



Multidisciplinary approach to the diagnosis and treatment of patients with potentially resectable colorectal cancer liver metastasis: results of a multicenter study

Lei Han^{1^}, Jun Xue^{1^}, Xueliang Wu^{1^}, Guanli Liang^{2^}, Yunshi Wu^{2^}, Fei Guo^{1^}, Shuquan Gao^{1^}, Guangyuan Sun^{1^}

¹General Surgery Department, The First Affiliated Hospital of Hebei North University, Zhangjiakou, China; ²Graduate School, Hebei North University, Zhangjiakou, China

Contributions: (I) Conception and design: J Xue; (II) Administrative support: X Wu; (III) Provision of study materials or patients: L Han, G Liang; (IV) Collection and assembly of data: L Han, Y Wu, G Sun; (V) Data analysis and interpretation: L Han, F Guo, S Gao; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Jun Xue, Xueliang Wu. General Surgery Department, The First Affiliated Hospital of Hebei North University, Zhangjiakou, China. Email: yfyxuejun@163.com; wuxl@hebeinu.edu.cn.

Background: This study sought to review colorectal cancer liver metastasis (CRLM) patients at multiple centers to analyze the factors affecting the success of conversion therapy in patients whose CRLM was initially evaluated as potentially resectable, to explore the effect of different treatment approaches on patient survival, and to provide a scientific reference for clinical treatment of CRLM.

Methods: Fifty patients whose CRLM was initially evaluated as potentially resectable at 3 large Chinese general hospitals were enrolled in this retrospective study. Statistical analyses were carried out on the general data and pathological characteristic data to examine the clinical efficacy of the treatment approaches. The factors affecting the success of conversion therapy were analyzed by logistic regression. Additionally, follow-up appointments were conducted to examine survival, and survival curves were plotted using the Kaplan-Meier estimator. The effect of different clinical and pathological characteristics on CRLM patients was analyzed.

Results: Seventeen patients achieved no evidence of disease (NED) status through surgical resection/ablation after undergoing conversion therapy. The multifactor analysis demonstrated that the number of liver metastases was the primary risk factor affecting the efficacy of conversion therapy ($P < 0.05$). Survival analysis results showed statistically significant difference in overall survival (OS) between the NED group and the inconspicuous/progressive group ($P < 0.0001$). Also, there was a statistically significant difference in the progression-free survival (PFS) between the NED group and the inconspicuous/progressive group ($P < 0.0001$). Patients in the surgical resection group had better OS and PFS than those in the ablation group ($P < 0.0001$ and $P < 0.01$, respectively). The monofactor analysis demonstrated that the number and maximum diameter of liver metastases, serum Carcino-Embryonic Antigen (CEA) level, and BRAF V600E mutation status were factors affecting the OS of CRLM patients ($P < 0.05$), of which BRAF V600E mutation was the primary determinant ($P < 0.05$).

Conclusions: Among the patients whose CRLM was initially evaluated as unresectable, those who underwent surgical resection of the primary lesions and liver metastases after receiving conversion therapy had the best prognosis. Thus, a thorough evaluation should be conducted to determine the effect of and survival factors affecting conversion therapy in the treatment of liver metastases.

[^] ORCID: Xueliang Wu, 0000-0001-5883-6597; Lei Han, 0000-0002-2322-1055; Jun Xue, 0000-0002-5614-7859; Guanli Liang, 0000-0003-1049-5409; Yunshi Wu, 0000-0002-1596-5185; Fei Guo, 0000-0001-8414-5626; Shuquan Gao, 0000-0001-5231-3875; Guangyuan Sun, 0000-0002-5615-459X.

Keywords: Multidisciplinary collaboration; colorectal cancer liver metastasis; diagnosis and treatment; efficacy; prognosis

Submitted Dec 14, 2021. Accepted for publication Feb 21, 2022.

doi: 10.21037/apm-22-87

View this article at: <https://dx.doi.org/10.21037/apm-22-87>

Introduction

The major target organs of distant metastases from colorectal cancer are the liver and lungs (1). Colorectal cancer liver metastasis (CRLM) is the most common cause of death in colorectal cancer patients. Approximately 15–25% of patients with confirmed colorectal cancer have synchronous liver metastases, and another 15–25% of patients will develop synchronous liver metastases following the radical resection of primary lesions. Among the latter patients, as the overwhelming majority of liver metastases are not initially suitable for radical (R0) resection, these patients must undergo a series of conversion therapies. Thus, the overall survival (OS) of patients with such lesions is short (2–4). According to relevant research, the median OS of patients with liver metastases who have received no treatment is only 6.9 months, and the 5-year survival rate of patients with unresectable liver metastases is <5%. Conversely, if the liver metastases can be completely resected or if patients can achieve no evidence of disease (NED) status, their median OS is 35 months, and their 5-year survival rate can be up to 30–57% (5,6).

