ORIGINAL ARTICLE

Conversion to resectability using transcatheter arterial chemoembolization alternating with mFOLFOX6 in patients with colorectal liver metastases

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Background: Colorectal cancer is one of the most common malignancies in the world, and about 25% of colorectal cancer patients present with colorectal cancer liver metastases (CRCLM) even at new diagnosis. The study was to evaluate the safety and efficacy of transcatheter arterial chemoembolization (TACE) alternating with mFOLFOX6 in Chinese patients with unresectable CRCLM. **Materials and Methods:** In this study, by combining the systemic and regional treatment, the resectability rate, overall survival, and progression-free survival were measured with addition of TACE. Included patients had Eastern Cooperative Oncology Group performance status 0–2. Sixty-two patients received mFOLFOX6 plus one TACE after 2 weeks of chemotherapy; after 2 weeks, the next periodical treatment repeated. Patients received operation when the liver metastases were converted to resectability or severe tumor-associated complications occurred. **Results:** We found that 28 patients (45.2%) patients received operation after the treatment of TACE combined with systemic chemotherapy. The median time from initial treatment to the operation was 6 months. The median follow-up period was 41 months in all the patients. The 3-year survival rate of resected patients and unresected patients was 54% and 17%, respectively. Post-TACE syndrome was the major adverse reaction (81%). Other adverse reactions were neutropenia, nausea, and neurotoxicity. No patient died of the adverse reactions. The resection rate was related to hepatic segments and vasculature involvement. **Conclusion:** Taken together, TACE alternating with mFOLFOX6 has been proved to be safe and effective for CRCLM treatment to improve resection rate and prolong the survival time.

Key words: Colorectal liver metastases, mFOLFOX6, respectability rate, survival time, transcatheter arterial chemoembolization

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INTRODUCTION

Colorectal cancer is the third most common malignancies worldwide with increasing incidence[1] and has become the fourth most common causes of cancer death in China.[2] The common metastatic site of colorectal cancer is the liver, which results in a poorer prognosis.[3] About 25% of newly diagnosed colorectal cancer patients present with colorectal cancer liver metastases (CRCLM).[4] The median survival of patients with untreated liver metastases is 6–12 months, and the 5-year survival rate is less than 10%.[5] For CRCLM patients, hepatic metastasis and resection of colorectal cancer have potential therapeutic effects. The 10-year survival rate is about 15%.[6] Only 10% to 20% patients of CRCLM have the opportunity to receive the resection of primary cancer and hepatic metastases despite advances in surgical technique.[7]

The standard first-line treatment of CRCLM is a combination of 5-fluorouracil (5-FU), leucovorin with

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irinotecan or oxaliplatin, and/or molecular biological agents such as bevacizumab, cetuximab, panitumumab, and regorafenib.[8] Nevertheless, the chemotherapy outcome for CRCLM patients is still poor, with only about 20% response rate for 5-FU plus leucovorin and 32%–48% response rate with the addition of irinotecan or oxaliplatin.[9,10] There are several regional liver therapies aiming at increasing resection rate, survival time, and quality of life. One such regional treatment is transcatheter arterial chemoembolization (TACE). Mechanism of TACE treatment bases on the theory that liver metastases predominantly derive their blood supply from the hepatic artery (HA) by inhibiting blood supply from branches of the HA whereas the liver tissue itself is mainly supplied by the portal vein and therefore unaffected.[11] TACE, when combined with chemotherapeutic agents, leads to tumor ischemia, apoptosis, and necrosis.[12] In addition, TACE, as a targeted drug delivery mechanism, increases localized drug concentration and extends exposure time by blocking the blood flow.[12,13]

Given the systemic nature of colorectal cancer, we alternated systemic chemotherapy with TACE in Chinese CRCLM patients. By combining the systemic and regional treatment, we hypothesized that the addition of TACE would increase the resectability rate, overall survival (OS), and progression-free survival (PFS).

MATERIALS AND METHODS

Kind of study

This was a cross-sectional study from 2010 to 2014.

