Original Article
Conversion therapy combined with individualized surgical treatment strategy improves survival in patients with colorectal cancer liver metastases

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Abstract: Objective: To explore surgical treatment strategies for patients with liver metastases from colorectal cancer (CRLM), and analyze the prognosis and influencing factors. Methods: The clinical data of 156 inpatients with CRLM admitted to our hospital from January 2009 to June 2019 were retrospectively analyzed. Patients were divided into initially resectable group (80 cases) and initially unresectable group (76 cases). For patients with initially unresectable CRLM, conversion therapy (chemotherapy plus targeted therapy) combined with individualized surgical treatment strategy was used. The individualized surgical treatment strategy mainly included hepatectomy combined with ablation. Portal vein ligation and staged resection were adopted according to the patients' specific conditions. All patients were followed up until death. The Kaplan-Meier method and Log-rank test were used for survival analysis. Results: Median overall survival (OS) time of patients in the initially resectable group and initially unresectable group were 36 months and 17 months, respectively ($P = 0.001$). Median OS time of 24 patients who underwent surgical resection after successful conversion therapy was significantly longer than that of 52 patients with unsuccessful conversion therapy (20 months versus 15 months, respectively, $P = 0.034$). Univariate analysis showed that a maximum diameter of liver metastases < 6 cm and a number of metastases ≤ 4 were independent factors associated with successful conversion therapy. According to patients' specific conditions, 6 cases accepted hepatectomy combined with ablation, and 1 case accepted portal vein ligation and staged resection. Conclusion: Treatment of patients with CRLM should follow the principles of standardization and individualization. For patients with initially unresectable CRLM, successful conversion therapy should be pursued whenever possible. The maximum size and number of liver metastases were significantly associated with successful conversion therapy. Surgical resection-based comprehensive treatment is key.

Keywords: Colorectal cancer, liver metastasis, initially resectable, initially unresectable, conversion therapy

Introduction

Colorectal cancer (CRC) is one of the most common malignant tumors of the digestive system, which ranks third in incidence, second only to lung cancer and gastric cancer among China's malignant tumors with an annual incidence of 31.39/10 million and an upward trend [1]. The liver is the most common site of distant metastasis from colorectal cancer. About 15% to 25% of patients with colorectal cancer have liver metastases [2, 3], and liver metastases are found earlier than primary colorectal cancer in some patients. Colorectal cancer liver metastases (CRLM) account for 60%-71% of

the deaths in all patients with colorectal cancer. At present, surgery to completely remove liver metastases is still considered to be the best way to treat CRLM, with significantly increased 5-year survival rate reaching 14% to 40% in patients undergoing surgical resection [4, 5]. However, the low surgical resection rate and high recurrence rate pose great challenges to surgical treatment. It has been reported that only about 20% of patients with CRLM are suitable for surgical treatment. For patients with initially unresectable CRLM, 10-30% of patients still have the opportunity for surgical resection after corresponding conversion therapy [6, 7]. This study analyzed the data of 156 inpatients

with CRLM admitted to our hospital from January 2009 to June 2019, aiming to explore surgical treatment strategies for patients with CRLM, and analyze factors associated with successful conversion therapy. The study was approved by the ethics committee of Peking University People's Hospital and all patients signed informed consent statements.

Materials and methods

Clinical data

A total of 156 inpatients with CRLM admitted to the Department of Hepatobiliary Surgery, People's Hospital of Peking University from January 2009 to June 2019 were included, including 101 males and 55 females, with a median age of 57.5 years (39-77 years).

Entry criteria were pathologic diagnosis of colorectal cancer and liver metastases as the first metastasis diagnosed by imaging techniques such as enhanced CT or MRI and/or pathologic examination of a biopsy or surgical specimen. All included patients had complete clinical data. Patients who had other primary tumors or incomplete clinical data were excluded from the study.

Preoperative assessment

Whole blood cell analysis, liver function tests and other biochemical indicators, coagulation function tests, tumor biomarkers and other serum measurements were routinely performed in all patients on admission. The primary colorectal cancer and liver metastases were routinely evaluated by enhanced MRI and/or enhanced CT of the abdomen and pelvis. Preoperative ultrasound localization assessment was performed for patients who planned to receive radiofrequency ablation.