Before 2018, China's guidelines for CRLM set R0 resection as the therapeutic goal for CRLM, requiring the complete resection of liver metastases and the surgical preservation of certain incisal edges. However, after 2018, the relevant consensus on diagnosis and treatment changed R0 resection to NED, which was extended to a larger CRLM patient population than the original R0 resection that was limited to a specific patient population (7,8). The treatment of such CRLM patients should be conducted to be evaluated comprehensively and systematically under the guidance of a multidisciplinary team (MDT) which includes internal medicine, radiotherapy, interventional imaging (MRI, CT and ultrasound), pathology and other related disciplines. MDT collaborations should seek to develop individualized therapeutic goals and administer comprehensive therapies (e.g., surgical resection, genetic testing, chemotherapy, radiotherapy, target therapy, radiofrequency, microwave, and embolotherapy) to treat primary and metastatic lesions

during one or several operations, thereby improving the overall surgical resection rate, ablation rate, and 5-year survival rate of CRLM patients.

Based on this concept, we invited three large regional general hospitals, including the Hebei Tumor Hospital and Tianjin Nankai Hospital, to retrospectively collect information on the incidence, diagnosis, and treatment of patients diagnosed with CRLM, with an emphasis on patients whose CRLM was initially evaluated as potentially resectable. The regimens and effects of conversion therapy were analyzed, and ablation therapy was added on the basis of previous surgical treatment, so as to expand the treatment indications of NED. Additionally, the survival of CRLM patients was analyzed based on survival follow-up results to provide a scientific basis for subsequent precision therapy and evaluation. We present the following article in accordance with the STROBE reporting checklist (available at <https://apm.amegroups.com/article/view/10.21037/apm-22-87/rc>).

Methods

Study design and study participants

CRLM patients at the General Surgery Department of The First Affiliated Hospital of Hebei North University, No. 2 Surgery Department of Hebei Tumor Hospital, and No. 1 Gastrointestinal Surgery Department of Tianjin Hospital of ITCWM Nankai Hospital between October 1, 2017 and October 1, 2018 were enrolled in this retrospective study. The general data of the patients were recorded, including their age, gender, degree of tumor differentiation, tumor pathological type, tumor clinical stage (in accordance with the 8th edition of staging criteria by the American Joint Committee on Cancer) (9), chemotherapy response score (CRS), metastatic tumor diameter, carcinoembryonic antigen (CEA) level, the number of liver metastases, the surgery method, genetic testing results, and conversion therapy data. All procedures performed in this study involving human participants were in accordance with the

Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committees of The First Affiliated Hospital of Hebei North University (approval ID 2021013), Hebei Tumor Hospital (approval ID 2017kf386) and Tianjin Hospital of ITCWM Nankai Hospital (approval ID 2022026). Individual consent for this retrospective analysis was waived.

Enrollment criteria

Colorectal adenocarcinoma was confirmed through colonoscopy and bite biopsy, while intestinal cancer with synchronous liver metastases was confirmed through enhanced abdominal and pelvic CT, rectal MRI, serum alpha-fetoprotein (AFP) levels, and medical history. Patients' medical records, including genetic testing, were well documented, and complete follow-up records were kept. A professional and official MDT at the hospital level was responsible for developing the therapeutic regimens and supervising the entire process.

Exclusion criteria

Patients who had lung or craniocerebral metastases detected by enhanced chest CT or other methods were excluded. Moreover, patients were not eligible for the study if they could not tolerate systemic therapy because of their poor physical condition, discontinued or abandoned therapy in the course of the treatment, did not follow the treatment regimens determined by the MDT, or did not cooperate, had incomplete medical records, or were lost during the follow-up period. Patients who underwent acute emergency surgery for acute hemorrhage, perforation, and obstruction were also excluded.

