



Retrospective Study

Role of a liver-first approach for synchronous colorectal liver metastases

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Abstract

AIM: To evaluate the feasibility and survival outcomes of a liver-first approach.

METHODS: Between January 2009 and April 2013, 18 synchronous colorectal liver metastases (sCRLMs) patients with a planned liver-first approach in the Hepatopancreatobiliary Surgery Department I of the Beijing Cancer Hospital were enrolled in this study. Clinical data, surgical outcomes, morbidity and mortality rates were collected. The feasibility and long-term outcomes of the approach were retrospectively analyzed.

RESULTS: Sixteen patients (88.9%) completed the treatment protocol for primary and liver tumors. The main reason for treatment failure was liver disease recurrence. The 1 and 3 year overall survival rates were 94.4% and 44.8%, respectively. The median survival time was 30 mo. The postoperative morbidity and mortality were 22.2% and 0%, respectively, following a hepatic resection, and were 18.8% and 0%, respectively, after a colorectal surgery.

CONCLUSION: The liver-first approach appeared to be feasible and safe. It can be performed with a comparable mortality and morbidity to the traditional treatment paradigm. This approach might offer a curative opportunity for sCRLM patients with a high

liver disease burden.

Key words: Liver metastases; Resection; Colorectal cancer; Synchronous

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Core tip: This is a retrospective study to investigate the feasibility and survival outcome of the liver-first approach for synchronous colorectal liver metastases. The postoperative morbidity and mortality were acceptable. The 1 and 3 year overall survival rates were 94.4% and 44.8%, respectively. The approach should be performed in patients with synchronous colorectal liver metastases with a high liver disease burden.

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INTRODUCTION

The liver is the most common organ for distant metastases from colorectal cancer^[1]. Up to 15%-42% of patients present with synchronous colorectal liver metastases at the time of diagnosis of their primary cancer^[2,3]. The synchronous presentation has been associated with poor survival outcomes^[4,5]. Nevertheless, surgical resection of all tumor sites is considered the only curative therapy for long-term survival from colorectal liver metastases (CRLMs)^[4,6]. Several large case series from tertiary centers have reported 5 year survival rates of 21%-58% and 10 year survival rates of 22%-26%^[4,7,8].

The traditional surgical strategy for resectable synchronous colorectal liver metastases (sCRLMs) is a two-stage approach that includes colorectal cancer resection followed by chemotherapy and a delayed hepatic resection of a CRLM. This approach might result in liver disease progression between the time of colorectal and hepatic resection and render the CRLM unresectable^[9]. This is a particular concern in patients who develop postoperative complications after colorectal cancer resection before the administration of chemotherapy and the hepatic resection of CRLMs^[10].

Upon the realization that liver metastases define the prognosis of a patient, the concept of a liver-first approach in patients with locally advanced rectal cancer and synchronous liver metastases was proposed^[11]. However, there has been limited data published on the feasibility and safety of the liver-first approach for sCRLMs. Therefore, the present study aims to describe the experience with the liver-first approach in a tertiary referral center. The feasibility, security and long-term outcomes of the liver-first

approach were also investigated.

MATERIALS AND METHODS

Study population

Between January 2009 and April 2013, 168 CRLM patients underwent hepatic resection in the Hepato-pancreatobiliary Surgery Department I of Beijing Cancer Hospital. All of the sCRLM patients were identified. Eighteen of these patients with a planned liver-first approach were included in the present study.

Preoperative evaluation

All the patients underwent a complete colonoscopy for colorectal cancer, abdominal and thoracic computed tomography scan and liver and pelvic (only rectal cancer patients) magnetic resonance imaging. The Response Evaluation Criteria for Solid Tumors were applied to the serial imaging studies obtained during a preoperative therapy to determine a chemotherapy response^[12]. The definition of advanced metastatic disease was based on a clinical risk score (CRS) described by Fong *et al.*^[13]. A CRS of 3 or higher has been validated as defining more severe disease.

Preoperative chemotherapy

Preoperative chemotherapy was considered in patients with initially unresectable disease or a high liver disease burden. Patients received oxaliplatin or irinotecan-based chemotherapy. In some recent cases, they also received cetuximab or bevacizumab. The response to chemotherapy was assessed after two or three cycles (more than four cycles for conversion chemotherapy) by MRI and carcinoembryonic antigen levels. When the liver metastases were resectable, a laparotomy was planned more than three weeks after the last course of systemic chemotherapy. Bevacizumab had to be excluded from the last course of chemotherapy to ensure an interval of at least six weeks.