A multidisciplinary team (MDT) participated in the consultation for all patients to determine the final treatment strategy and make decisions to solve any emergency during medical treatment.

Treatment strategies

For patients with initially resectable CRLM, the primary colorectal cancer and liver metastases were resected at one stage, and then oxaliplatin combined with capecitabine chemotherapy was routinely given after surgery. For patients with initially unresectable CRLM, the following treatment strategies were used:

(I) Conversion therapy: Bevacizumab (5 mg/kg, intravenous infusion, day 1) combined with XELOX regimen (oxaliplatin 130 mg/m^2 intravenous infusion, day 1; capecitabine 1500 mg/m^2 orally, 2/day, day 1-14), once every three weeks. Cetuximab (500 mg/m^2, intravenous infusion, day 1) combined with FOLFIRI regimen (irinotecan 180 mg/m^2, intravenous infusion, day 1; calcium folinate 200 mg/m^2, intravenous infusion, day 1, day 2; 5-FU 400 mg/m^2, intravenous injection, day 1; 2400 mg/m^2, intravenous infusion for 48 h), once every two weeks. After 4-6 cycles of the above treatment, patients were re-evaluated by imaging examination, liver and kidney function tests, tumor biomarkers, and blood coagulation function to assess resectability of liver metastases.

(II) Resection combined with ablation: Patients with initially unresectable CRLM but who turned resectable after conversion therapy were evaluated for feasible surgery. For patients with multiple and deep liver metastases, intraoperative liver resection combined with radiofrequency ablation was used to achieve radical treatment as necessary.

(III) Portal vein ligation and staged resection: One patient had multiple liver metastases, of which the metastasis to the right liver was huge and the metastasis to the left liver was small. The patient was obese, and had hepatitis B with HBsAg (+), HBeAg (+) and HBcAb (+). Therefore, the left liver lesion was resected and the right portal vein was ligated during the first stage surgery, and right hepatectomy was performed in the second stage four weeks later.

Follow-up

All patients were followed until death, by telephone, WeChat, and outpatient visits, for a median of 23 months (3-84 months).

Statistical analysis

SPSS22.0 version software was used for statistical processing. The chi-square test was used for univariate analysis. Kaplan-Meier method was used to draw a survival curve, and Log-rank test was used for survival analysis. $P < 0.05$ was considered significant.
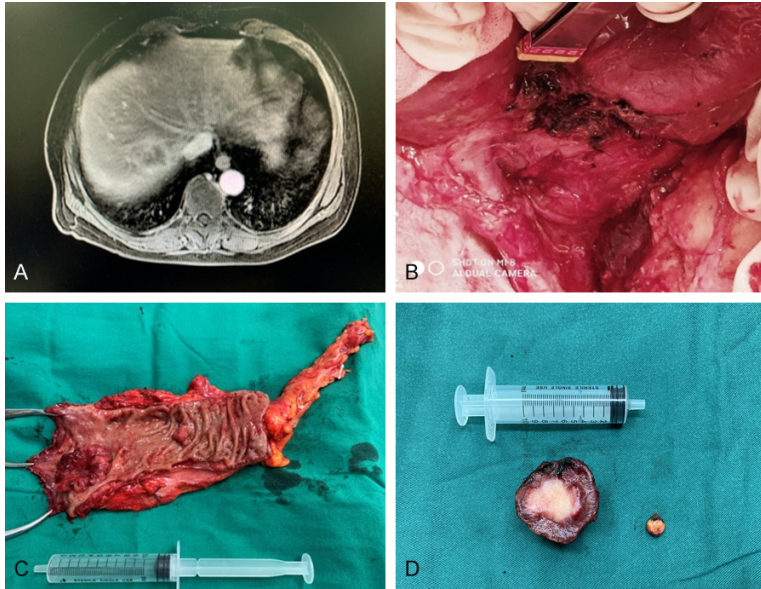
Figure 1. One-stage resection of primary rectal cancer and liver metastases. A. Imaging findings of liver metastases. B. Intraoperative situation. C. Resection of primary rectal cancer. D. Specimen with liver metastases.
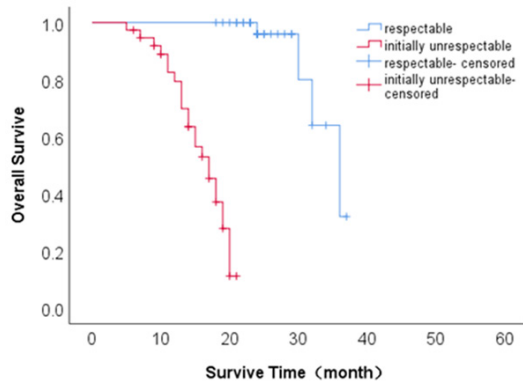
Figure 2. Survival analysis of initially resectable and unresectable patients.
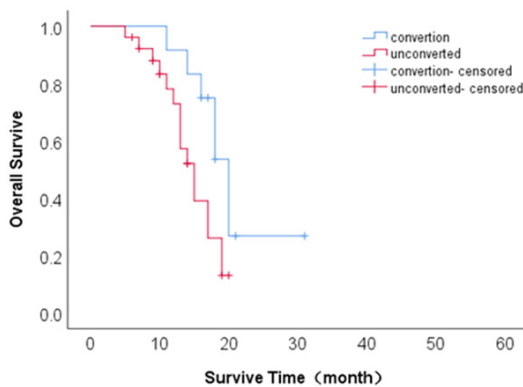
Figure 3. Survival analysis of initially unresectable patients who converted or remained unconverted to resectable.

