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Preliminary Results of 'Liver-First' Reverse Management for Advanced and Aggressive Synchronous Colorectal Liver Metastases: A Propensity-Matched Analysis

Kuniya Tanaka[a, b] Takashi Murakami[a] Kenichi Matsuo[a] Yukihiko Hiroshima[b] Itaru Endo[b] Yasushi Ichikawa[c] Masataka Taguri[d] Keiji Koda[a]

[a]Department of Surgery, Teikyo University Chiba Medical Center, Chiba, Departments of [b]Gastroenterological Surgery, [c]Clinical Oncology, and [d]Biostatistics and Epidemiology, Yokohama City University Graduate School of Medicine, Yokohama, Japan

Key Words
Colorectal cancer · Liver metastasis · Liver-first

Abstract
Background: Although a 'liver-first' approach recently has been advocated in treating synchronous colorectal metastases, little is known about how results compare with those of the classical approach among patients with similar grades of liver metastases. ***Methods:*** Propensity-score matching was used to select study subjects. Oncologic outcomes were compared between 10 consecutive patients with unresectable advanced and aggressive synchronous colorectal liver metastases treated with the reverse strategy and 30 comparable classically treated patients. ***Results:*** Numbers of recurrence sites and recurrent tumors irrespective of recurrence sites were greater in the reverse group then the classic group ($p = 0.003$ and $p = 0.015$, respectively). Rates of freedom from recurrence in the remaining liver and of freedom from disease also were poorer in the reverse group than in the classical group ($p = 0.009$ and $p = 0.043$, respectively). Among patients treated with 2-stage hepatectomy, frequency of microvascular invasion surrounding macroscopic metastases at second resection was higher in the reverse group than in the classical group ($p = 0.011$). ***Conclusions:*** Reverse approaches may be feasible in treating synchronous liver metastases, but that strategy should be limited to patients with less liver tumor burden.

Introduction

Approximately half of the patients with colorectal cancer develop liver metastasis during the course of their disease. Among patients developing metastases, 15 to 42% present with liver metastases synchronous with the primary [1–3]. Classically, interval (i.e., delayed) hepatic resection has been recommended to permit detection and resection of initially occult hepatic metastases after they become evident during the waiting period after resection of the primary. Another aim of the classical strategy is to eliminate the primary tumor as a source of potentially disseminating neoplastic cells. Alternatively, a combined strategy, with simultaneous resection of primary and liver lesions, has been used to avoid delaying surgical resection of either metastatic disease or the primary.

Over the last decade, major advances in chemotherapy have substantially improved chances of cure for patients with advanced liver metastases from colorectal cancer.

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E-Mail karger@karger.com
www.karger.com/dsu

Kuniya Tanaka, MD
Department of Surgery
Teikyo University Chiba Medical Center
3426–3 Anesaki, Ichihara Chiba 299-0111 (Japan)
E-Mail U17–92TS@med.teikyo-u.ac.jp

Improved responses of colorectal liver metastases to chemotherapy offer possible curative hepatectomy after tumor downsizing in patients with initially unresectable metastases [4]. In the presence of unresectable metastases synchronous in emergence with the primary, the classical approach is resection of the primary tumor followed by effective chemotherapy, eventually succeeded by liver surgery if sufficient reduction in volume of metastases was obtained by chemotherapy. Performing chemotherapy to reduce size of the metastatic tumors prior to resection of the primary tumor represents another way to treat synchronous unresectable liver metastases according to reports advocating leaving the primary tumor in place with no immediate need for primary tumor resection in patients with stage IV disease [5, 6]. As recently developed high-impact chemotherapy sometimes can render initially unresectable liver metastases resectable, a 'liver-first' approach, also known as a reverse strategy, has been advocated [7].

