude surgery. Resection of this disease is linked to a 20% cure rate for patients who acquire liver metastatic disease, and 5-year survival rates can surpass 50%.[5,6] Unfortunately, there is still a controversy about the surgical therapy techniques for CRLM. This is probably influenced by misconceptions, even among surgeons, about resectable and unresectable CRLM.[7]

Chemotherapy has conventionally been the first line of treatment for resectable CRLM, with liver resection as a last resort depending on the effectiveness of systemic therapy. There are three different therapeutic modalities available for individuals with resectable or borderline resectable synchronous CRLM: classic, combination, and reversed.[8,9]

In the three treatment modalities, neoadjuvant chemotherapy should be thoroughly studied and chosen in a multidisciplinary manner. The traditional method involves removing the CRLM after surgery for the original colorectal tumor and adjuvant chemotherapy. Adjuvant chemotherapy is used after a combined liver and colon resection in the combination method. The reversal strategy involves surgery for the CRLM, followed by adjuvant chemotherapy and then resection of the primary colorectal tumor.[2,10]

In carefully selected patients, the liver-first technique, with or without neoadjuvant chemotherapy strategy, has exhibited reasonable short- and long-term outcomes.[8,11] It is a promising therapeutic strategy since it concentrates on the liver, which is the prognostically important site of the disease since first proposed in 2006. There is still some uncertainty about whether chemotherapy-related liver damage may be prevented, such as sinusoidal injury and steatosis.[12]

For patients with resectable SCLM, the ideal surgical approach—whether simultaneous or phased excision of primary colorectal cancer and hepatic metastases—remains unknown. The authors were inspired to undertake this study because there is ongoing debate among clinicians about which SCLM patients are most eligible for surgical resection and whether the liver-first approach can be a preferable strategy in certain patients.

Materials and Methods

Study Design and Subjects

The current retrospective study included 25 patients who presented with SCLM to the surgical oncology unit of Benha University Hospital throughout the period from July 2015 to July 2020. The ethical and research committees of the Faculty of Medicine of Benha University approved the study, which followed the ethical principles of the Declaration of Helsinki.

The research was registered at https://www.researchregistry.com/browse-the-registry#home/ under identification number 8409.

The study included 25 patients with SCLM who were eligible for liver-first approach with an "intention-to-treat" goal. The inclusion criteria were the absence of extrahepatic disease, adequate future liver remnant (FLR) calculated by volumetric computed tomography (CT) scan, and positive response or at least stabilization after induction of neoadjuvant chemotherapy. The exclusion criteria were patients with SCLM with extrahepatic disease or in adequate future liver remnant. Patients with progressive disease with neoadjuvant chemotherapy and those demanding urgent operation at any time during the study period were also excluded.

Data Collection

Data were collected up to July 2020 from the hospital records, with at least 3 years postoperative follow-up, including demographics, characteristics of primary tumor and CRLM, neoadjuvant chemotherapy, the extent of liver resection, and postoperative complications and mortality within 30 days and 3 months of treatment, respectively. The significance of postoperative complications was graded according to the Clavien-Dindo classification.[13] Severe complications were correlated with Clavien grade 3 or 4. Disease recurrence was considered if a lesion appeared and was histologically proven to be adenocarcinoma or when there was a suspicious lesion on a CT scan (morphological) with an elevated carcinoembryonic antigen (CEA) level (biological). Overall survival (OS) was estimated from the diagnosis until death or the date of the last follow-up if the patient was still alive.

Multidisciplinary Team (MDT) Meeting

All records of the patients were discussed in the MDT meeting, comprising of a hepatobiliary surgeon, colorectal surgeon, oncologist, hepatologist, radiologist, and pathologist. All members of the MDT were professors at Benha University. After a multidisciplinary approach, eligible patients were counseled on the treatment strategy, with all the other strategies being explained to them. The patients who accepted the management protocol signed an informed consent.

