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ORIGINAL ARTICLE

Feasibility of the liver-first approach for patients with initially unresectable and not optimally resectable synchronous colorectal liver metastases

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Abstract
Purpose To investigate the outcomes of patients with colorectal cancer and initially unresectable or not optimally resectable liver metastases, who were treated using the liver-first approach in the era of modern chemotherapy in Japan.
Methods We analyzed and compared data retrospectively on patients with asymptomatic resectable colorectal cancer and initially unresectable or not optimally resectable liver metastases, who were treated either using the liver-first approach ($n = 12$, LF group) or the primary-first approach ($n = 13$, PF group).
Results Both groups of patients completed their therapeutic plan and there was no mortality. Postoperative morbidity rates after primary resection and hepatectomy, and post-hepatectomy liver failure rate were comparable between the groups ($p = 1.00$, $p = 0.91$, and $p = 0.55$, respectively). Recurrence rates, median recurrence-free survival since the last operation, and 3-year overall survival rates from diagnosis were also comparable between the LF and PF groups (58.3 vs. 61.5 %, $p = 0.87$; 10.5 vs. 18.6 months, $p = 0.57$; and 87.5 vs. 82.5 %, $p = 0.46$, respectively).
Conclusions The liver-first approach may be an appropriate treatment sequence without adversely affecting perioperative or survival outcomes for selected patients.

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Keywords Colorectal liver metastases · Reverse strategy · Initially unresectable · Conversion therapy

Introduction

By the time of diagnosis of colorectal cancer, about 19 % of patients have synchronous liver metastases [1]. Hepatic resection is the only curative therapy for colorectal liver metastases (CLM) [2, 3]; however, only 25 % of these patients undergo hepatic resection with curative intent [4–6]. Most patients with initially unresectable CLM are treated with systemic chemotherapy, with high response rates, and 30–40 % then undergo R0 resection [7, 8]. Preoperative chemotherapy is also recommended for patients with not optimally resectable CLM, to increase the R0 resection rate [9]. The prognosis of patients with high liver tumor burden may depend on their hepatic lesions. Therefore, the most important goal of their treatment process is to perform curative hepatic resection at the appropriate time.

The traditional therapeutic strategy for patients with advanced synchronous CLM comprises resection of the primary colorectal tumor, systemic chemotherapy, and then hepatic resection when the tumors become resectable. One drawback of this strategy is that resection of an asymptomatic primary tumor unnecessarily delays the start of chemotherapy if the liver metastases are not completely resected. Another option is simultaneous resection of the primary tumor and liver metastases, but this approach is associated with an increased risk of postoperative morbidity for patients with high liver tumor burden who require major hepatectomy [10].

A "liver-first approach", which involves preoperative chemotherapy, followed by hepatic resection, and then

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primary tumor resection, was described recently [11]. We applied this approach to treat patients with an asymptomatic primary tumor and initially unresectable or not optimally resectable CLM. The conceivable advantages of this therapeutic strategy are that it avoids an unnecessary primary tumor resection if the patient cannot undergo R0 resection of CLM, and hepatic resection can be performed within the optimal time frame, during responses to preoperative chemotherapy that are unsusceptible to the primary tumor treatment. However, the perioperative safety and oncological outcomes of this strategy are not clear, especially for patients with initially unresectable or not optimally resectable CLM.

We conducted this retrospective study to compare the results and oncological outcomes of the liver-first approach with those of traditional primary-first approach in patients with initially unresectable or not optimally resectable CLM in the era of modern chemotherapy in Japan.

Methods

Patients

Patients who underwent hepatic resection for CLM at the Kyoto University Hospital between January 2006 and October 2013 were identified from a prospectively maintained institutional database. We defined "not optimally resectable CLM" according to the criteria in a previous report; namely, the number of metastases (>4), metastatic tumor size (diameter >5 cm), and/or the existence of resectable extra hepatic metastases [9]. Initially, unresectable CLM was defined as major vascular invasion and/or a future liver remnant that was predicted to be less than 30 % of total liver volume even with portal vein embolization or two-staged hepatectomy. From a total of 62 patients with synchronous CLM who underwent hepatic resection during the study period, 25 patients with initially unresectable or not optimally resectable CLM were included in this analysis. We used the clinical risk score for CLM, the Beppu nomogram score [12], and the Basingstoke Predictive Index [13] to evaluate individual prognostic risk at the time before initial treatment.