A liver-first approach in which liver metastases are resected before the primary tumor initially was proposed for patients with advanced synchronous liver metastases and/or metastases from rectal cancer who required chemo-radiotherapy prior to primary resection. In patients with substantial burdens of liver metastases, the traditional approach would permit progression of liver disease following primary resection and while waiting to begin downstaging chemotherapy. Complications of colorectal surgery could further delay starting treatment of liver metastases. The rationale behind the liver-first approach is control of liver metastases first, thus optimizing chances of potentially curative liver resection, which strongly influences long-term survival [8]. In patients with a large liver tumor burden, one strives to control the disease with downstaging chemotherapy and then consider liver resection first as this possibly can improve long-term survival. The several previous studies of the liver-first approach, [7, 9–15] however, did not focus on patients with heavy liver tumor burdens likely to lead to their death. The median number of metastases was only 2–6, and bilobar metastases were present only in 50–70% of patients. Further, the liver metastases were not always unresectable or life-threatening. However, the greatest impact of the reverse approach might be on allowing radical resectability of extensive liver lesions.

In this preliminary study we therefore aimed to clarify the impact of the reverse strategy upon oncologic outcomes in patients with initially unresectable, aggressive liver metastases.

Patients and Methods

Patients

Beginning in 2009 our department used the liver-first approach for initially unresectable liver metastases presenting synchronously with a colorectal primary. As a tertiary care hospital, our institution mainly treated received referred patients whose colorectal primary already was resected, often with various chemotherapy regimens already given after primary resection. In contrast, the present preliminary study included 10 consecutive patients treated with the reverse strategy. Numbers of metastases were 4 in 1 patient, 6 in 2 patients, 8 in 1 patient, and 10 or more in 6 patients; the median number of metastases at hepatectomy was 13 (range, 4–46). In all patients, metastases were present in both major lobes.

From 1992 to 2012, we treated 464 patients in whom colorectal liver metastases were diagnosed at liver resection with curative intent. Among these patients, metastases synchronous with colorectal primaries were diagnosed in 244 (47.9%). Bilobar distribution of metastases was recognized in 151 of patients with synchronous metastases. These 151 patients included 92 men and 59 women whose median age was 64 years (range, 21–80). The median number of metastases was 6 (range, 2–46). These 151 patients included 10 patients treated with the reverse strategy. The other 141 patients all remained eligible for analysis by propensity matching the reverse strategy cohort. We used a logistic regression model to estimate the propensity score using a 'greedy' 5-to-1 digit-matching algorithm for 1:3 matching [16]. Finally, 30 patients of the 141 were selected as an appropriate classically treated comparison group by propensity matching analysis, using age, gender, number of metastases, maximum size, primary site, and presence or absence of extrahepatic metastases as variables for matching. Members of this classically treated group included 1 patient with simultaneous resection of both primary tumor and liver metastases, 24 with resection of the primary site followed by liver resection, and 5 in whom colorectal resection was combined with the first, smaller stage in a 2-stage hepatectomy.

Oncologic outcomes of the 2 groups were compared. Tumor progression activity was also compared between patients treated with 2-stage hepatectomy in each group by determining frequency of micrometastases surrounding macroscopic metastases.

This study protocol was approved by the Institutional Ethical Committee at Yokohama City University. Written informed consent was obtained from all patients involved in this study.

Hepatectomy Procedures

To determine whether or not a hepatectomy procedure was acceptably safe for a patient, we used a prediction score (PS) introduced by Yamanaka et al. [17]. The PS was calculated using the formula PS = –84.6 + 0.933 a + 1.11 b + 0.999 c, where 'a' was the anticipated resection fraction (%) calculated from computed tomography (CT) volumetry; b, indocyanine green retention rate at 15 min (%), and 'c', patient age in years. A PS less than 50 indicated that a given hepatectomy would be acceptable. Patients with a PS of 50 or more were considered for a 2-stage approach with or without prehepatectomy portal vein embolization.

Assessment of complications followed a recently published standardized complication classification system (Clavien-Dindo classification) [18]. Complications were defined as any deviation from an uneventful postoperative course within 30 days of operation.