Patient eligibility

62 CRCLM patients were recruited in this trial; median age was 63 ranging from 28 to 75. The inclusion criteria of this study include ages between 18 and 75 years, Eastern Cooperative Oncology Group (ECOG) performance status score was no more than 2 scores,and If the ECOG score of patients over 70 years is 0, then these patients are eligible. All patients had biopsy-confirmed CRCLM in primary and liver metastases. All cases were discussed at a multidisciplinary conference involving medical oncologists, surgeons, radiologists, and pathologists, where patients were confirmed unresectable. Hepatic metastases were considered unresectable if metastasis included all segments and three main liver veins, either inflow pedicles or inadequate liver remnant for resection. All patients had no or minimal symptoms related to CRCLM. Adequate marrow and liver function was required: white blood cell count ≥3000 cells/μl, hemoglobin ≥8 g/dl, platelets ≥100,000 cells/μl, albumin ≥30g/L, and total bilirubin ≤2 mg/dl. Main exclusion criteria were occurrence of extrahepatic metastases, tumor involvement ≥ 75% of liver, and other previous or concurrent malignant tumors.[14] Informed consent was obtained and signed by all patients, and the protocol was approved by the institutional review board of our hospital.

The clinical data collected included gender, age, location of colorectal cancer, number and volume of hepatic metastases, relevant baseline level of laboratory tests, side effects reactions, time from initial treatment to operation, OS, and PFS.

Treatment plan

The evaluation of pretreatment included complete clinical information, laboratory tests of CBC and physical examination as well as liver function tests (total bilirubin, albumin, alkaline phosphates, lactate dehydrogenase, and aspartate transaminase), and carcinoembryonic antigen (CEA). During treatment, Liver function and CBC tests were evaluated every two weeks. Enhanced computed tomography (CT) of chest, abdomne, and pelvis was performed before initial treatment and then repeated every 8 weeks. Pathological biopsy of liver metastases was obtained when enhanced CT gave uncertain result.[15]

All patients received the combined treatment (one cycle's treatment: two cycles mFOLFOX6 plus one TACE treatment after 2 weeks of chemotherapy), which repeated every 2 weeks of treatment.[16] mFOLFOX6 consists of a 120-min infusion of leucovorin at a dose of 200mg/m^2,and an intravenous injection of 5-FU at a dose of 400mg/m^2 follwed by a 46-h continuous infusion of 5-FU up a total dose of 2400mg/m^2. Chemotherapy agents of TACE procedure are composed of oxaliplatin, 5-FU, mitomycin, and lipiodol and infused through selective HA. 5-FU (1000mg) and oxaliplatin (100–150 mg) are diluted with normal saline and 5% dextrose, respectively, and then infused through HA. The chemoembolization is conducted with mitomycin (10mg) mixed with lipiodol (10–30 ml). After the procedure, patients were monitored for adverse reactions (post-TACE syndrome, elevated transaminases, leukopenia, or other potential adverse events). All patients received preventive treatments against nausea and vomiting before systemic chemotherapy and TACE. Adverse events such as fever, abdominal pain, and infection after TACE were given routine treatment according to standard hospital procedure. Patients withdrew from the trial if one of the following events occurred: excessive toxicity, tumor progress, and reduction of CRCLM that rendered patient eligible for resection. Dose adjustment of chemotherapy agents was made following the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Combined treatment response was evaluated by enhanced CT scan according to the RECIST criteria 1.0 and independently confirmed by two radiologists. Resection

of colorectal cancer was performed if intestinal obstruction or massive gastrointestinal hemorrhage occurred. Intraoperative ultrasound was performed in the resection of liver metastases.

Statistical analyses

SPSS 18.0 (SPSS Inc., Chicago, Illinois, USA) was used for statistical analyses. Data were shown as mean ± standard deviation (SD). The primary outcome was resection rate. OS was defined as time from treatment initiation to the time of the last follow-up or the date of death. Survival rates were calculated in 1-, 2-, and 3-year survival from the start of treatment. OS, time to disease progression (PD), and PFS were estimated by Kaplan–Meier method,[17] and a univariate analysis was performed using Cox's proportional hazard regression model.[18] The predictive factors associated with resectability were analyzed by Fisher analysis for categorical variables, or by Wilcoxon rank test for continuous variables. Statistical analyses were conducted in SPSS 17.0. Results were considered statistically significant at $P < 0.05$.