This study was approved by the institutional review board of Kyoto University.

Preoperative therapy

A multidisciplinary cancer board comprising medical oncologists, radiation oncologists, colorectal surgeons and hepato-biliary surgeons made decisions on treatment strategies for all patients with CLM. The consensus approach at our institution is to consider the "liver-first approach" for patients with initially unresectable or not optimally resectable synchronous CLM, when the primary tumor is asymptomatic and not locally advanced. Conversely, the "primary-first approach" is applied for patients with resectable CLM and symptomatic or locally advanced primary tumor. Patients who underwent the liver-first approach received systemic chemotherapy initially, followed by radiological examinations after every 3–4 cycles to evaluate resectability. Hepatic resection was planned when liver metastases were considered resectable. The multidisciplinary cancer board decided on the indications for and sequence of preoperative chemotherapy in patients who underwent the primary-first approach and systemic chemotherapy was administered before or after primary tumor resection. Radiological examinations were performed as for the liver-first approach.

Surgical procedure

All liver resections were performed with curative intent. Portal vein embolization or two-staged hepatectomy were performed when the remnant liver functional volume was considered insufficient based on CT volumetry and the indocyanine green test. Intraoperative contrast-enhanced ultrasonography was used to identify occult lesions, which were undetectable using preoperative imaging studies, and delineate anatomical relationships between tumors and vascular structures. Parenchymal dissection was performed using ultrasonic dissectors. Hepatic resection was combined with concurrent radio frequency ablation in selected patients when all visible tumors could not be treated using resection alone. Colorectal resection was performed using complete mesorectal excision for rectal cancers and lymph node dissection for colonic cancers.

Additional treatment

Patients with extrahepatic metastases underwent additional metastasis removal after primary and hepatic resections. Adjuvant chemotherapy was added to the treatment strategy in most cases, with the chemotherapy regimen and duration decided by the multidisciplinary cancer board.

Statistical analysis

Data were analyzed using Mann–Whitney U tests and the χ^2 test or Fisher's exact test where appropriate. Overall survival (OS) was calculated from the date of diagnosis and estimated using the Kaplan–Meier method. All tests were two-tailed and $p < 0.05$ was considered significant.

Results

Patient characteristics

A total of 25 patients were eligible for this study, 12 of whom underwent the liver-first approach (LF group), and 13 of whom underwent the primary-first approach (PF group). Table 1 compares the preoperative characteristics of patients in each group just before their initial treatment. The median ages of the LF and PF groups were 58 and 68 years, respectively ($p = 0.02$). The number of metastatic liver tumors (7 vs. 5, $p = 0.03$) and serum levels of CA19-9 (455 vs. 28.1, $p = 0.04$) were significantly higher in the LF group than the PF group. The other variables were comparable between the groups. The clinical risk scores revealed that the Beppu nomogram score in the LF group was significantly higher than that in the PF group (18 vs. 14, $p = 0.04$). The Basingstoke Predictive Index was also higher in the LF group than the PF group, but this difference was not significant (14.5 vs. 11, $p = 0.17$). This result suggests that the patients in the LF group have a higher risk of recurrence after hepatectomy than those in the PF group.

Preoperative therapy

One patient from each group required a temporary colostomy for obstruction caused by the primary tumor before the initiation of chemotherapy. All of the patients in the LF group received prehepatectomy chemotherapy. Chemotherapy in the PF group was administered before primary resection to one patient, before and after primary resection to two patients, and between primary and hepatic resection to seven patients. Table 2 summarizes the details of preoperative chemotherapy in the two groups. No patient in either group underwent surgery because of primary tumor-related symptoms before elective surgery.