Treatment procedures

The enrolled subjects were divided into the following two groups: (I) patients with lesions initially evaluated as resectable (the resectable group); and (II) patients with lesions initially evaluated as unresectable (the initially unresectable group). Phase I resection for primary lesions with liver metastases was performed on patients in the resectable group. Patients from the initially unresectable group were subdivided into an unresectable group and a potentially resectable group. Under the guidance of a MDT, regimens of conversion therapy, and targeted regimens of mFOLFOX and FOLFIRI were determined

based on the results of clinical staging and genetic testing. The surgical resection of liver metastases, microwave ablation, radiofrequency ablation, and other therapies were performed on patients who had undergone successful conversion therapy. Systemic therapy was continued for patients (who indicated their willingness to participate) in whom conversion therapy was unsuccessful and whose lesions were still considered unresectable and non-ablatable.

Survival follow-up

The clinical data of all the CRLM patients were included in each center's database of colorectal tumors. Follow-up appointments were carried out by the professional personnel of each center's team through the clinic service, telephone, or the WeChat messaging application. The re-examination results were reviewed, including results related to the physical examination, serum CEA level, AFP tumor marker test, analysis of peripheral blood cells, biochemical indexes, hepatic and renal function, CT scans of the chest and abdomen, and electronic colonoscopy. The survival data were recorded in detail. OS was defined as the time from diagnosis to death or discontinuation of follow-up. PFS was defined as the time from diagnosis to tumor progression or death. The last follow-up appointment was conducted on October 30, 2021.

Statistical analysis

The statistical analysis was conducted using SPSS 17.0 software. The measurement data are expressed as the mean \pm standard deviation, and a *t*-test was used to determine if the means of two data sets differed significantly. The enumeration data are represented by the number of cases, and a chi-square test was conducted. A logistic regression analysis was conducted to determine the factors affecting the success of conversion therapy. Kaplan-Meier survival curves were used for the monofactor survival analysis and a log-rank test was used to compare the differences in the survival rates. The significance of all statistical comparisons was set to $P < 0.05$.