Chemotherapy before Hepatectomy

Components of regimens, numbers of lines used for treatment administration and numbers of courses usually depended upon individual patient responses to chemotherapy, or upon oncologists' opinions. Regimens usually were combinations of 5-fluorouracil, l-folinic acid, and oxaliplatin and/or irinotecan, with or without use of a monoclonal antibody. Response to chemotherapy was evaluated using CT, according to the Response Evaluation Criteria in Solid Tumors criteria (RECIST) criteria [19].

Pathologic Examination

Existence of microscopic vasculobiliary invasion surrounding macroscopic metastatic liver tumors was evaluated using resected liver specimens stained with hematoxylin. Vasculobiliary invasion was defined as tumor cells invading the portal vein, hepatic vein, and/or intrahepatic bile duct, irrespective of continuity or discontinuity with macroscopic liver tumors.

Patient Follow-Up

One week after liver resection, CT was performed to confirm liver regeneration status and to check for any intraabdominal abnormality related to the operation. In patients with a planned 2-stage hepatectomy, CT was also performed 3 weeks after liver resection to evaluate future liver remnant volume and to estimate tolerability of the second resection. Patients underwent follow-up evaluation monthly at an outpatient clinic. Serum carcinoembryonic antigen (CEA), carbohydrate antigen 19–9, and p53 were measured every month and CT was performed every 3–4 months for 5 years after the most recent operation.

Statistical Analysis

Statistical comparisons of baseline data were performed by the Mann-Whitney U test, the χ^2 test, or Fisher's exact test as appropriate. Survival rates were calculated by the Kaplan-Meier method. A difference was considered significant when the 2-sided p value was below 0.05.

Results

In addition to the matched variables (age, gender, number of metastases, maximum size, primary site, and presence or absence of extrahepatic metastases), no differences of treatment-related variables were observed between groups (table 1). Prehepatectomy chemotherapy was performed in all patients in the reverse group and 24 patients (80%) in the classical group. Numbers of lines used and of courses of prehepatectomy chemotherapy respectively were a median of 3 (1–4) and 6 (6–33) in the reverse group, and 1 (1–5) and 5 (2–16) in the classic group. Responses to final chemotherapy in the reverse group were partial response (PR) in 7 patients and stable disease (SD) in 3; these were PR in 14, SD in 6, and disease progression in 4 in the classical group. Two-stage hepatectomy was planned for 6 patients in the reverse group and 17 patients in the classical group. Among these patients, 1 in the reverse group and 2 in the classical group could not undergo the second stage because of insufficient future remnant liver volume (1 patient each in both groups) or disease progression in an extrahepatic site during treatment of postoperative complications after the first stage. As a result, 1 patient in the reverse group and 2 patients in the classical group had noncurative (R2) liver resections. Another patient in the classical group who had concomitant extrahepatic metastases at liver resection could not have extrahepatic resection, resulting in R2 status with curative liver resection. As for primary tumor resection in the reverse group, only 2 patients finally underwent primary resection. The other 8 patients did not have primary resection because of recurrence requiring multidisciplinary treatment. Accordingly, the rate of completion of the reverse program was 20%.

Perioperative Variables and Morbidity

Operative time, intraoperative blood loss, incidence of blood transfusion, and postoperative hospital stay did not differ significantly between the 2 groups at both first and second hepatectomy, except for hospital stay at first hepatectomy (table 2). Severity and incidence of postoperative complications at first hepatectomy were grade I in 1 patient (10%) and grade IIIa in 1 (10%) in the reverse group, being grade I in 2 patients (6.7%), grade II in 6 (20%), and grade IIIa in 2 (6.7%) in the classical group. At second hepatectomy these were grade I in 1 patient (20%) and grade II in 1 (20%) in the reverse group, and grade II in 6 (40%), grade IIIa in 1 (6.7%), and grade IVa in 1 (6.7%) in the classical group.