RESULTS

Patient baseline and disease characteristics

Sixty-two CRCLM patients were recruited in this trial. Detailed baseline characteristics are shown in Table 1. The median number of combined treatment cycles per patient was 5 (range, 1–9).

Tumor response

Forty-one patients (66.1%) had a partial response (PR) and 11 patients had stable disease (SD) (17.7%) in the liver metastasis, and no one had a complete response (CR). The primary site of local control rate (cr + PR + sd) was 95.2%, including 3 cases of CR (4.8%), 36 cases of PR (58.1%) and 20 cases of SD (32.3%). A typical patient's CT images are shown in Figure 1. The CT image of a typical patient is shown in Figure 1. Three patients (4.8%) progressed in the primary site. 10 patients (16.1%) had PD at the liver, and 3 (4.8%) developed extrahepatic metastases [Table 2].

Characteristics of resection

After a median of 5 cycles (range 2-8), 31 patients were assessed as suitable for resection. Among them, 22 cases underwent simultaneous colon and liver resection, 6 cases underwent resection of colon cancer, followed by hepatectomy or ablation.

Twenty-eight patients underwent curative-intent resection (45.2%, R0 in 22, R1 in 6). Median time to resection was 7.2 months (range, 5.6–12.2 months), and the median interval from the stop of chemotherapy/chemoembolization to resection was 28 days (range, 25–35 days). Eighteen cases

Table 1: Baseline characteristics of all 62 patients

Baseline characteristics	Value
Age (years)	
Median	63
Range	28-75
Gender	
Male	35 (56.5)
Female	27 (43.5)
ECOG performance status	
0	20 (32.3)
1	32 (51.6)
2	10 (16.1)
Site of primary cancer	
Right colon	28 (45.2)
Left/sigmoid colon	34 (54.8)
Hepatic involvement (%)	
<25	11 (17.7)
25-50	16 (25.8)
>50	35 (56.5)
Lobular involvement	
Bilobar	42 (67.7)
Unilobar	20 (32.3)
Baseline of CEA (ng/ml)	
≤200	33 (53.2)
>200	29 (46.8)
Baseline of LDH	
Normal	17 (27.4)
Abnormal	45 (72.6)

LDH=Lactate dehydrogenase; CEA=Carcinoembryonic antigen; ECOG=Eastern Cooperative Oncology Group

Table 2: Sites of disease progression during the treatment

Location of disease progression	Number of patients (*n*=62), *n* (%)
Liver	9 (14.5)
Lung	2 (3.2)
Both liver and lung	1 (1.6)
Primary cancer	3 (4.8)

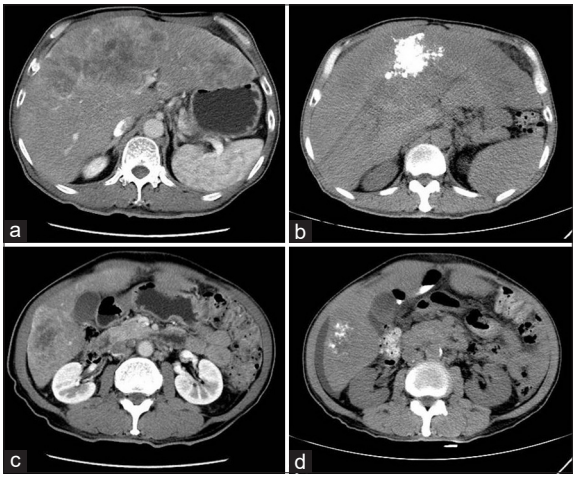

Figure 1: Typical patient's computed tomography images after 2 cycles of combined treatment. (a and c) Baseline data of the liver metastases before the treatment; (b and d) liver metastases shrink after 2 cycles of treatment. The patient received a simultaneous colon and liver resection. No evidence of recurrence at 40 months after surgery (at the end of follow-up)

