

Successful treatment of conversion chemotherapy for initially unresectable synchronous colorectal liver metastasis

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Abstract

A 72-year-old woman with a sigmoid colon cancer and a synchronous colorectal liver metastasis (CRLM), which involved the right hepatic vein (RHV) and the inferior vena cava (IVC), was referred to our hospital. The metastatic lesion was diagnosed as initially unresectable because of its invasion into the confluence of the RHV and IVC. After she had undergone laparoscopic sigmoidectomy for the original tumor, she consequently had 3 courses of modified 5-fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) plus cetuximab. Computed tomography revealed a partial response, and the confluence of the RHV and IVC got free from cancer invasion. After 3 additional courses of mFOLFOX6 plus cetuximab, preoperative percutaneous transhepatic portal vein embolization (PTPE) was performed to secure the future remnant liver volume. Finally, a right hemihepatectomy was performed. The postoperative course was uneventful. The patient was discharged from the hospital on postoperative day 13. She had neither local recurrence nor distant metastasis 18 mo after the last surgical intervention. This multidisciplinary strategy, consisting of conversion chemotherapy using FOLFOX plus cetuximab and PTPE, could contribute in facilitating curative hepatic resection for initially unresectable CRLM.

Key words: Initially unresectable; Colorectal liver metastasis; Conversion chemotherapy; Cetuximab; Percutaneous transhepatic portal vein embolization

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Core tip: A 72-year-old woman with a sigmoid colon

cancer and a synchronous colorectal liver metastasis (CRLM) was referred to our hospital. The metastatic lesion was diagnosed to be initially unresectable. After she had undergone laparoscopic sigmoidectomy for the original tumor, she consequently had 6 courses of modified 5-fluorouracil, leucovorin, and oxaliplatin plus cetuximab, resulting in conversion chemotherapy. Preoperative percutaneous transhepatic portal vein embolization was performed to secure the future remnant liver volume. Finally, a right hemihepatectomy was successfully performed. The postoperative course was uneventful. She had no recurrence for 18 mo. This multidisciplinary strategy could contribute in facilitating curative hepatic resection for initially unresectable CRLM.

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INTRODUCTION

The incidence of colorectal cancer is increasing, and it is now the fourth leading cause of cancer deaths worldwide^[1]. According to GLOBOCAN 2008 estimates, about 12.7 million cancer cases and 7.6 million cancer deaths were estimated to have occurred in 2008^[2]. Over half of patients with colorectal cancer will develop metastatic disease, with a quarter having distant metastatic lesions at diagnosis, often in the liver^[3]. Although hepatic resection remains the only potentially curative treatment in patients with colorectal liver metastasis (CRLM)^[4-7], only 15% to 20% of patients with CRLM are suitable for surgical resection^[8,9]. Here, we report a case of conversion chemotherapy using 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) plus cetuximab, combined with portal vein embolization, which led to a successfully curative liver resection in a patient with initially unresectable synchronous CRLM.

CASE REPORT

A 72-year-old woman with a high level of carcinoembryonic antigen (CEA) was referred to our hospital for the further diagnosis from a previous physician. She had no previous history of serious diseases, operations, or hospitalizations. She had a family history of gastric cancer on her mother's side. Laboratory workup showed that CEA level had increased to 27.0 ng/mL, and serum levels of transaminases were slightly elevated. Total