Hepatic resection

All the patients underwent a hepatic resection with curative intent to achieve R0 and preserve as much normal functional liver parenchyma (with adequate vascular inflow, outflow and biliary drainage) as possible. A resection of three or more segments was considered a major hepatectomy^[14]. The normal liver parenchyma remnant volume was more than 40% if a patient received preoperative chemotherapy.

Chemoradiation and primary surgery

Preoperative chemoradiation was used in only two situations: (1) mid-to-low rectal cancer, defined as \leq 10 cm distance from the lower edge of the tumor to the anal verge; and (2) a pre-treatment staging by MRI was T3/T4, or any T category, and N positive^[15]. Radiation therapy consisted of either a long course (total dose of 50 Gy) therapy or a modified short

Table 1 Patients and tumor characteristics

Variable	No. of patients, <i>n</i> = 18
Patient characteristics	
Age (yr), median (range)	54 (21-74)
Sex (male)	10
Pre-operative CEA level (μg/L), median (range)	26.3 (1-860)
Primary tumor site	
Colon	2
Rectum	16
Symptoms caused by the primary tumor	13
Symptoms at the time of presentation	
None	5
Rectal blood loss	7
Changes in bowel habits	6
AJCC T-stage on pathology	
ypT1/ypT2	1
ypT3/ypT4	15
Lymph node status on pathology	
ypN1/ypN2	14
ypN0	2
Hepatic metastasis	
Size of largest metastasis (cm), median (range)	4 (2-16)
No. of metastasis, median (range)	4 (1-12)
Location (unilobular)	11
CRS score	
< 3	2
≥ 3	16
Preoperative chemotherapy	14
Cycles, median (range)	3 (0-5)
Indication	
Conversion	4
Locally advanced liver metastases	10
Regimens of preoperative chemotherapy	
Oxaliplatin	10
Irinotecan	4
Cetuximab	4
Bevacizumab	2
Response of preoperative chemotherapy	
PR	9
SD	4
PD	1

course (total dose of 30 Gy) therapy with capecitabine 825 mg/m² twice per day only on radiotherapy days. A total mesorectal/complete mesocolic excision was performed in all patients.

Follow-up

All the patients had a follow-up visit every 3 mo for the first 2 years, with a physical examination, CEA and CA19-9 serum measurement and abdominal ultrasonography. The patients had a computed tomography scan and colonoscopy every 6 mo. No patients were lost to follow-up.

Statistical analysis

Continuous variables were summarized as a mean. Categorical variables were summarized as a frequency and percentage. A Kaplan-Meier survival was calculated from the date of initial treatment. Statistical analyses were performed using SPSS 17.0 (SPSS, Inc., Chicago, IL, United States).

Table 2 Details of the surgical procedures and early outcomes

Variable	No. of patients, <i>n</i> = 18
Type of hepatic resection	
Major	14
Minor	4
Extent of hepatic resection	
Partial	10
Hemihepatectomy	3
Extended hepatectomy	5
Type of colorectal resection	
Low anterior resection	12
Abdominoperineal resection	2
Left hemicolectomy	2
Resected lymph nodes, median (range)	11 (6-20)
Complications	
Hepatectomy-related	
Hydrothorax	3
Abdominal abscess	1
Minor (Clavien grade < 3)	4
Major (Clavien grade ≥ 3)	0
Post-operative mortality (within 90 d)	0
Surgery on primary cancer	
Anastomotic leakage	1
Abdominal abscess	2
Minor (Clavien grade < 3)	3
Major (Clavien grade ≥ 3)	0
Post-operative mortality (within 90 d)	0

RESULTS

Patient characteristics

Between January 2009 and April 2013, 48 sCRLM patients were identified. The liver-first approach was planned for 18 of them (37.5%). There were 10 male and 8 female patients. The median age was 54 years (range: 21-74; mean: 51.9). At the time of presentation, 13 (72.2%) patients had clinical symptoms. The median size of the liver metastases was 4 cm (range: 2-16; mean: 5.33). The median number of metastases was 4 (range: 1-12; mean: 4.06). The median preoperative CEA blood level was 26.3 ng/mL (range: 1-861; mean: 87.37). The median CRS was 3 (range: 2-4; mean: 3.17). The most common site of the primary tumor was the rectum (*n* = 16; 88.9%). The characteristics of these patients are detailed in Table 1.