Table 1 Preoperative characteristics of patients in the two groups

	Liver first ($n = 12$)	Primary first ($n = 13$)	p
Age (years)	58 (36–69)	68 (57–81)	0.03
Primary tumor location, *n* (%)			
Colon	5 (41.7)	5 (38.4)	1.00
Rectum	7 (58.3)	8 (61.6)	
T stage, *n* (%)			
T1	1 (8.3)	0	0.71
T2	2 (16.7)	2 (15.4)	
T3	4 (33.3)	6 (46.2)	
T4	5 (41.7)	5 (38.5)	
N stage, *n* (%)			
N0	7 (58.3)	3 (23.1)	0.18
N1	1 (8.3)	3 (23.1)	
N2	4 (33.3)	7 (53.8)	
Primary tumor related symptoms, *n* (%)			
Yes	6 (50.0)	8 (61.5)	0.70
No	6 (50.0)	5 (38.5)	
Number of hepatic metastases (*n*)	7 (1–30)	5 (1–12)	0.03
Largest hepatic tumor diameter (cm)	5.7 (1–20)	5 (1–20.8)	0.87
Extrahepatic metastases, *n* (%)			
Yes	6 (50.0)	3 (23.1)	0.23
No	6 (50.0)	10 (76.9)	
Resectability, *n* (%)			
Unresectable	9 (75.0)	6 (46.2)	0.22
Not optimally resectable	3 (25.0)	7 (53.2)	
CEA (ng/ml)	105.5 (1.2–8456)	39.3 (2.1–17,508)	0.24
CA19-9 (U/ml)	455 (1–4733)	28.1 (1–307)	0.04
Beppu nomogram score	18 (12–25)	14 (5–21)	0.04
Basingstoke Predictive Index	14.5 (6–20)	11 (4–21)	0.17

Table 2 Details of preoperative chemotherapy in each group

	Liver first ($n = 12$)	Primary first ($n = 13$)
L-OHP based and CPT-11 based	5	4
+Cet and Bev	2	1
+Cet	1	0
+Bev	2	1
–	0	2
L-OHP based	7	6
+Cet and Pani	0	1
+Cet	3	0
+Pani	0	1
+Bev	1	1
–	3	3
No chemotherapy	0	3
Number of cycles	12 (4–40)	13 (4–23)
Response to chemotherapy		
CR	1	0
PR	10	4
SD	0	3
PD	1	3

Hepatic resection

Table 3 compares the intraoperative characteristics and postoperative outcomes of patients in each group. Intraoperative blood loss and operative times were not significantly different between the groups. Postoperative morbidities (Clavien-Dindo classification 2 and 3/greater) in the LF group and PF group were 25.0/16.7 and 23.1/23.1 %, respectively, and postoperative liver failure (ISGLS definition) rates were 25.0 and 15.4 %, respectively. No patient from either group died within 90 days after hepatic resection. A microscopically positive margin was observed in four patients (33.3 %) in the LF group vs. 1 patient (7.7 %) in the PF group ($p = 0.11$). Likewise, the rate of a grossly positive margin was higher in the LF group [two patients (16.7 %)] than in the PF group (0 patient), but this difference was not significant ($p = 0.22$). The median intervals from diagnosis to hepatic resection were 276 days (135–638 days) in the LF group and 318 days (49–2002 days) in the PF group ($p = 0.42$).

Primary tumor resection

Table 4 shows the perioperative characteristics in each group. Intraoperative blood loss, operative times and postoperative morbidity rates were comparable between the groups. There was no postoperative mortality in either group. All patients underwent pathological R0 resection. The median intervals from diagnosis to primary resection were 362 days (189–689 days) in the LF group and 26 days (13–171 days) in the PF group ($p < 0.0001$).