Preoperative Evaluation

The included patients underwent medical history taking, physical examination, and laboratory assessment, including CEA and CA 19–9 levels at the first diagnosis. Colonoscopy was done to exclude synchronous lesions. Preoperative staging included chest, abdomen, and pelvis CT, liver magnetic resonance imaging (MRI) with triphasic contrast examination, and pelvic MRI (only for rectal cancer). Positron emission tomography (PET-CT) was done only in selected patients. A clinical risk score (CRS) was used to predict long-term outcomes for patients subjected to CRLM resection.[14] A more aggressive disease was described with CRS 3 or more.

Induction of Neoadjuvant Chemotherapy

All patients received neoadjuvant chemotherapy regardless of the resectability of their lesion. The policy was to treat all patients with stage IV CRC first with neoadjuvant chemotherapy.

Chemotherapy Regimens

The patients received an irinotecan-based regimen (FOLFIRI), oxaliplatin-based regimen (FOLFOX), or OCFL combination using oxaliplatin (OHP), 5-fluorouracil (FU)/leucovorin (LV), and irinotecan (CPT-11). Few patients received targeted therapies (Bevacizumab or Cetuximab) depending on KRAS typing.

Evaluation of the Response to Chemotherapy

The patients received up to six cycles of chemotherapy. Response to chemotherapy was evaluated after the third cycle with chest CT, abdomen and pelvis CT, liver MRI, and CEA and CA 19–9 levels. Radiological assessment was based on the Response Evaluation Criteria for Solid Tumors (RECIST).[15] Treatment was shifted to the second line of chemotherapy in cases with non-responsive or progressive disease. The patients were reevaluated at the MDT meeting. Liver surgery was performed when CRLM became technically resectable with a decrease in the CEA level.

Liver Resection of CRLM

The remaining liver had to include at least two contiguous segments with appropriate vascular out- and inflow and sufficient biliary draining with at least 1 mm safety margin confirmed by intraoperative frozen section. If these conditions could not be achieved, a two-stage liver resection approach was accomplished with or without portal vein embolization.

Follow-up and Outcomes

All included patients were followed up for at least 3 years.

The primary outcome was **to** improve overall survival.

The secondary outcome was to decrease postoperative complications and improve the clinical prognosis.

Data Analysis

The data were statistically analyzed using the statistical software IBM SPSS Statistics for Windows, version 28.0 (IBM Corp., Armonk, NY, United States). Quantitative data were expressed as numbers and percentages. The numerical data normality was tested using direct data visualization methods and the Shapiro-Wilk test. Accordingly, the numerical data were presented as mean ± standard deviation (SD)