Recurrence after Hepatectomy

After liver resection, recurrences were detected in all 9 patients (100%) in the reverse group who underwent curative liver resection (table 3). Among 28 patients with curative resection in the classical group, curative resection of concomitant extrahepatic metastases was precluded in a single patient as described earlier; recurrence was observed in 23 of the remaining 27 patients (85%, p = 0.55 vs. the reverse group). Numbers of initial recurrence sites were greater in the reverse group than the classical group (p = 0.003). All patients with recurrence in the classical group developed recurrence within a single organ. When total numbers of recurrent tumors were compared between groups irrespective of recurrence sites, a greater proportion of patients in the reverse group had multiple tumors than in the classical group (p = 0.015).

Table 1. Overall patient profiles for the 2 groups

	Reverse approach (n = 10)	Classical approach (n = 30)	p value
Age, years	63.5 (39–74)	61.0 (37–80)	0.696
Gender, %			
Male	5 (50)	8 (27)	0.246
Female	5 (50)	22 (73)	
Primary site, %			
Colon	8 (80)	22 (73)	>0.999
Rectum	2 (20)	8 (27)	
Liver metastasis			
Number	13 (4–46)	11 (2–24)	0.416
Maximum size, mm	53 (25–130)	47 (5–140)	0.563
Extrahepatic metastasis			
Present, %	1 (10)	2 (15)	>0.999
Serum CEA, ng/ml	29.9 (5.8–990.5)	113.7 (1.8–10.535)	0.303
Treatment-related, %			
Prehepatectomy chemotherapy			
Performed	10 (100)	24 (80)	0.307
Portal vein embolization			
Performed	6 (60)	15 (50)	0.721
Staged hepatectomy			
Performed	6 (60)	17 (57)	>0.999
Extent of hepatectomy			
Trisection (+partial)	0	5 (17)	0.527
Extended hemiliver (+partial)	3 (30)	8 (27)	
Hemiliver (+partial)	4 (40)	5 (17)	
Bi-section (+partial)	0	2 (7)	
Mono-section (+partial)	1 (10)	5 (17)	
Mono-segment (+partial)	1 (10)	1 (3)	
Partial	1 (10)	4 (13)	
Curability of liver metastasis			
R0	5 (50)	9 (30)	0.496
R1	4 (40)	18 (60)	
R2	1 (10)	3 (10)	

Values of continuous variables are medians. Ranges are shown in parentheses. CEA = Carcinoembryonic antigen; R0 = resection with tumor-free margin of >0 mm; R1 = resection with tumor-free margin of 0 mm; R2 = incomplete macroscopic resection.

Table 2. Perioperative variables and morbidity

	Reverse approach	Classical approach	p value
First hepatectomy	(n = 10)	(n = 30)	
Operative time, min	393 (300–566)	430 (222–640)	0.822
Blood loss, ml	436.5 (199–864)	500 (5–4,047)	0.833
Transfused patients, %	20	36.7	0.451
Hospital stay, days	9 (7–30)	13 (5–44)	0.043
Morbidity, %	20	33.3	0.693
Second hepatectomy	(n = 5)	(n = 15)	
Operative time, min	399 (332–517)	384.5 (255–765)	0.833
Blood loss, ml	560 (49–984)	988.5 (223–8,000)	0.170
Transfused patients, %	20	40	0.613
Hospital stay, days	12 (9–27)	18 (7–81)	0.316
Morbidity, %	40	53.3	>0.999

Values of continuous variables are medians. Ranges are shown in parentheses.