Surgery details and early postoperative outcomes

Of the 18 patients in whom a liver-first approach was planned, a major hepatectomy was performed in 14 patients (77.8%). Due to liver recurrence after the hepatectomy, only 2 patients did not undergo surgery for the primary tumor. The operative characteristics of primary and liver metastases are detailed in Table 2. The complication rates after the hepatic and primary resections were 22.2% (*n* = 4) and 18.8% (*n* = 3), respectively. According to the Clavien-Dindo classification system^[16], all the complications were minor (Clavien grade < 3). Importantly, there was no postoperative mortality after the liver or primary

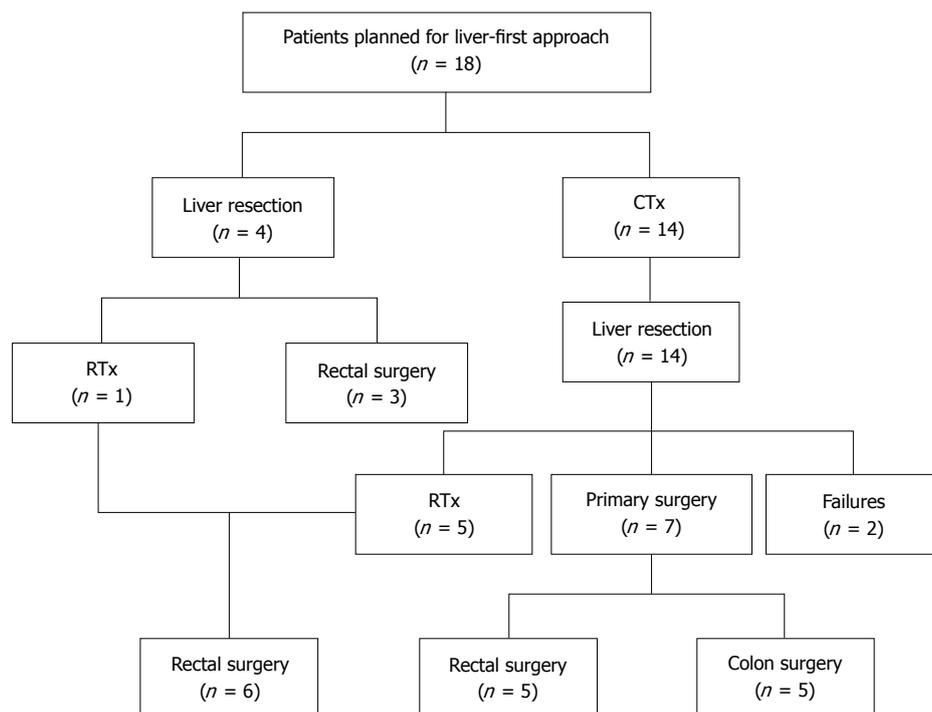


Figure 1 Flow chart of the 18 patients enrolled in the study.

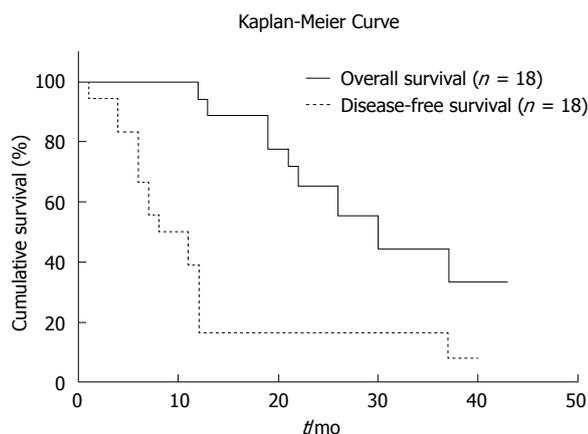


Figure 2 Kaplan-Meier Curve showing the overall and disease-free survivals of the 18 patients who underwent the liver-first approach.

surgeries. The specifics are detailed in Table 2.

Preoperative chemotherapy and chemoradiation

A flow diagram of the treatment overview of all 18 patients is shown in Figure 1. At the time of the initial presentation, 4 patients had unresectable CRLMs and received conversion chemotherapy. Ten patients had locally advanced liver metastases and received neoadjuvant chemotherapy. Two patients refused any neoadjuvant therapy and the other 2 patients had a CRS of less than 3. All of them immediately underwent a hepatic resection. The median preoperative chemotherapy cycle was 3 (range: 0-5; mean: 2.5). It included an oxaliplatin-based chemotherapy in 10 patients and an irinotecan-based chemotherapy in 4

patients. During the first courses of the preoperative chemotherapy, cetuximab was added to 4 patients and bevacizumab was added to 2 patients. Between the window of the hepatic and colorectal surgeries, six patients received radiation therapy, 3 patients a short course of radiation therapy and 3 patients a long course of radiation therapy. The specifics are detailed in Table 3.