Results

One hundred and fifty-six patients with CRLM admitted to our hospital from January 2009 to June 2019 were retrospectively analyzed. Among them, 80 patients were classified as initially resectable, whose primary colorectal cancer and liver metastases can be completely resected in one stage. The other 76 patients were classified as initially unresectable, whose liver metastases were too large and/or too numerous and could not be resected on admission.

For patients in the initially unresectable group, conversion strategies with chemotherapy plus targeted agents were used. After conversion therapy, liver metastases in some patients with initially unresectable CRLM became fewer and/or smaller and could be resected. Then, patients after successful conversion therapy underwent surgical resection with individualized strategy, some receiving hepatectomy combined with intraoperative radiofrequency ablation and others receiving two-step liver resection.

Treatment efficacy

All 156 patients were followed until death, median duration 23 months (3-84 months). For 80 patients with initially resectable CRLM, one-stage resection of primary colorectal cancer and liver metastases was performed (**Figure 1**). The median OS time of initially resectable patients was 36 months (95% CI: 30.004-41.996 months). In contrast, the median OS time of 76 patients with initially unresectable CRLM was 17 months (95% CI: 14.215-19.785 months) (P = 0.001) (**Figure 2**). The median OS time of 24 patients who underwent surgical resection after successful conversion therapy was 20 months (95% CI: 17.479-22.521 months) whereas the median OS time of 52 patients who failed to undergo surgical resection because of conversion therapy failure was only 15 months (95% CI: 12.514-17.486 months) (P = 0.034) (**Figure 3**). Liver metastases in the patients with successful conver-
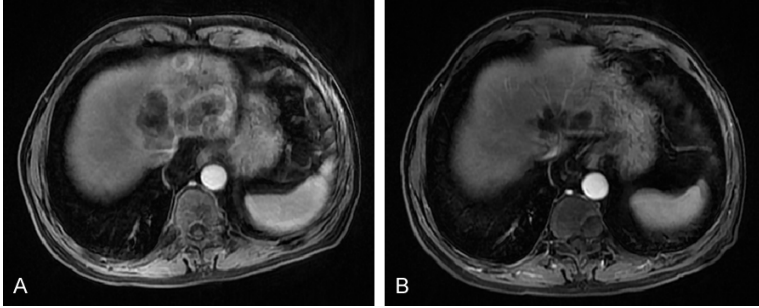
Figure 4. Imaging findings of patients with conversion therapy. A. MR findings before conversion therapy. B. MR findings after conversion therapy.

sion therapy were significantly reduced (**Figure 4**).