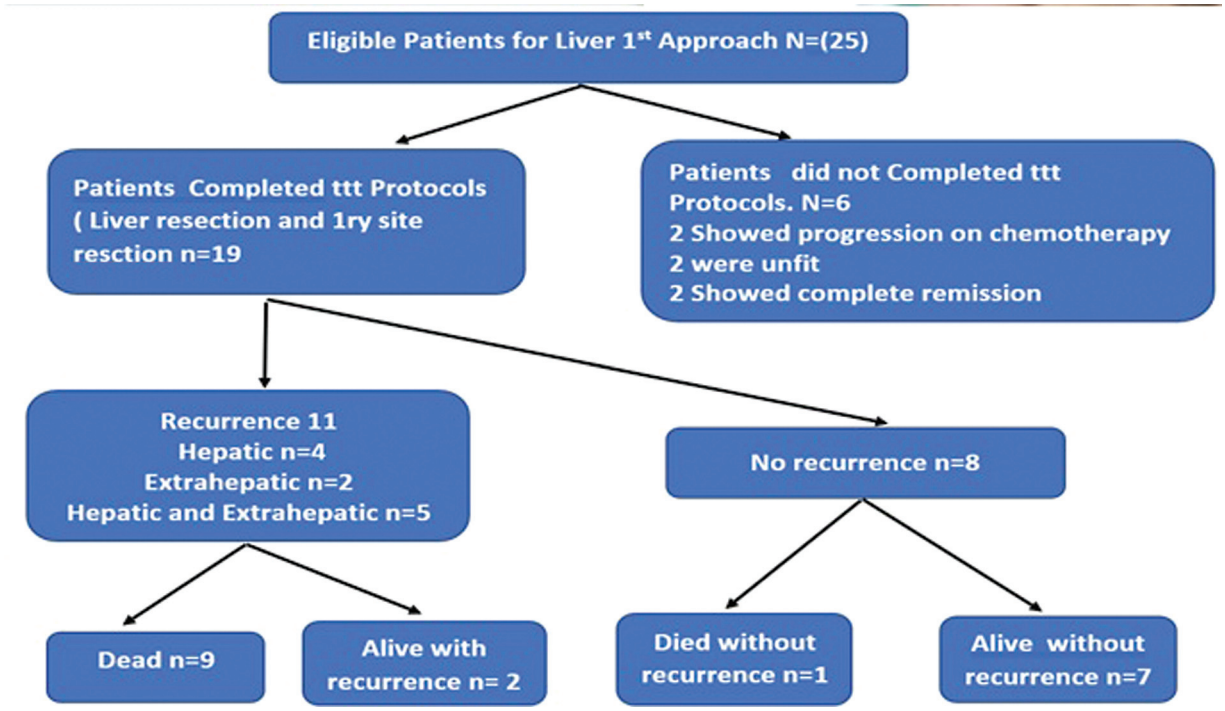

Fig. 1 Flowchart of subjects enrolled in the study and long-term treatment outcomes (Consolidated Standards of Reporting Trials [CONSORT] flowchart).

or median and range values. Kaplan Meier analysis was conducted to estimate survival. The log-rank test was used for univariate analysis of prognostic factors to evaluate their effect on the survival probability. Values of $p < 0.05$ were considered significant.

Results

A total of 25 patients were identified for the present study, but only 19 could complete the treatment paradigm. The details of the six patients who deviated from the treatment protocol were as follows: two patients showed disease progression with neoadjuvant chemotherapy and were shifted to palliative chemotherapy; two patients underwent liver resection but were deemed unfit for resection of primary CRC (one patient had disease progression after liver resection, whereas the other died after two-stage hepatectomy due to progressive hepatocellular failure); two patients showed complete remission after downstaging with new adjuvant chemotherapy and did not need liver resection but operated for the primary tumor. One of them developed hepatic recurrence after 6 months of primary tumor resection at the same site of previous CRLM and underwent liver resection after neoadjuvant chemotherapy (►**Fig. 1**).

Table 1 General characteristics of the study patients

Variables		N = 19
Age (years)	**Mean ± SD**	49 ± 9
Sex		
Male	**n (%)**	10 (52.6)
Female	**n (%)**	9 (47.4)
CRC site		
Left colon	**n (%)**	3 (15.8)
Rectum	**n (%)**	11 (57.9)
Right colon	**n (%)**	3 (15.8)
Sigmoid	**n (%)**	2 (10.5)
T stage of the CRC		
T2	**n (%)**	3 (15.8)
T3	**n (%)**	12 (63.2)
T4	**n (%)**	4 (21.1)
N stage of the CRC		
N0	**n (%)**	4 (21.1)
N1	**n (%)**	11 (57.9)
N2	**n (%)**	4 (21.1)
Site of liver metastasis		
Unilobar	**n (%)**	11 (57.9)
Bilobar	**n (%)**	8 (42.1)
Size of liver metastasis (cm)	**Mean ± SD**	4.5 ± 0.9
Number of metastases	**Median (mi.-max.)**	4 (2–7)
Clinical risk score		
2	**n (%)**	6 (31.6)
3	**n (%)**	11 (57.9)
4	**n (%)**	2 (10.5)

Abbreviations: CRC, colorectal cancer; max., maximum; min., minimum; N, node; SD, standard deviation; T, tumor.