needed embolization of portal vein in order to increase the size of the remaining liver in the future. Ten patients were considered for a planned two-stage resection. To treat distal hepatic metastasis, 17 lesions of 7 patients were treated by radiofrequency percutaneous ablation. In patients undergoing two-stage surgery, no patients received additional chemotherapy during the interval. Ten patients underwent right enlarged surgery and two patients underwent left enlarged surgery. The liver parenchyma was normal 25%, focal congestion in 16%, and mild to moderate steatosis in 59%. No mortality occurred during the first 3 months. Of the 28 resection patients, 24 (85.7%) received postoperative mFOLFOX6 (range, 2–4) and four patients did not receive postoperative chemotherapy. Median disease-free survival among the patients who underwent R0 resection was 10 months (95% confidence interval [CI], 7.1–14.2).

Characteristics of unresection

The characteristics of the 34 unresected patients were summarized as the following: 30 (88%). Six or more segments of the liver were involved in 30(88%) patients, including three hepatic veins (40%), two portal veins (37%) and vena cava (41%). Twelve patients received second-line chemotherapy and six patients received third-line chemotherapy. However, after treatment, they were not converted to resectability. Results of univariate analysis showed the hepatic involvement, segments involvement, and vascular invasion affected resectale rate. The resectale rate did not differ according age, gender, sex, site of primary cancer, lobular involvement, and baseline CEA [Table 3].

Prognosis

The 3-year survival rate was estimated to be 54% (95% confidence interval, 46% - 68%) for resected patients and 17% (95% confidence interval, 7% - 29%) for unresected patients. OS in patients with resection was significantly better than that in patients without resection ($P < 0.001$) [Figure. 2].

Fifteen patients discontinued treatment because of PD. No patient died as a result of adverse events. Among the 28 resected patients, recurrence was found in 18 patients. First recurrence site was intrahepatic only in 7 patients (38.9%), extrahepatic only in 5 patients (27.8%), and both intra- and extra-hepatic in 6 patients (33%). Four patients required emergency surgery because of complications associated with primary cancer (3 with intestinal obstruction and 1 with bleeding). The median time interval from diagnosis to emergency operation was 10 months (2-20 months), and the median survival time after operation was 3.8 months (1-7.5 months).

Table 3: Univariate analysis of predictors for resectability

Characteristics	Resected (*n*=28)	Unresected (*n*=34)	*P*
Age (years)			
Median	64	62	0.815
Range	35-75	28-75	
Gender			
Male	9	19	0.710
Female	20	15	
Site of primary			
Right colon	15	21	0.125
Left/sigmoid colon	13	13	
Hepatic involvement (%)			
<50	19	14	0.015*
≥50	9	20	
Lobular involvement			
Bilobar	19	22	0.318
Unilobar	9	12	
Segments involvement			
<6	20	13	0.013*
≥6	8	21	
Vascular invasion			
Yes	7	25	0.025*
No	21	9	
Baseline of CEA (ng/ml)			
<200	18	23	0.025*
≥200	10	11	

*P<0.05. Name of statistical test: Cox's proportional hazard regression model. CEA=Carcinoembryonic antigen

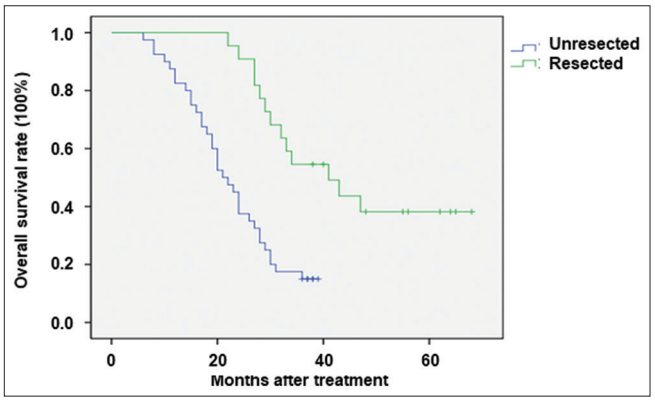

Figure 2: Kaplan–Meier estimates of OS for resected (n = 28) and unresected (n = 34) patients, calculated from the date of treatment initiation ($P < 0.001$, log-rank test)

Safety

Post-TACE syndrome was the most common treatment related by effect (81%); it usually could be reversed, or some patients were administered pain relievers or antipyretics. Increased enzyme levels were often seen after TACE treatment, but most cases were reversible and needed no further treatment. In the first two courses of treatment, the patients treated had the following toxicities: Grade 3 neutropenia (22%) and Grade 2 diarrhea (12%). At the end of the first two courses of treatment, the late side

effects included Grade 3 diarrhea (9%), Grade 3 aspartate aminotransferase (12%), Grade 3 or 4 neutropenia (15% and 11%) and neurotoxicity (19%). As more cycles were administered, more dose reductions occurred.