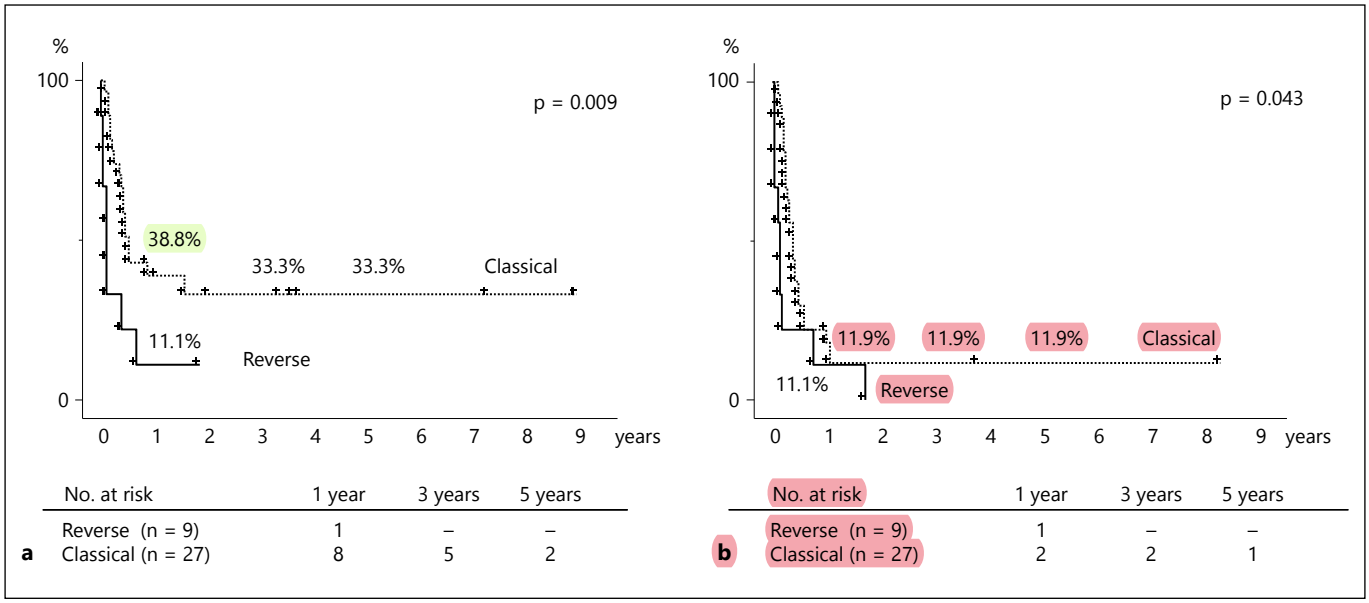

Fig. 1. Cumulative remnant liver recurrence-free rates and disease-free rates after final liver resection for patients in the classical group (broken line) and the reverse group (continuous line). Both liver recurrence-free rates (**a**, p = 0.009) and disease-free rates (**b**, p = 0.043) were significantly poorer in the reverse group than the classical group.

Table 3. Details of recurrence after hepatectomy

	Reverse approach (n = 9)	Classical approach (n = 23)	p value
Number of initial recurrence sites, %			
1	5 (56)	23 (100)	0.003
2	3 (33)	0	
3	1 (11)	0	
Site of initial recurrence, %			
Liver	4 (44)	11 (48)	0.022
Lung	1 (11)	7 (30)	
Lymph node	0	2 (7)	
Bone	0	2 (7)	
Brain	0	1 (4)	
Multiple	4 (44)	0	
Total number of initial recurrences, %			
1	3 (33)	12 (52)	0.015
2	0	4 (17)	
3	0	3 (13)	
4	1 (11)	3 (13)	
≥5	5 (56)	1 (4)	

Long-Term Survival and Freedom from Recurrences

When long-term and recurrence-free survival was compared between groups, the remnant liver recurrence-free rate was significantly poorer in the reverse group than the classical group (p = 0.009, fig. 1a). The disease-free rate was also poorer in the reverse group than the classical group (p = 0.043, fig. 1b). Overall survival after final hepatectomy did not differ between groups, on account of both small numbers of patients and a short follow-up period in many patients.