Table 3 Perioperative characteristics of patients in each group at hepatectomy

	Liver first ($n = 12$)	Primary first ($n = 13$)	p
Type of hepatic resection, *n* (%)			
Major	7 (58.3)	9 (69.2)	0.69
Minor	5 (41.7)	4 (30.8)	
Blood loss (ml)	902 (290–11,980)	530 (200–5379)	0.24
Operative time (min)	422 (230–636)	383 (256–500)	0.53
Postoperative morbidity, *n* (%)			
Grade 2 and greater	3 (25.0)	3 (23.1)	1.00
Grade 3 and greater	2 (16.7)	3 (23.1)	1.00
Postoperative liver failure, *n* (%)	3 (25.0)	2 (15.4)	0.64
Macroscopically positive margin, *n* (%)	2 (16.7)	0	0.22
Microscopically positive margin, *n* (%)	4 (33.3)	1 (7.7)	0.16
Postoperative hospital stay (days)	16 (10–49)	13 (9–95)	0.43

Table 4 Perioperative characteristics of patients in each group at primary resection

	Liver first ($n = 12$)	Primary first ($n = 13$)	p
Operative time (min)	250 (151–611)	240 (178–443)	0.98
Blood loss (ml)	36 (0–670)	20 (0–700)	0.52
Postoperative morbidity, *n* (%)			
Grade 2 and greater	2 (16.7)	3 (23.1)	1.00
Grade 3 and greater	2 (16.7)	0 (0)	0.22
Postoperative hospital stay (days)	15 (9–65)	14 (8–101)	0.93

Interval of therapies

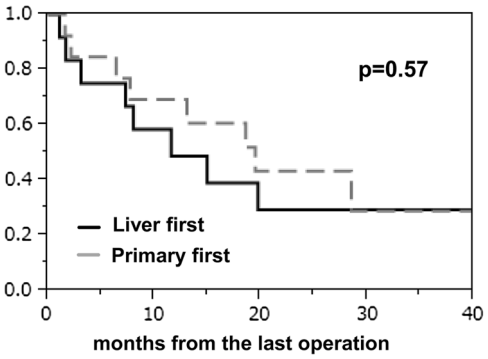
The median intervals from diagnosis to the beginning of chemotherapy in patients who received chemotherapy were 26 days (15–44 days) in the LF group and 39 days (22–81 days) in the PF group ($p = 0.004$). The median intervals between both operations were 64 days (35–251 days) in the LF group and 222 days (28–1981 days) in the PF group ($p = 0.11$). The median intervals from diagnosis to the completion of each therapeutic plan were 276 days (135–638 days) in the LF group and 318 days (49–2002 days) in the PF group ($p = 0.81$).

Extrahepatic metastases

Lung metastases in patients with extrahepatic metastases were observed in five patients from the LF group and three patients from the PF group. One patient in the LF group had distant lymph node metastases at the time of diagnosis of colorectal cancer. Two patients in the LF group and one patient in the PF group underwent R0 lung resection after primary and hepatic resections. Two patients in the LF group and one patient in the PF group showed a complete response to chemotherapy.