Univariate analysis showed that the size of liver metastases was related to the efficacy of conversion therapy

The successful conversion rate was 50% among 32 patients with a maximum diameter of liver metastases < 6 cm, whereas the successful conversion rate was only 18.2% among 44 patients with a maximum diameter ≥ 6 cm. (P = 0.037). The number of liver metastases was also significantly related to the successful conversion rate. Among 36 patients with ≤ 4 liver metastases, 18 patients were successfully converted with a conversion rate of 50%, whereas among 40 patients with > 4 liver metastases, only 6 patients were successfully converted with a conversion rate of 15% (P = 0.020). Gender, age, location of primary lesion, degree of differentiation, CEA, and anemia were not related to the conversion rate (all P > 0.05). The successful conversion rates among different groups of patients are shown in **Table 1**.

Effect of hepatectomy combined with intraoperative radiofrequency ablation

During preoperative imaging evaluation, 6 patients were found with liver metastases scattered in the left and right lobes, and some lesions were deeply located. If only hepatectomy was carried out, it was inevitable that more than half of the liver would be resected without completely removing the lesions. Therefore, after preoperative evaluation and ultrasound localization, the patients underwent hepatectomy combined with intraoperative ultrasound-guided radiofrequency ablation (**Figure 5**), with

the benefit of achieving complete removal of liver metastases without large-scale hepatectomy. Notably, intraoperative ultrasound imaging was helpful to find more lesions, so as to achieve the purpose of more thorough removal of liver metastases. **Table 2** shows that one patient was found to have 3 liver lesions on preoperative CT and ultrasound examination, whereas another lesion was found on intraoperative ultrasound and was ablated. In the other case, 2 lesions were found by preoperative CT and ultrasound, and another lesion was found by intraoperative ultrasound and ablation was performed.

Portal vein ligation + two-step liver resection

One patient underwent portal vein ligation + two-step liver resection. He has survived tumor-free for nearly 4 years so far.

Discussion

At present, the main methods of treating CRLM in clinical practice include surgical resection, systemic or interventional chemotherapy, cell biological therapy, molecular targeted therapy, radiotherapy, and radiofrequency ablation. Surgical resection is the first choice for possible cure of CRLM [8, 9].

In our study, 80 patients with CRLM were classified on admission as initially resectable whose primary colorectal cancer and liver metastases could be completely resected in one stage. The other 76 patients were classified as initially unresectable. For patients in the initially unresectable group, conversion strategies with chemotherapy plus targeted agents were used, and liver metastases in some patients became fewer and/or smaller and could be resected. Then, these patients, after successful conversion therapy, underwent surgical resection with individualized strategies, some receiving hepatectomy combined with intraoperative radiofrequency ablation and others receiving two-step liver resection.

Survival analysis showed that the median overall survival time of patients in the initially

Table 1. Univariate analysis of factors affecting conversion effect in 76 patients with initially unresectable CRLM [case (%)]