Survival analysis

At the time of the last follow-up, 16 (88.9%) patients completed a curative paradigm. The median follow-up was 30 mo (range: 12-43; mean: 30.54). The 1 and 3 year overall survival rates were 94.4% and 44.8%, respectively (Figure 2). The median disease-free survival after surgery was 11 mo (range: 1-40; mean: 13.4). After the hepatic resection, 16 patients had a recurrence during the follow-up. Nine died of disease recurrence. The patterns of recurrence were intrahepatic only (10, 62.5%) and combined intra and extrahepatic (6, 37.5%).

DISCUSSION

In the current series, 18 patients who were scheduled to undergo the liver-first approach were included in this study. Sixteen (88.9%) of them completed the treatment protocol for liver and primary tumors. The percentage of feasibility is in concordance with those reported in assorted cohorts of sCRLM^[17,18]. The remaining two patients deviated from the protocol as a result of recurrence of liver metastasis after resection. For the patients who underwent the liver-

Table 3 Characteristics of 18 patients who underwent the formalized treatment plan

Patient	Largest size (cm)	CEA level (μg/L)	cTN	No. of mets	CTx	Response on CTx	Liver surgery	RTx	Primary surgery
1	16	861.4	cT3N1	1	Xelox	PD	Hemihep	None	Left Hemicol
2	2	1	cT4N2	4	Folfox	PR	Extended hemihep	None	LAR
3	3.5	13.4	cT4N1	1	None	None	Partial	30 Gy/Xeloda	LAR
4	6	113.4	cT3N1	5	Folfox	SD	Partial	None	Left Hemicol
5	2.5	16.8	cT3N1	6	Xelox	PR	Extended hemihep	30 Gy/Xeloda	None
6	7.9	30.4	cT4N1	4	Xelox	PR	Extended hemihep	None	LAR
7	4	3.2	cT2N1	3	Folifiri + Cet	PR	Hemihep	None	LAR
8	2.4	2.4	cT3N2	3	Folifiri + Cet	PR	Partial	50 Gy/Xeloda	LAR
9	5	78.1	cT4N2	1	None	None	Partial	50 Gy/Xeloda	APR
10	3.8	160.9	cT3N2	1	Folfox	SD	Partial	None	APR
11	4	3.7	cT3N0	6	Folifiri + Cet	PR	Partial	30 Gy/Xeloda	LAR
12	1.5	19.7	cT3N1	4	Folfox + Bev	PR	Partial	None	LAR
13	8.5	87.2	cT3N1	5	None	None	Partial	None	LAR
14	12	22.1	cT4N1	6	Folfox + Cet	PR	Hemihep	None	LAR
15	6	79.4	cT3N1	3	Folfoxiri	SD	Extended hemihep	None	LAR
16	4.3	6.1	cT3N0	12	Xelox + Bev	PR	Partial	None	LAR
17	3	34.7	cT3N1	2	None	None	Partial	None	LAR
18	3.5	39.0	cT3N2	6	Xelox	SD	Extended hemihep	50 Gy/Xeloda	None

LAR: Low anterior resection; APR: Abdominal perineal resection; Hemihep: Hemihepatectomy; Hemicol: Hemicolectomy; Partial: Partial hepatectomy; Cet: Cetuximab; Bev: Bevacizumab; xelox: Oxaliplatin plus capecitabine; Folfox: Oxaliplatin, leucovorin and 5-FU; Folfiri: Irinotecan, leucovorin and 5-FU; Folfoxiri: Oxaliplatin, irinotecan, leucovorin and 5-FU.

first approach, the 1 and 3 year overall survival rates were 94.4% and 44.8%, respectively. The median disease free survival time after surgery was 10 mo (range: 1-40; mean: 13.3). The complication rate after hepatic resection and primary resection was 22.2% ($n = 4$) and 18.8% ($n = 3$), respectively. These surgical outcomes were comparable with other results associated with the liver-first approach^[19,20]. In addition, our results may need to be confirmed in a prospective, randomized clinical trial with a larger sample size.