Table 2 Chemotherapy and surgical characteristics of the studied patients

Variables		N = 19
Number of cycles of chemotherapy	median (min.–max.)	5 (2–6)
Chemotherapy regimen		
FOLFIRI	**n (%)**	3 (15.8)
FOLFOX	**n (%)**	11 (57.9)
FOLFOX + FOLFIRI	**n (%)**	2 (10.5)
FOLFOX + OCFL	**n (%)**	1 (5.3)
OCFL	**n (%)**	2 (10.5)
Targeted therapy	**n (%)**	7 (36.8)
Clinical response to chemotherapy		
Partial	**n (%)**	15 (78.9)
Stable	**n (%)**	4 (21.1)
Hepatectomy level		
Non-anatomical resection	**n (%)**	3 (15.8)
One-stage major resection	**n (%)**	10 (52.6)
One-stage minor resection	**n (%)**	2 (10.5)
Two-stage hepatectomy	**n (%)**	4 (21.1)

As shown in ►**Table 1**, the mean age of the studied patients was 49 ± 9 years. About half of the patients were male (52.6%). The most frequent location of the primary tumor was the rectum (57.9%). About ⅔of the patients had T3 stage tumors (63.2%), and more than half (57.9%) had N1 stage tumors. Uilobar meaning one lobe of the liver was present in 57.9% of the patients. The mean size of liver metastasis was 4.5 ± 0.9 cm. The median number of metastases was 4, ranging from 2 to 7. The most frequent clinical risk score was 3 (57.9%).

The median number of chemotherapy cycles was 5, ranging from 2 to 6. The most frequent chemotherapy regimen was FOLFOX (57.9%). About 1/3 of the patients received targeted therapy (36.8%). Most patients showed partial response to chemotherapy (78.9%). The most frequent hepatectomy was one-stage major resection (52.6%). Most patients (84.2%) had R0 pathological margin (►**Table 2**). As shown in ►**Table 3**, more than half of the patients (75.9%) had postoperative complications. The most frequent complication was a transient liver failure (27.3%). Recurrence was reported in more than half of the patients (57.9%). The most frequent recurrence pattern was hepatic and extrahepatic (45.5%). A Kaplan-Meier analysis was done to estimate the overall survival of the studied patients. The

Table 3 Postoperative findings of the studied patients

Variables		
Postoperative complications	**n (%)**	11 (57.9)
Type of complication*	**n (%)**	
Anastomotic leak	**n (%)**	2 (18.2)
Biliary leak	**n (%)**	2 (18.2)
Chest infection	**n (%)**	1 (9.1)
Paralytic ileus	**n (%)**	2 (18.2)
Transient liver failure	**n (%)**	3 (27.3)
Wound infection	**n (%)**	1 (9.1)
Recurrence	**n (%)**	11(57.9)
Pattern of recurrence†		
Extrahepatic only		2 (18.2)
Hepatic and extrahepatic		5 (45.5)
Hepatic only		4 (36.4)

Notes: *Percentage was calculated based on 11 patients who presented complications.
†Percentage was calculated based on 11 patients who presented recurrence.

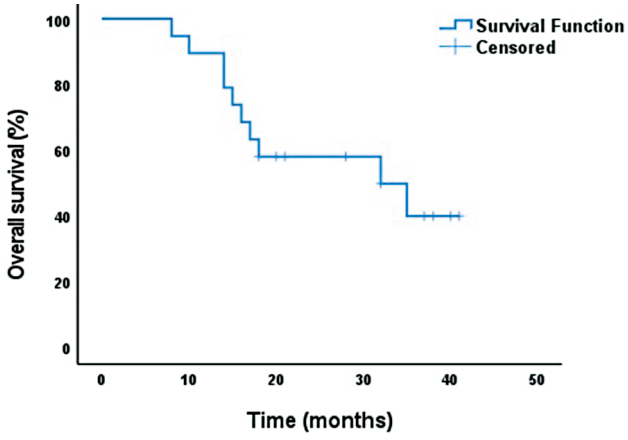

Fig. 2 Overall survival of the studied patients.

survival rate was 89.5% at 12 months, 57.9% at 24 months, and 42.1% at 36 months until the end of follow-up. The median overall survival time was 32 months, with a 95% confidence interval ranging from 9.357 to 54.643 months (►**Fig. 2**).