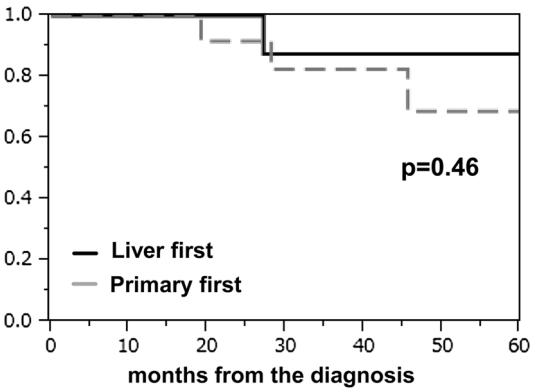
Survival and recurrence

The median follow-up from the last operation in each group was 26 months, during which recurrence was detected in seven patients from the LF group (58.3 %) and eight from the PF group (61.5 %; $p = 0.87$). Liver and lung recurrences were found in six and two patients from the LF group, respectively, whereas liver, lung, and lymph node recurrences, and peritoneal dissemination were found in seven, four, four, and two patients, respectively, from the PF group, with some overlap. The median recurrence-free survival (RFS), 1-year RFS, and 3-year RFS rates following the last operation were 10.5 months, 48.6 % (95 % CI = 22.8–75.2 %) and 29.2 % (95 % CI = 9.9–60.6 %), respectively, in the LF group, and 18.6 months, 59.7 % (95 % CI = 39.9–76.8 %), and 29.4 % (95 % CI = 13.5–52.7 %), respectively, in the PF group ($p = 0.57$) (Fig. 1). The 1- and 3-year OS rates from diagnosis were 100 and 87.5 % (95 % CI = 46.3–98.3 %), respectively, in the LF group, and 100 and 82.5 % (95 % CI = 50.5–95.6 %), respectively, in the PF group ($p = 0.46$) (Fig. 2).



	Median RFS (months)	1-y. RFS	3-y. RFS
Liver first	10.5	48.6%	29.2%
Primary first	18.6	59.7%	29.4%

Fig. 1 Comparison of recurrence-free survival from the last operation for colorectal cancer between patients who underwent the liver-first approach vs. those who underwent the primary-first approach. There were no significant differences between the groups ($p = 0.57$). *RFS* recurrent free survival



	1-y. OS	3-y. OS
Liver first	100.0%	87.5%
Primary first	100.0%	82.5%

Fig. 2 Comparison of overall survival from the diagnosis of colorectal cancer between patients who underwent the liver-first approach vs. those who underwent the primary-first approach. There were no significant differences between the groups ($p = 0.46$). *OS* overall survival

Discussion

We conducted this study to evaluate our experience of using the novel therapeutic strategy "liver-first approach" to treat initially unresectable or not optimally resectable simultaneous CLM. Several previous reports have reported the feasibility and effectiveness of the liver-first approach in clinical series [11, 14–19], but only one has examined the liver-first approach for patients with initially unresectable CLM [20]. This study showed a higher incidence of recurrence in patients treated with the liver-first approach than in patients treated with the primary-first approach, but only 20 % of patients for whom the liver-first approach was

planned were able to complete the therapeutic consequence [20]. In contrast, all 12 of our patients for whom the liver-first approach was planned completed their therapeutic plan.

Precedent procedures for patients with resectable primary tumor and advanced liver metastases included the primary-first approach concomitant with systemic chemotherapy between primary and hepatic resections. This approach is reasonable for patients with symptomatic primary tumors because it prevents chemotherapy-related primary tumor symptoms, such as bleeding and intestinal perforation. However, primary resection is not always required if the primary tumor is asymptomatic and not all of the metastatic tumors can be resected completely [21, 22]. Moreover, postoperative complications such as anastomotic leakage or ileus, which occur in 10–40 % of patients after colorectal cancer surgery, may delay prehepatectomy chemotherapy [23–27]. Another traditional procedure, simultaneous resection of primary and CLM, may be beneficial because it requires a shorter total hospital stay, but it is associated with high morbidity rates in patients with advanced CLM who need major hepatectomy [10, 28].