colonoscopy revealed a tumor at the sigmoid colon. Computed tomography (CT) revealed a synchronous CRLM. It was diagnosed as unresectable due to its invasion of the right hepatic vein (RHV) and the inferior vena cava (IVC) (Figure 1A and B). Thus, she underwent just a sigmoidectomy with lymph node dissection. Histopathological analysis resulted in the diagnosis of a well-to-moderately differentiated adenocarcinoma. Since the cancer cells were found to have wild-type KRAS, a combination therapy of mFOLFOX6 with cetuximab [Day 1: 5-fluorouracil (5-FU) 400 mg/m² bolus injection; leucovorin (LV) 200 mg/(m².2 h) with oxaliplatin (L-OHP) 85 mg/(m².2 h); cetuximab 250 mg/(m².2 h); 5-FU 2400 mg/(m².46 h) continuous infusion; Day 8: cetuximab 250 mg/(m².1 h), every 2 wk] was chosen as the first-line chemotherapy, considering the possibility of conversion chemotherapy. Follow-up CT revealed that the CRLM had a partial response, and that the confluence of the RHV and IVC was free from cancer invasion after 3 courses of systemic chemotherapy (Figure 1C and D). In addition, the serum level of CEA decreased significantly (Figure 2). The residual liver volume was regarded as insufficient for right hemihepatectomy. Thus, percutaneous transhepatic portal embolization (PTPE) was carried out after an additional 3 courses of chemotherapy. Three weeks after PTPE, CT revealed an increase of the estimated future remnant liver ratio from 36.2% to 46.9%, with no detectable presence of any other metastatic lesion. This CRLM was finally regarded as resectable with a normal hepatic functional reserve (Table 1). Six weeks after the last course of chemotherapy, a right hemihepatectomy and cholecystectomy were performed because of the invasion to the right branch of the portal vein. After the mobilization of the right lobe and the completion of hepatic transection, the RHV and a part of the IVC was side-clamped with a Satinsky clamp and divided. The surgical margins, observed with a frozen section, had no malignancy. The side-clamped IVC was simply closed with a continuous suture without severe stenosis. The postoperative course was uneventful. The patient was discharged on postoperative day 13. The histopathological analysis revealed a well-differentiated adenocarcinoma, consistent with CRLM. The tumor was comprised of approximately 50% viable cancer cells, and the remainder was necrotic (Figure 3). The patient had an additional 6 courses of mFOLFOX6 after hepatectomy. She had neither local recurrence nor distant metastasis 18 mo after the last surgical intervention.

DISCUSSION

Liver resection is the only potentially curative treatment with an expectation of long-term survival in patients with CRLM^[4-7]. However, approximately 80% of patients with CRLM have unresectable disease,