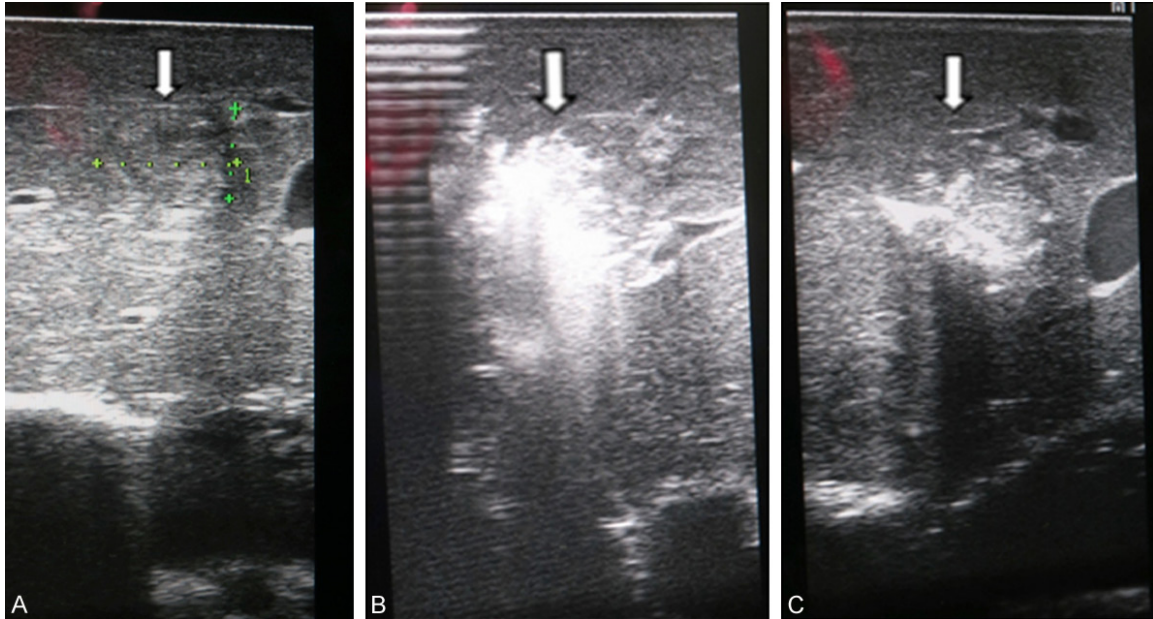| Clinical case data	n	Converted (%)	Not converted (%)	P
Gender				0.510
Male	50	14 (28.0)	36 (72.0)	
Female	26	10 (38.5)	16 (61.5)	
Age				0.416
< 60	26	6 (23.1)	20 (76.9)	
≥ 60	50	18 (36.0)	32 (64.0)	
Primary lesion site				0.405
Left colon	36	14 (38.9)	22 (61.1)	
Right colon	24	4 (16.7)	20 (83.3)	
Rectum	16	6 (37.5)	10 (62.5)	
Differentiation				0.096
Mid to high	34	6 (17.6)	28 (82.4)	
Low	42	18 (42.9)	24 (57.1)	
Maximum diameter of liver metastasis				0.037
≥ 6	44	8 (18.2)	36 (81.8)	
< 6	32	16 (50.0)	16 (50.0)	
Number of liver metastases				0.020
> 4	40	6 (15.0)	34 (85.0)	
≤ 4	36	18 (50.0)	18 (50.0)	
CEA				0.970
≥ 10	32	10 (31.3)	22 (68.8)	
< 10	44	14 (31.8)	30 (68.2)	
Anemia				0.632
Yes	36	10 (27.8)	26 (72.2)	
No	40	14 (35.0)	26 (65.0)	

It is especially important to identify potentially resectable lesions from patients with CRLM who cannot undergo initial surgical resection. Literature shows that the number and size of liver metastases are the main factors for success of conversion therapy [10]. In this study, the successful conversion rate was higher in patients with liver metastases < 6 cm in maximum diameter and ≤ 4 liver metastases, which was consistent with other literature. More numbers and larger diameter of liver metastases indicate a large tumor burden that directly affects prognosis. These are the main reasons: (1) The tumor burden is too large, and it takes a long time to reach the resectable standard through conversion therapy with the need of increased chemotherapy cycles. It has been reported that the successful conversion rate of patients with preoperative chemotherapy ≤ 6 cycles is significantly higher than that of patients with > 6 cycles [11]. (2) More numbers and larger diameter of metastases may suggest that the tumor is growing fast and has greater invasive ability. If there are metastases in more than half of the liver it may suggest that the tumor is spreading quickly with a higher degree of malignancy. It is difficult for these patients to prereserve remnant liver volume > 30% after surgical resection so as to have enough residual liver with good blood supply and bile drainage without successful conversion therapy. Even after the surgery is performed, the probability of recurrence and metastasis is higher than that of patients with fewer and smaller liver metastases [12-14]. (3) In addition, more preoperative chemotherapy cycles are corrrlated with the risk of liver damage. Severe liver damage may result in

resectable group was significantly longer than that of patients in the initially unresectable group (36 months versus 17 moths). When it comes to the patients in initially unresectable group, the overall survival time of 24 patients following successful conversion therapy who then underwent surgical resection with individualized strategies was significantly longer than that of 52 patients with unsuccessful conversion therapy (20 months versus 15 months).