Results

General data and pathological characteristics of CRLM patients

One hundred and seventy-five CRLM patients from three

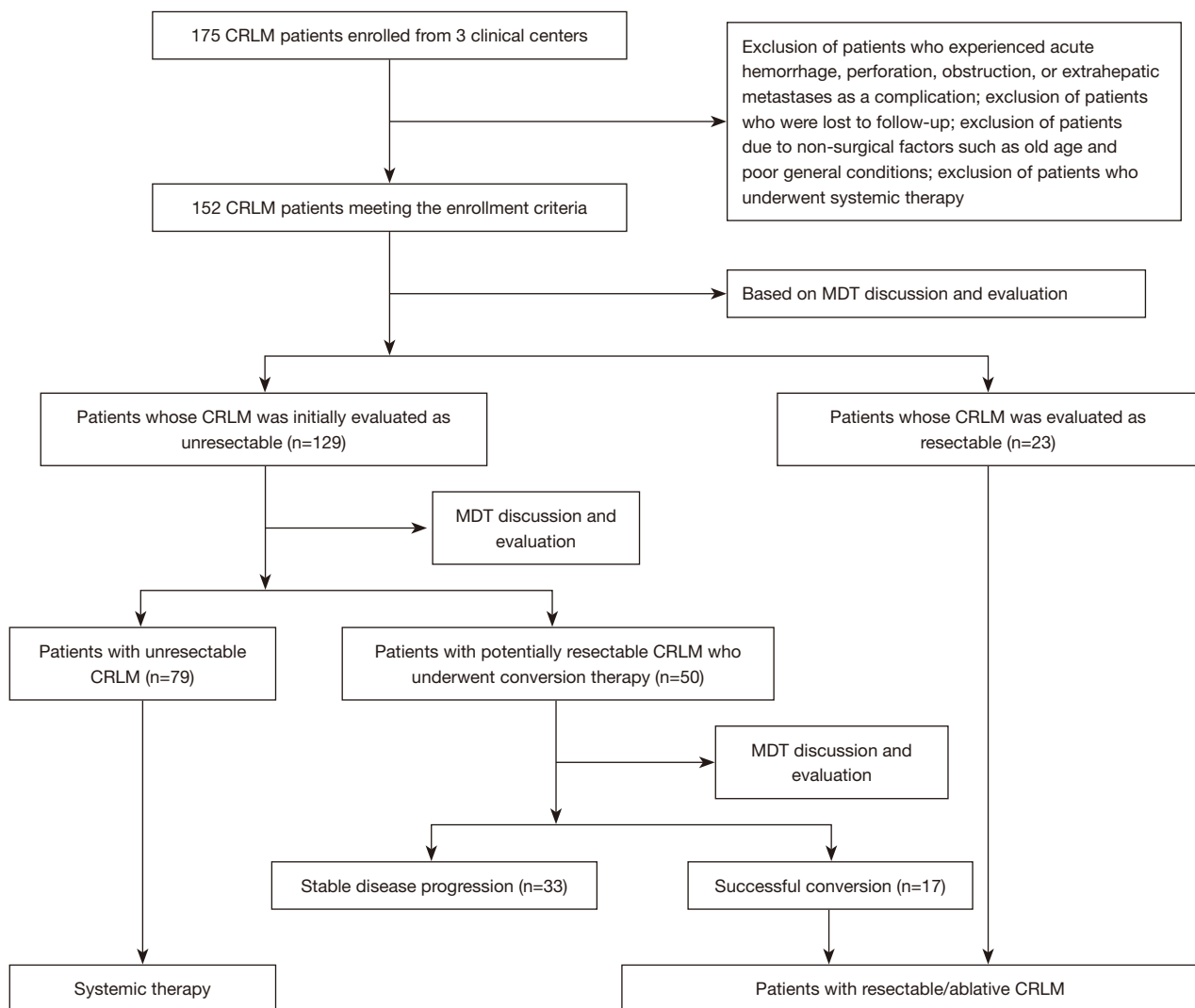


Figure 1 Enrollment flow chart of CRLM patients. CRLM, Colorectal Cancer Liver Metastasis; MDT, multidisciplinary.

medical centers were enrolled in this study. After excluding patients who underwent emergency surgery, developed extrahepatic metastases, or were lost during the follow-up period, 50 CRLM patients with potentially resectable liver metastases were enrolled for conversion therapy. Among them, 17 patients achieved NED status after undergoing therapy, 12 underwent surgical resection, 4 were treated with radiofrequency ablation, and 1 with microwave ablation (see *Figures 1-3*).

Analysis of factors affecting conversion therapy in patients whose CRLM was initially evaluated as unresectable

The general data and pathological characteristics of the

patients, such as gender, age, the site of the primary lesion/s, the status of genetic testing, the serum CEA level, and the number of liver metastases, were analyzed. The results of the monofactor analysis indicated that the number and maximum diameter of liver metastases, the serum CEA level, the KRAS/NRAS and BRAF V600E mutation status, and the use of targeted drugs may be risk factors in determining whether NED status can be achieved through surgery/ablation following conversion therapy (see *Table 1*). The results of the logistic multifactor analysis demonstrated that the number of liver metastases had a significant effect on the efficacy of conversion therapy ($P=0.048$). The use of targeted drugs also affected the conversion therapy, but not significantly ($P=0.063$) (see *Table 2*).

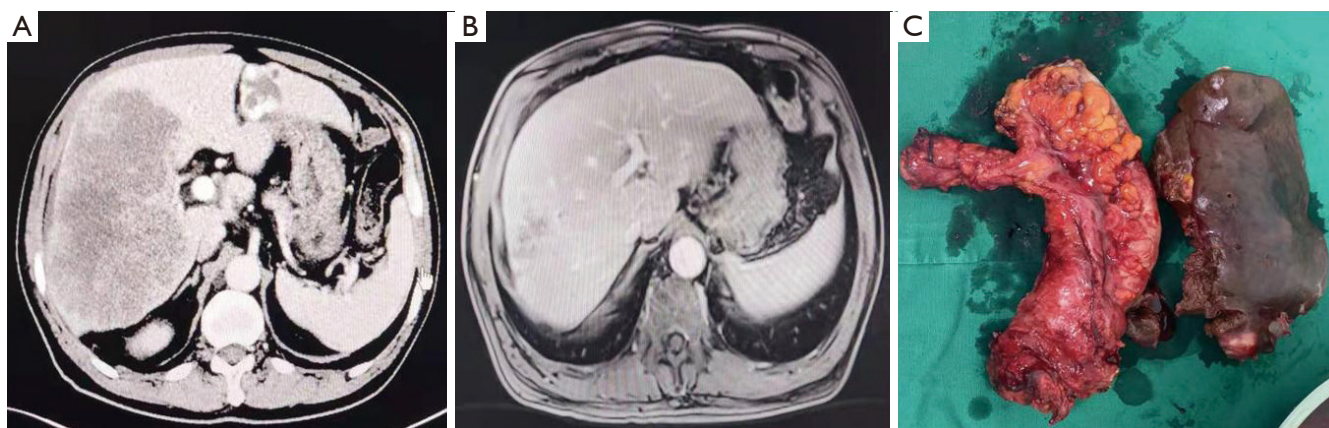


Figure 2 Cases of surgical resection of primary lesions and liver metastases after conversion therapy. (A) Abdominal CT of a patient whose CRLM was initially evaluated as potentially resectable; (B) abdominal CT of the patient at a follow-up visit after 8-cycle treatment with FOLFIRI + Cetuximab injections (biweekly); (C) primary lesions and liver metastases removed at the same resection. CT, computerized tomography; CRLM, Colorectal Cancer Liver Metastasis.