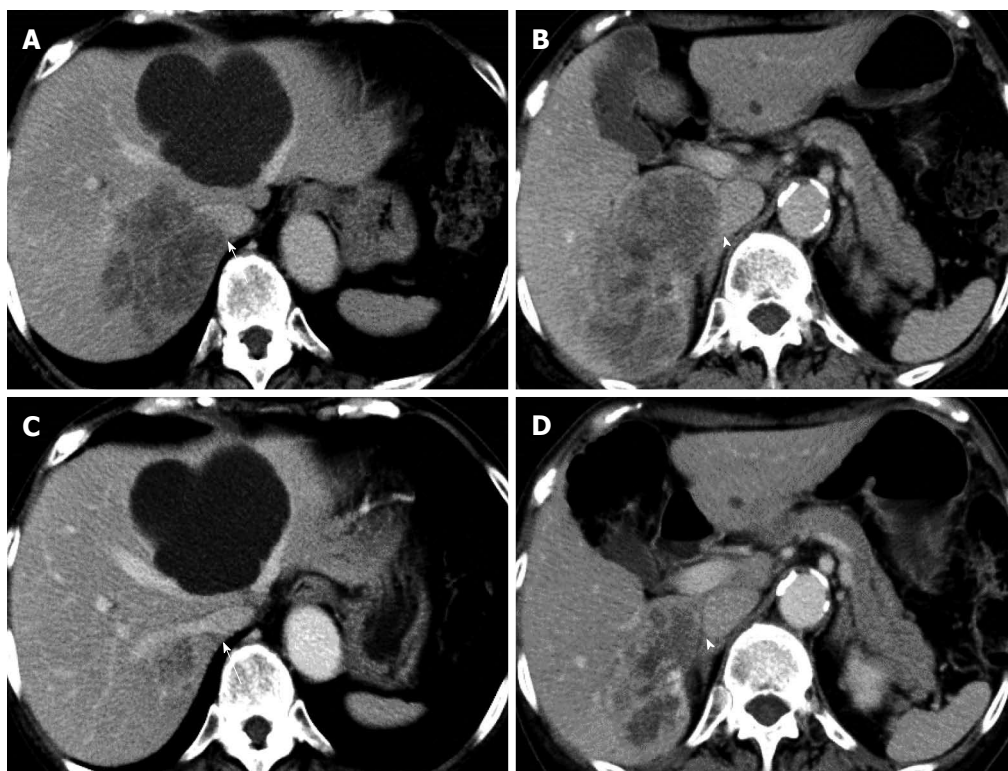


Figure 1 Enhanced computed tomography. A, B: Before chemotherapy. A huge synchronous colorectal liver metastasis was involving the right hepatic vein (RHV; arrow) and the inferior vena cava (IVC; arrowhead); C, D: After chemotherapy. The tumor was dramatically reduced, and the IVC was isolated from the tumor (arrowhead).

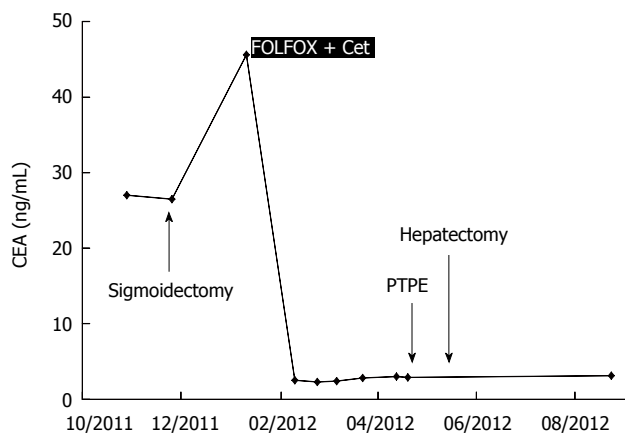


Figure 2 Serum levels of carcinoembryonic antigen. FOLFOX: 5-fluorouracil, leucovorin, and oxaliplatin; Cet: Cetuximab; PTPE: Percutaneous transhepatic portal vein embolization.

and long-term survival is poor in this setting^[10]. In selected patients with unresectable metastases, CRLM may be down-staged by systemic chemotherapy with or without molecular targeted therapy, so that liver resection may be completed^[11-15]. Once a complete curative resection is achieved, long-term survival would be expected, even in patients with initially unresectable CRLM^[10,16-19]. Moreover, there is a positive correlation between the response rate to chemotherapy and the resection rate of liver metastases^[20]. Therefore, response rates are very important when selecting

patients for resection.

Currently, L-OHP and irinotecan have been widely used for patients with CRLM. The resection rate is significantly higher in patients receiving FOLFOX (5-FU + LV + L-OHP) than in those receiving FOLFIRI (5-FU + LV + irinotecan), according to a randomized GERCOR study^[21]. To make matters worse, pre-operative treatment with irinotecan has been reported to be associated with an increased risk of steatohepatitis. Steatohepatitis is associated with an increase in 90-day mortality after hepatic surgery^[22]. While, L-OHP-based chemotherapy is associated with a significantly higher incidence of sinusoidal obstruction syndrome (SOS)^[23,24]. SOS resulted in a poorer hepatic functional reserve and in a higher complication rate after major hepatectomy^[24], but with no increase in mortality^[22]. Therefore, we selected mFOLFOX6 as first-line chemotherapy, considering the future possibility of liver surgery.