A Kaplan-Meier analysis was done to compare survival according to different factors. The survival significantly differed according to the site of liver metastasis (longer OS in patients with unilobar presentation [logrank $p < 0.001$]), number of metastases (longer OS in patients with less than 4 metastases [logrank $p < 0.001$]), and number of chemotherapy cycles (longer OS time in patients with ≥ 5 chemotherapy cycles [logrank $p = 0.008$]) (►**Fig. 3**). However, no significant differences were reported according to sex (Log-rank $p = 0.719$), site of primary tumor ($p = 0.695$), size of metastasis ($p = 0.084$), targeted therapy ($p = 0.414$), and hepatectomy level ($p = 0.507$) (►**Fig. 4**).

Discussion

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.[16] The liver-first, or reverse strategy, has been proposed to treat SCLM. 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 and impressive survival outcomes of this approach in 20 patients with advanced disease.[12]

In the current study, 19 (76%) patients completed the treatment paradigm of the liver first approach for SCLM. This percentage is higher than that reported by Verhoef et al.[17] (69.6%) and Mentha et al.[12] (66%). In the present study, ~25% of the patients did not fulfill their treatment regimen. In line, Mechteld et al.[18] and Hudden et al.[19] report that patients develop extrahepatic disease following chemotherapy. Interestingly, in the present study, while other patients showed some form of morbidity following chemotherapy or liver resection, one patient had a complete clinical response following neoadjuvant chemotherapy.

The median survival time in the present study was 32 months. The survival probability was 89.5% at 1 year, 57.9% at 2 years, and 42.1% at 3 years. Comparable results have been reported by Wang et al.,[20] who report a 3-year survival probability of 44.8%, and Su et al.[21], who report a long median OS of 93.1%, 56.5% at 1 and 3 years, respectively. In contrast, chemotherapeutic drugs have shown a median OS of ~ 20 months, yet even with newer drugs, 5-year survival is, to some extent, still impossible.[22]

In the present study, nine patients died of recurrence. Two remained alive with recurrence. One died due to causes other than recurrence, while seven had no recurrence after the complete treatment. The overall recurrence rate was 57.9%. Various recurrence rates, ranging from 25 to 75%, have been reported in many studies.[23–26] The high recurrence rates may be explained by the poor prognosis of patients presenting with SCLM. Such patients carry a high disease burden and aggressive tumors, making recurrence highly likely. Consequently, these patients should be offered close monitoring and follow-up.

While the liver-first approach focuses on liver metastasis, it is possible to develop primary lesion complications, such as obstructive complications.[22] However, in the present study, such complications were not encountered.

The prognostic factors for long-term survival were incorporated into a univariate analysis to assess the advantages of this treatment regimen. The number of metastases, unilobar or bilobar metastasis, and the number of chemotherapy cycles were identified as prognostic factors for OS. The prognostic significance of these factors is extensively discussed in the literature.[21,22] Surprisingly, the primary tumor location (rectum *vs.* colon) showed no significant effect on survival. Previous studies report a decreased survival probability for patients presenting with primary rectal tumors