The liver-first approach may alleviate the disadvantages of the traditional approach. Patients with advanced synchronous CLM and asymptomatic primary tumor are good candidates for this therapeutic strategy, for the following two reasons. First, systemic chemotherapy can be performed immediately after the diagnosis of synchronous CLM and hepatic resection may be performed during the tumor response to chemotherapy. The intervals from diagnosis to first chemotherapy were significantly shorter in patients treated using the liver-first approach than in patients treated using the primary-first approach, in our study. Second, unnecessary non-curative primary tumor resection can be avoided, unless the liver metastases respond to the chemotherapy and become resectable. One concern about the liver-first approach is that primary tumor-related complications of chemotherapy may occur if the primary tumor is left in situ. Bevacizumab use previously raised concerns about an increased risk of tumor perforation when the primary tumor was left in place. However, a recent report described the safety of an initial non-operative approach using bevacizumab, with major morbidity related to the primary tumor seen in 14 % of patients, including perforation in 2.3 %, but no serious bleeding [29]. One patient from each group in the present study required a temporary colostomy before preoperative chemotherapy, but no other patients underwent urgent surgery for the primary tumor. In terms of systemic chemotherapy with or without primary tumor resection, Faron et al. recently reported that primary tumor resection was independently associated with the better overall survival of colorectal cancer patients with unresectable synchronous metastases [30]. However, the selection criteria for primary tumor resection prior to systemic chemotherapy were unclear in the study and the reported 3-year overall survival of approximately 20 % was much lower than the 85 % in our study. Moreover, Slesser et al. reported that upfront primary tumor resection in patients with synchronous CLM resulted in progressive disease [31]. According to another report, overall survival did not significantly differ between the two therapeutic options [32]. Thus, it remains controversial whether the primary tumor should be resected before systemic chemotherapy in patients with initially unresectable synchronous CLM. Another concern about this approach is that the primary tumor may become unresectable because of progression during the treatment of liver metastases or perioperative complications of hepatectomy. In several previous reports, 3–80 % of patients could not complete the liver-first approach because of primary tumor progression [14–17, 19, 20]. However, all patients in our LF group, who had undergone hepatic resection, completed the subsequent primary resection with negative tumor margins. One possible explanation for this contradiction is that all of our patients who underwent the liver-first approach had resectable primary tumors, unlike in the previous reports. Moreover, the interval period between both operations in the LF group was comparable to that in the PF group, which indicates that hepatic resection as the first surgery in the LF group did not delay primary tumor resection. The macroscopically and microscopically R0 resection rates at hepatectomy were lower in the LF group than in the PF group. This result may be attributed to the different number of liver tumors in the two groups. There were no perioperative deaths in either group, and there were no significant differences in perioperative morbidity during each operation between the groups. These results support the safety and feasibility of the liver-first approach for CLM patients with a resectable primary tumor and high liver tumor burden.

The overall survival from diagnosis was comparable between the LF and PF groups; however, the predictive recurrence risk was higher in the LF group, by using the prognostic scores of CLM [12, 13]. Brouquet et al. compared primary-first resection, combined resection, and liver-first resection in patients with synchronous CLM and intact primary tumors, and found no significant differences among these strategies in overall survival [18], which is consistent with our results. The recurrence rates and patterns were similar in both groups, but some clinicians may be afraid that the liver-first approach promotes micrometastases from the primary tumor, which were left in situ. All of the patients in our LF group had initially unresectable or borderline resectable CLM, and the recurrence rate of 58.3 % in our study was comparable to that of previous reports about the liver-first approach [14, 15, 17–20] and conversion therapy for initially unresectable

CLM [33]. The median recurrence-free survival time from the last operation for the LF group was shorter than that for the PF group, but the difference was not significant and can be explained by the higher recurrence risk of the patients in the LF group, as judged by the nomogram score. These results support the oncological safety of the liver-first approach.

Our study had the following limitations: First, the study population was small, and patient data were analyzed retrospectively at a single institution. Second, the treatment sequence in each patient was not randomly decided, and comparisons of outcome between the groups were not appropriate because of selection bias and differences in patient characteristics. Nevertheless, our results provided evidence to support the feasibility and benefit of the liver-first approach for selected patients.

In conclusion, we evaluated the feasibility of the liver-first approach, in comparison with the primary-first approach, for colorectal cancer patients coincident with initially unresectable or not optimally resectable CLM. Both strategies were associated with similar perioperative and survival outcomes; however, the liver-first approach did not delay or preclude treatment of the primary tumor. The therapeutic strategy for synchronous CLM is complicated, but the liver-first approach may be the appropriate treatment sequence for selected patients with an asymptomatic resectable primary tumor and advanced liver metastases, in the era of modern chemotherapy.

Compliance with ethical standards

Conflict of interest We have no conflicts of interest to disclose.

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