The development of efficient molecular-targeted drugs, such as cetuximab or bevacizumab, have opened new perspectives in the treatment of resectable and unresectable liver metastases. In patients with KRAS wild-type tumors, chemotherapy with cetuximab yields high response rates compared with historical controls, and leads to significantly increased resectability^[25-29]. The phase III NORDIC7 and COIN trials reported that first-line L-OHP-based chemotherapy plus cetuximab has no confirmed

Table 1 Laboratory data

WBC	6000/L
RBC	343 × 10 ⁴ /L
Hb	10.7 g/dL
Hct	34.6%
Plt	24.8 × 10 ⁴ /L
PT	100.1%
HPT	75.7%
AT3	107%
CEA	2.9 ng/mL
CA19-9	14.1 U/mL
ICG-R15	6.7%
CRP	0.077 mg/dL
T-Bil	0.5 mg/dL
AST	29 IU/L
ALT	24 IU/L
LDH	220 IU/L
γ-GTP	72 IU/L
ALP	385 IU/L
CHE	112 IU/L
T-cho	164 mg/dL
TP	6.1 g/dL
Alb	3.4 g/dL
BUN	15 mg/dL
Cre	0.62 mg/dL
Na	141 mEq/L
K	4.2 mEq/L
Cl	108 mEq/L
Ca	8.6 mEq/L

Hb: Hemoglobin; Hct: Hematocrit; Plt: Platelet; PT: Prothrombin time; HPT: Hepaplastin test; AT3: Antithrombin III; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; ICG-R15: Indocyanine green retention rate at 15 min; CRP: C-reactive protein; T-Bil: Total bilirubin; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase; γ-GTP: Gamma-glutamyl transpeptidase; ALP: Alanine phosphatase; CHE: Cholinesterase; T-cho: Total cholesterol; TP: Total protein; Alb: Albumin; BUN: Blood urea nitrogen; Cre: Creatinine.

benefit^[30,31]. However, in the NORDIC7 trial, patients received FLOX plus cetuximab, and in the COIN trial, patients received FOLFOX or XELOX (capecitabine + L-OHP) plus cetuximab. On the other hand, in the CELIM study^[32], the response rates were significantly higher in patients whose tumors were wild type for KRAS (46 of 67 patients, 70%) than in those with KRAS mutations (11 of 27 patients, 41%). The R0 resection rates were 38% vs 30% (25 of 52 vs 18 of 44 patients) for FOLFOX plus cetuximab vs FOLFIRI plus cetuximab, respectively. Therefore, we selected FOLFOX plus cetuximab as the chemotherapy regimen.

It is quite difficult to predict the response to the tumor with chemotherapy. Negri *et al*^[33] and Catalano *et al*^[34] reported that mucinous histology predicts for poor response rate and overall survival in patients with colorectal cancer with fluorouracil-based or oxaliplatin-based chemotherapy. In our case, the histology of the original site was well-to-moderately differentiated adenocarcinoma. It might lead a good response with mFOLFOX6 plus cetuximab.

To secure the future remnant liver volume, PTPE may be considered as an option in selected patients^[35-37].