Microscopic Vascular Invasion Surrounding Macroscopic Metastases

Microscopic vascular invasion surrounding the liver tumor could be detected in 67% (6/9) of patients in the reverse group and 32% (9/28) in the classical group at first liver resection (p = 0.118). In the former and latter groups, 5 and 14 patients respectively underwent 2-stage hepatectomy. All of these patients underwent portal vein embolization concurrently with the first hepatectomy. Among 5 patients in the reverse group and 14 patients in the classical group who underwent 2-stage hepatectomy, frequency of such microscopic invasion at second hepatectomy was higher in the reverse group (100% or 5/5) than in the classical group (29% or 4/14; p = 0.011).

Discussion

This study included only patients with advanced and aggressive unresectable metastases, and investigated efficacy of the reverse strategy. Numbers of initial recurrence

sites and total numbers of recurrent tumors irrespective of recurrence sites were significantly greater in the reverse group than the classical group, and the remaining liver-recurrence free rates and disease-free rates were also poorer in the reverse group. Patients most likely to be offered the liver-first approach are those with liver metastases requiring down-staging therapy in an effort to enable potentially curative liver resection. Overall oncologic results in patients who received prehepatectomy chemotherapy are dependent on the response to neoadjuvant therapy [20]. Although numbers of administration lines and of cycles of prehepatectomy chemotherapy tended to be higher in the reverse group than the classical group, the response to such chemotherapy was more favorable in the reverse group than in the classical group. Thus, our results suggest that poor outcome of patients in the reverse group probably reflected ongoing activity of the primary tumor left behind or circulating tumor cells derived from the primary tumor. As for frequency of microscopic vascular invasion surrounding liver tumors, no difference was seen between groups at first hepatectomy, but microscopic invasion in patients treated with 2-stage hepatectomy could be detected more frequently at the second liver resection in the reverse group than in classically treated patients. These findings support our belief in the importance of circulating tumor cells from primary tumors when hepatectomy precedes primary resection. Early hepatectomy as the first operation has been reported to control liver metastases, optimizing the chance of curative liver resection, while subsequently preventing loss of primary tumor-induced inhibition of metastases [21, 22]. However, our results suggest that acceleration of liver metastasis development by remaining primary tumor may also occur.

Ferrand et al. [23] recently reported that in patients with synchronous unresectable metastasis from a colorectal primary, resection of the primary tumor improved outcomes in a pooled analysis involving individual patient data from 4 first-line chemotherapy trials. Those authors found primary tumor resection to be an independent predictor of better overall and progression-free survival, even in patients whose metastases never were curatively resected. This report supports our impression of a poor overall outcome with the reverse strategy.

Although reverse strategy protocols were completed in 65–73% of patients in previous reports [8–10, 12, 13], only 20% of our reverse-strategy patients completed the planned therapy. Our patients had a median of 13 metastatic nodules, and all had a bilobar distribution of lesions. This was worse than for subjects of previous reports, whose median metastatic tumor number was 2 to 6 [8, 9, 11–13, 15], with 52–71% of patients showing a bilobar distribution [8, 10, 12–15]. Further, 2-stage hepatectomy was performed in 0–38% of patients in previous studies [8–10, 12, 13], but was performed in 60% of patients in our study. Therefore, our low completion rate of the full plan including primary resection probably reflects greater severity of disease than in previous study populations. The liver-first approach is intended to avoid missing a limited chance of curative liver resection for metastases that require highly effective down-staging therapy, which might not be achievable after metastases have grown further. Accordingly, the cohort in this study was thought to be more in need of a reverse strategy than many patients in previous reports.

Our present study results suggest that the reverse strategy can be effective in eliminating liver metastases initially considered unresectable, while yet having potential for stimulating primary cancer activity. For patients with a high liver tumor burden, more potent perioperative chemotherapy or resection of the primary tumor before liver resection is required. The liver-first approach should be limited to patients with fewer metastases from rectal cancer, that is, to those who require preoperative chemoradiotherapy.

Disclosure Statement

The authors declare that they have no disclosure of financial interests.

The authors declare that they have no conflicts of interest.

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