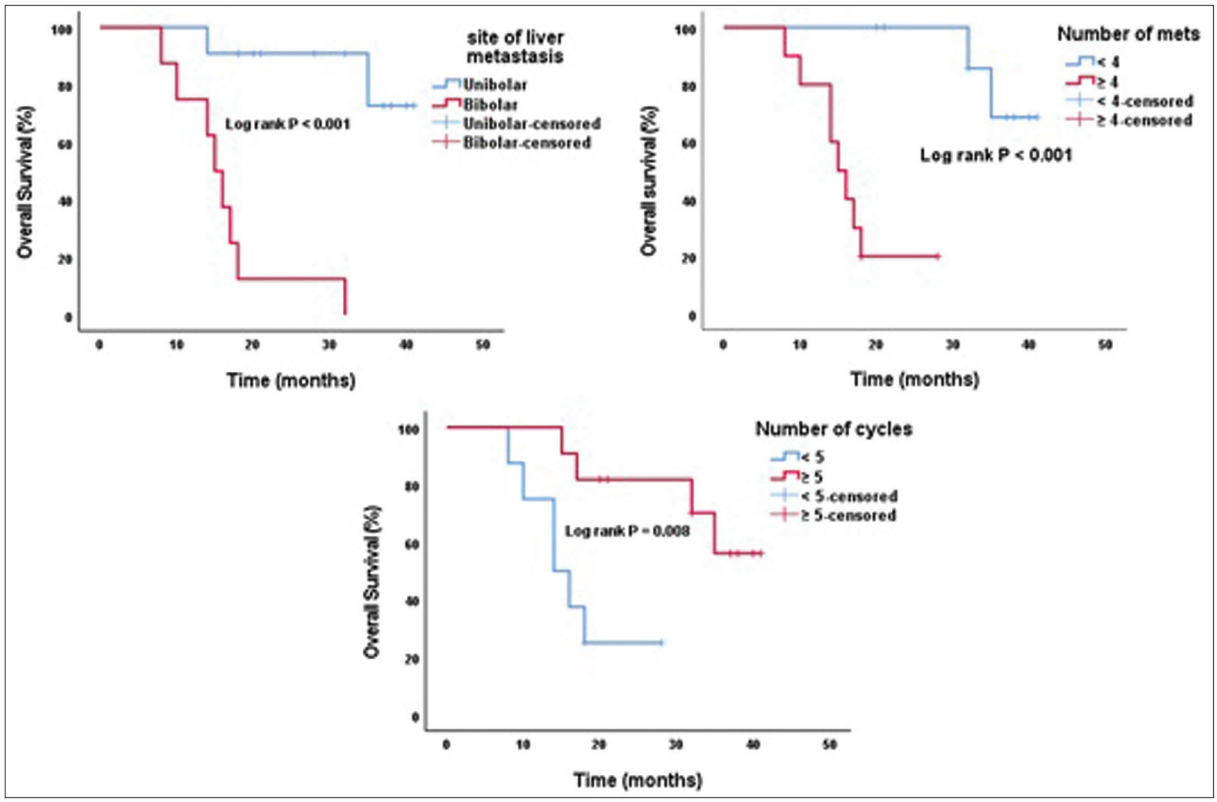

Fig. 3 Factors significantly affecting the survival of the studied patients.

owing to a higher local recurrence rate and difficulty in rectal surgeries. [27,28] This difference might be attributed to the relatively small sample size of this study and the patients' ethnicity to some extent.

Adam et al.[22] report that the site of the primary tumor (rectum), lesion size > 10 cm, metastases number ≥ 3, R1 resection, and incomplete tumor necrosis are the worst prognostic factors for OS and disease-free survival (DFS).