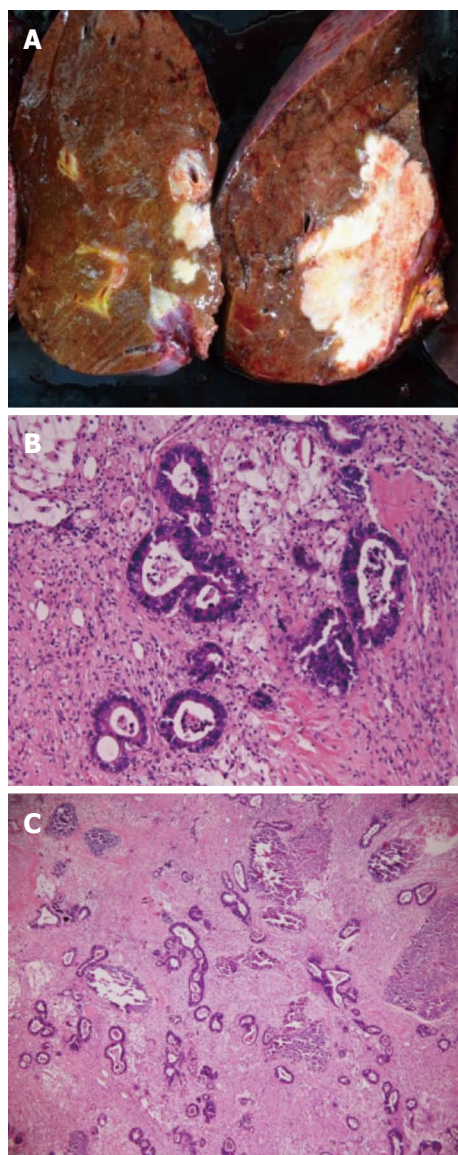


Figure 3 Resected specimen. A: Cut surface. The tumor was 70 mm × 40 mm in size. The tumor was grayish-white and stony hard; B, C: Hematoxylin and eosin (HE) staining of the resected specimen; B: HE staining, × 400. Adenocarcinoma; C: HE, × 100. Approximately 50% of the adenocarcinoma was necrotic.

The purpose of preoperative PTPE is to initiate compensatory hypertrophy in the future remnant liver in an attempt to counteract liver failure after major hepatectomy^[38-40]. Nagino *et al*^[41] underlined that indocyanine green clearance of the future liver remnant after PTPE should be more than 0.05 for major hepatectomy in patients with biliary cancers. However, liver function of our case was damaged due to 6 courses of FOLFOX. As an indication of PTPE for the patient with chemotherapy associated steatohepatitis remains controversial, it is to be elucidated.

There is no evidence on how many courses are the most effective for facilitating surgical resection in patients responsive to chemotherapy. It has been reported that the median duration of response to

FOLFOX ranges from 4 to 6 courses^[21,42]. Use of more than 6 courses of L-OHP-based chemotherapy is significantly associated with SOS^[24]. Among patients undergoing a major hepatectomy, SOS was associated with significantly higher morbidity and longer hospital stays^[24]. Therefore, preoperative chemotherapy was performed for total of 6 courses.

In conclusion, we herein report a case successfully treated with a multidisciplinary strategy, consisting of conversion chemotherapy using FOLFOX plus cetuximab and PTPE. This strategy may contribute to improve resectability for initially unresectable CRLM, thus leading to prolonged survival.

COMMENTS

Case characteristics

A 72-year-old female with a high level of carcinoembryonic antigen (CEA) was referred to our hospital.

Clinical diagnosis

The patient had no clinical symptoms.

Differential diagnosis

A high level of CEA are associated with adenocarcinoma; colon cancer, stomach cancer, lung cancer, pancreatic cancer, and so on.

Laboratory diagnosis

Laboratory workup showed that CEA level increased to 27.0 ng/mL.

Imaging diagnosis

Computed tomography revealed a synchronous colorectal liver metastasis, which involved the right hepatic vein and the inferior vena cava.

Pathological diagnosis

Histopathological analysis resulted in the diagnosis of a well-to-moderately differentiated adenocarcinoma, and the cancer cells were found to have wild-type KRAS.

Treatment

The patient underwent laparoscopic sigmoidectomy, followed by 5-fluorouracil, leucovorin, and oxaliplatin plus cetuximab, portal vein embolization for future remnant liver volume, and a right hemihepatectomy.

Term explanation

Conversion chemotherapy is a method that liver resection becomes possible by intensive chemotherapy, in patients with initially unresectable colorectal liver metastases (CRLM).

Experiences and lessons

In selected patients with unresectable metastases, CRLM may be down-staged by systemic chemotherapy with or without molecular targeted therapy, so that liver resection may be completed.

Peer-review

Conversion chemotherapy might lead to a successfully curative liver resection in a patient with initially unresectable synchronous CRLM. However, it depends on patients if systemic chemotherapy is effective.

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