Numerous surgical series have demonstrated that a hepatic resection for CRLM may offer the possibility of long-term survival^[5,6]. Additionally, except for the hepatic resection, no other treatment has shown a survival plateau. These results support that a hepatic resection is the standard practice and only curative treatment for CRLM. Apparently, metastatic disease, rather than primary colorectal cancer, has been proposed to be the main determinant of patient survival. Thus, treating a CRLM should be the first priority^[11,17]. It has been suggested that liver disease burden rather than the primary cancer leads to subsequent systemic metastatic disease^[6,21].

The optimal timing and sequence of surgical resection for sCRLM has been a topic of much debate. The timing of when to undergo a "classic", "simultaneous" or "liver-first" approach remains controversial^[22]. Following the EORTC trial^[23], many centers still favor the classical approach. The rationale for this approach was that the colorectal primary

tumor was the usual source of symptoms and thus should be removed first^[24]. Recent studies have demonstrated that a primary resection in patients with metastatic colorectal cancer significantly increased the 30 d mortality by 10% when compared with a non-metastatic setting^[25]. Therefore, a CRLM might progress beyond resectability during the primary tumor resection (especially in patients with postoperative complications after the colorectal resection).

In the past decade, a simultaneous resection for sCRLMs has been performed more often. The strategy for the simultaneous resection was to avoid missing the surgical opportunity^[26]. Equivalent perioperative morbidity and mortality and survival outcomes were achieved if the colorectal resection was combined with a minor hepatic resection^[19,27]. Compared with a staged resection, a simultaneous resection in patients was accompanied with much milder complications^[28]. Thus, a simultaneous resection was preferred in highly selected patients^[29,30].

The alternative paradigm for the management of sCRLMs is the reverse, or so-called liver-first approach. This modern procedure has evolved as a result of the increasing complexity of care of primary colorectal cancer with the development of preoperative chemoradiotherapy and colonic stenting^[31]. It allows the ability to first control the CRLM and optimizes the chance of a potentially curative hepatic resection, which improves the long-term survival in these patients^[32]. The approach also evaluates the biological behavior of the neoplasm, treats the occult disease

and avoids an operation in patients with rapidly progressing tumors^[33].

De Rosa *et al.*^[34] summarized the indications for the liver-first approach or patients with a high or low liver disease burden with a locally advanced primary tumor. In fact, the ideal patient is likely to be someone who has advanced synchronous liver metastatic disease and rectal cancer^[35]. In our study, 12 patients had locally advanced liver metastases and 4 patients had initially unresectable liver tumors. All of them had a high liver disease burden, which was largely in accordance with the attitude of van der Pool *et al.*^[27] who reported that the appropriate patients for the liver-first approach had a heavier tumor size, diameter and distribution for liver disease burden.

Knowledge of the natural history and pattern of metastatic dissemination in patients with colorectal cancer has revolutionized the understanding and management of this disease. It may be more appropriate to first use chemotherapy to provide early systemic treatment^[18]. Current evidence indicates that colorectal cancer is a chemosensitive disease. Thus, it is logical to start early systemic treatment^[31,36]. Additionally, in patients with a high liver tumor burden, it is crucial to control the disease with down-staging chemotherapy^[37].

Generally, candidates for the liver-first approach include those with a heavy liver disease burden and/or required down-staging therapy with a hepatic resection containing more than three segments.

COMMENTS

Background

The liver is the most common organ for distant metastases from colorectal cancer. Up to 15%-42% of patients present with synchronous colorectal liver metastases (sCRLMs) at the time of a primary cancer diagnosis. However, a standard surgical approach for sCRLM remains undetermined. There were three surgical strategies, including the traditional or classic resection, liver-first resection and simultaneous resection. In this study, the authors retrospectively analyzed the feasibility and survival outcome of the liver-first approach.

Research frontiers

In fact, liver metastases define the prognosis of CRLM patients. The liver-first approach was performed and compared with patient outcomes in the last decades. There were only 4 studies that analyzed the feasibility and survival outcomes of the approach.

Innovations and breakthroughs

Based on present results and daily work experience, the liver-first approach is an appropriate surgical strategy for sCRLM patients with a high liver disease burden. We proposed exact indications for the liver-first approach.

Applications

The candidates for the liver-first approach included those with a heavy liver disease burden and/or who required down-staging therapy with a hepatic resection containing more than three segments.

Terminology

The classic approach is a primary cancer resection followed by a hepatic resection. The liver-first approach is a colorectal liver metastases hepatic resection followed by a primary cancer resection. The simultaneous approach

is a resection for a primary cancer and liver metastasis that is performed simultaneously.

Peer-review

This is an interesting study about the liver first approach for synchronous colorectal liver metastases.

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