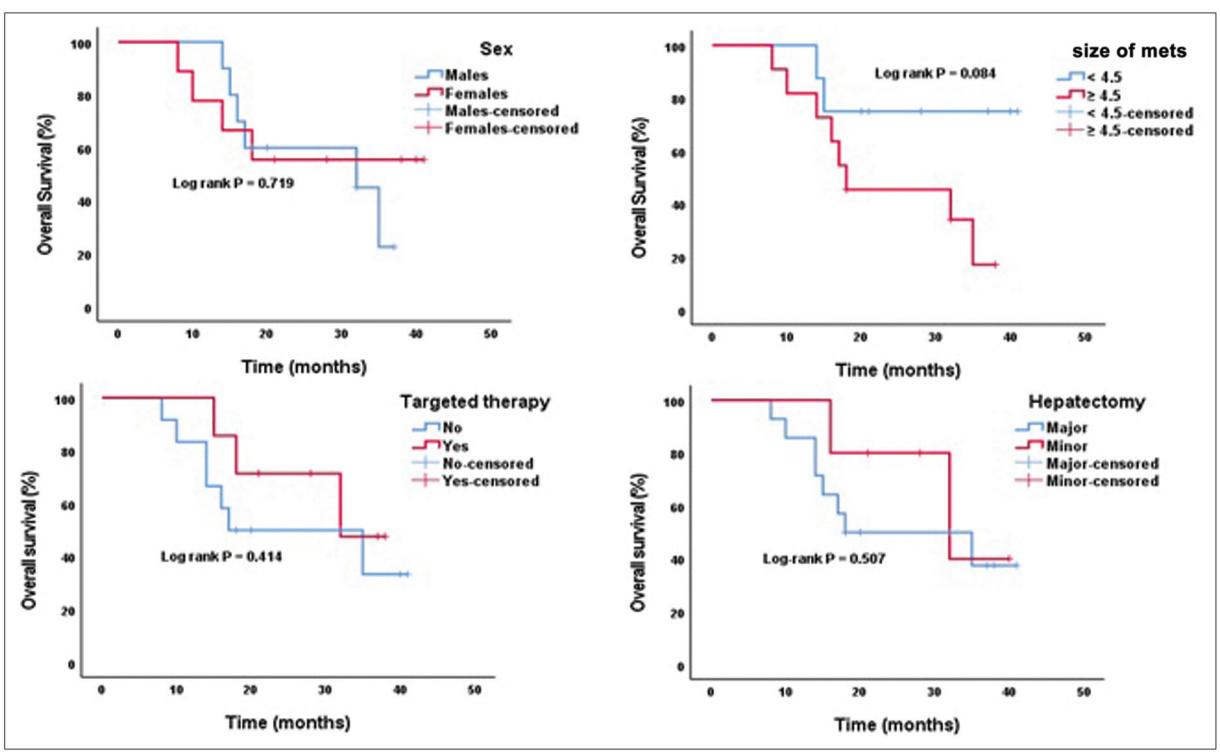

Fig. 4 Factors NOT significantly affecting the survival of the studied patients.

In the present study, the number of metastases ≥ 4, bilobar distribution, and the number of chemotherapy cycles > 5 were poor prognostic factors for OS. These factors are believed to be indicators of aggressiveness and poor biological behavior of the disease. Other prognostic factors should be further evaluated in future studies.

In the present study, 2 (8%) of the initially selected 25 subjects showed disease progression with neoadjuvant chemotherapy and were shifted to palliative chemotherapy. Patients can also develop a chemotherapy-associated liver injury, making them more liable to postoperative morbidity and hepatic complications.

Some patients may show complete clinical response to neoadjuvant chemotherapy, with a complete disappearance of SCLM. This was observed in 2 patients (8%), who were then directly operated on for the primary tumor. One patient later showed recurrence of liver metastasis and was treated with hepatectomy, while the other remained alive without any recurrence. The incidence of complete disappearance of SCLM following chemotherapy alone ranges from 0 to 6%.[29] However, residual microscopic disease is still observed upon resection and can impose a challenge for the surgeon.[30] It was decided in the MDT meeting that patients should be operated upon as soon as the tumor was reduced to a resectable size, and treatment should not be delayed until the complete disappearance of the metastasis.

Limitation of the Study

The main limitation associated with the current study is the small sample size, with only a univariate analysis of predictive factors of survival being performed, and multivariate analysis was not possible. Additionally, patients with extrahepatic disease were not included in the study, although a resectable extrahepatic disease is not a contraindication. Further well-designed prospective randomized clinical trials with larger and diverse cohorts should be conducted to support the results of this study, especially the predictive factors of OS.

Conclusion

The liver-first approach for treating primary CRC can yield acceptable success rates comparable to the conventional curative regimen for SCLM. In cases in which the tumor is unresectable, or the disease burden is high, incorporating a neoadjuvant chemotherapeutic approach can create an opportunity for the liver-first approach. The selection of patients should be critically analyzed, and patients should be regularly followed-up to attain optimal treatment outcomes.

Complete removal of cancerous tissue remains mandatory for the long-term treatment of patients.

It is our recommendation that further multicenter studies including large number of patients should be done.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Conflict of Interests

The authors have no conflict of interests to declare.

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