Those patients with initially unresectable liver metastases who turned resectable after conversion therapy had a greater chance of prolonged survival. So, for patients with initially unresectable CRLM, conversion therapy using chemotherapy plus targeted therapy should be pursued to turn liver metastases resectable, and then, resection should be performed after successful conversion therapy.

Figure 5. Radiofrequency ablation of liver metastases. A. Lesion before ablation. B. Lesion during ablation. C. Appearance after ablation.

Table 2. 6 cases who accepted liver resection combined with radiofrequency ablation

Case	Operative method	Number of preoperative CT lesions	Number of preoperative ultrasound lesions	Number of intraoperative ultrasound lesions	Number of ablated lesions	Number of removed lesions
1	Liver resection + Ablation	7	7	7	1	6
2	Liver resection + Ablation	3	3	4	2	2
3	Liver resection + Ablation	2	2	3	2	1
4	Liver resection + Ablation	3	3	3	2	1
5	Liver resection + Ablation	5	5	4	2	2
6	Liver resection + Ablation	2	2	2	1	1

inability to perform surgery or increase the risk of serious complications during perioperative period.

A reasonable treatment model for potentially resectable CRLM patients should be effective systemic chemotherapy first, and then to reassess whether they can accept resection.

For patients with potentially resectable or unresectable CRLM, MDT consultation should be carried out, and radiotherapy and chemotherapy aimed at downgrading the liver metastases to be resectable should be performed. Therefore, dual or triple chemotherapy combined with targeted drugs is more suitable [15, 16]. The first-line regimen includes FOLFIRI combined with bevacizumab or anti-epidermal growth factor receptor (EGFR) therapy and the dual regimen includes bevacizumab or anti-

EGFR therapy. The choice of conversion therapy should follow the principle of individualization, with comprehensive consideration of the patient's characteristics, including age, tumor stage, immune status, genetic testing, as well as socioeconomic situation. Ablation therapy is a very important and useful supplement to surgical resection [17], aiming to remove the metastases while minimizing destruction of non-tumor liver parenchyma so as to expand the indications for surgery [18]. It has been reported that patients with CRLM who undergo surgical resection combined with intraoperative radiofrequency ablation have a significantly better prognosis than patients undergoing chemotherapy [19, 20]. In this study, 6 patients were confirmed to have liver metastases scattered in the left and right lobes, and the lesions were eliminated under the guidance of ultrasound during the surgery. Among them, 2

patients were found to have more lesions by ultrasound during surgery, and the deep liver metastases were imaged more sufficiently, which provided a basis for the maximum removal of liver metastases. However, it is still unclear whether surgery combined with intraoperative radiofrequency ablation in patients with unresectable CRLM can achieve an effect similar to patients with resectable CRLM [21-25].

One patient who underwent portal vein ligation + two-step hepatectomy has survived nearly 4 years without tumor. This strategy is suitable to patients with liver metastases who have good general condition, good heart and lung function, good liver function, and who can tolerate liver resection and radical resection of colorectal cancer. They should have a ratio of residual liver volume to standard liver volume < 40%, evaluated by three-dimensional CT digital imaging technology, without extrahepatic and other organ metastases. However, the risk of this surgery is relatively high, and the mortality rate is high, so they should be fully evaluated and carefully selected before surgery [26-28].

In summary, the surgical treatment strategy of CRLM should follow the principles of standardization and individualization [29, 30]. Surgical resection-based comprehensive treatment is the key to improve efficacy. The evaluation the possibility of resectability is important to determine the treatment strategy and treatment goals. However, some patients who are not suitable for surgical resection can obtain surgical opportunities after comprehensive treatment. The establishment of an efficient and accurate evaluation system and selection of a reasonable surgical approach are key.

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Disclosure of conflict of interest

None.

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