DISCUSSION

Liver metastases have an elemental role in determining colorectal cancer patients' prognosis.[19,20] Resection of liver metastases is feasible only if the patient has solitary or unilobar involvement.[21-23] However, often, that is not the case and unresectable metastases challenge physicians and significantly affect patient survival.

Chosen of the initial treatment strategy for colorectal CRCLM patients relies on the symptoms associated with colorectal cancer and the resectable status of hepatic metastases. For asymptomatic and unresectable patients with colorectal cancer, the first-line treatment of double chemotherapy combined with antibody is generally preferred. According to the modern systemic chemotherapy, the reported resection rate varied from 15% to 47%.[24,25] Antibody therapy is expensive; so, those drugs are not widely used in China, especially in the rural areas. Reports have demonstrated the superior activity of combining both irinotecan and oxaliplatin (FOLFOXIRI) therapy in unresectable CRCLM.[25] TACE could be an option for gaining similar benefits with less toxicity. However, the use of irinotecan drug-eluting beads (DEBIRI) with concomitant FOLFOX was safe and well tolerated with limited adverse events; furthermore, it also enhanced overall response rate (35%), and there was improved median PFS (15.3 months).[26]

Combined TACE with systemic chemotherapy has been proved to generate higher hepatic response rate.[27,28] Jiang *et al*. showed that TACE combined with radiofrequency ablation therapy can effectively control the growth of liver cancer lesions, reduce the levels of tumor-related serum markers, and inhibit the activity of tumor cells.[29] Furthermore, Cao's findings suggest that thalidomide combined with TACE shows better clinical efficacy and tolerable adverse events in patients with primary HCC when compared with TACE alone.[30] Li *et al*. presented that it is safe and effective to use TACE combined with microwave ablation in the treatment of advanced HCC, and the effect of combined treatment is better than that of TACE alone.[31] In this study, we investigated our treatment strategy for those with unresectable synchronous liver metastases. We observed that 66.1% of patients achieved PR in liver metastases and 45.2% of patients were converted to resectable.

The principal goal of the present study was to resect primary tumors and liver metastases in order to achieve a cure effect. Other reports have demonstrated that this approach is the best way when primary tumors are asymptomatic or easy to treat.[32,33] In contrast, major hepatectomy was necessary when we chose two-stage resection. In the present study, 28 patients suitable for resection following successful trial treatments underwent pre-planned surgery. Among the patients who could be operated on, the 3-year survival rate was 54%, which was obviously higher than the 17% survival rate of the patients who had not been resected.

These results are somewhat similar to previous studies using mFOLFOX as a first-line treatment. Obviously, the lower emergency operation rate is largely due to the role of systemic mFOLFOX6 local control.[34] Additonally, 45.2% of eligible patients received regression and received selective surgery after treatment because of the conversion power of combined treatment. Potential complications of primary tumors are removed before they occur. It may be the another reason for the lower incidence of emergency surgery.

CONCLUSION

We observed that initial TACE and systemic mFOLFOX6 treatment strategy led to a higher resection rate of asymptomatic colorectal cancer and unresectable liver metastases, and a lower incidence of complications associated with primary cancer. However, the study was limited by the small sample size and lacked a control group with similarly unresectable CRCLM, which was initially only received systemic chemotherapy. To asess whether TACE treatment can improve the resectability of surgery, a multicenter randomized trial is needed to compare the optimal systemic chemotherapy regimen and unresectable TACE regimen for unresectable patients with liver metastases from colorectal cancer.

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Conflicts of interest
There are no conflicts of interest.

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