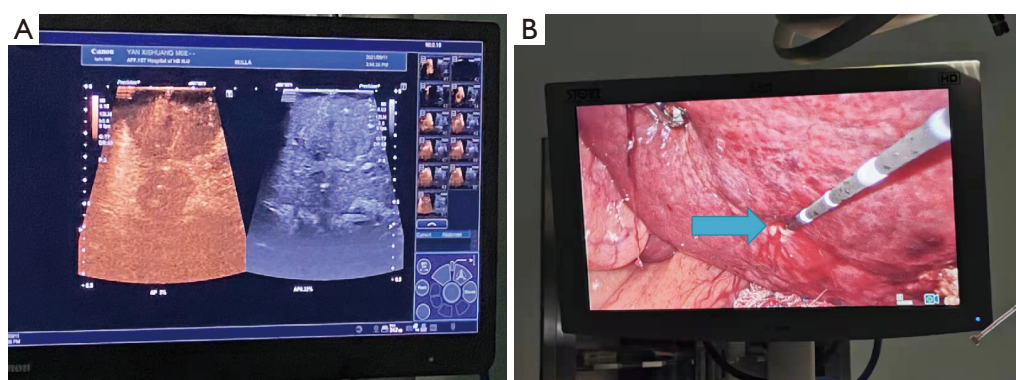


Figure 3 Intraoperative endoscopic ultrasound-guided microwave ablation of liver metastases. (A) Intraoperative ultrasound location and ablation of metastases; (B) laparoscopic ablation of metastases. The blue arrow means the location of liver metastases.

Statistical analysis during the follow-up period

The last follow-up appointment in this study was conducted on October 30, 2021. Overall, patients had an OS of 3–33 months with a median of 14 months. The OS of patients who successfully achieved NED through conversion therapy was 16–33 months with a median of 22 months, while the OS of patients with inconspicuous/progressive lesions after undergoing conversion therapy was 3–20 months with a median of 11 months, which was significantly different between NED group and inconspicuous/progressive lesions group ($P < 0.0001$) (see *Figure 4*). The OS of patients who underwent surgical resection was 16–32 months with a median of 23 months, while the OS of patients

treated with ablation was 16–19 months with a median of 17 months, indicating statistical differences between surgical resection group and ablation group ($P < 0.05$; see *Figure 5*). Additionally, the PFS was 1–28 months with a median of 10 months. The PFS of patients who successfully achieved NED through conversion therapy was 13–28 months with a median of 18 months, while the PFS of patients with inconspicuous/progressive lesions after undergoing conversion therapy was 1–17 months with a median of 7 months, showing statistically significant differences between NED group and inconspicuous/progressive lesions group ($P < 0.0001$; see *Figure 6*). The PFS of patients who received a surgical resection was 14–28 months with a median of 22 months, while the PFS of patients treated with

Table 1 General data and clinical and pathological characteristics of patients undergoing conversion therapy

Parameter	Resection/ablation of liver metastases after conversion therapy NED (n=17), n (%)	Progressive/inconspicuous liver metastases after conversion therapy (n=33), n (%)	χ^2	P
Gender			1.367	0.242
Male	9 (52.94)	23 (69.70)		
Female	8 (47.06)	10 (30.30)		
Age (years)			0.271	0.603
36–60	8 (47.06)	13 (39.39)		
61–79	9 (52.94)	20 (60.61)		
Site of primary lesions			0.500	0.480
Left hemicolon	6 (35.29)	2 (6.06)		
Right hemicolon	3 (17.65)	12 (36.36)		
Rectum and colon	8 (47.06)	19 (57.58)		
Number of liver metastases			14.489	0.000
≥ 3	8 (47.06)	32 (96.97)		
< 3	9 (52.94)	1 (3.03)		
Maximum diameter of liver metastases			5.704	0.017
≥ 5 cm	4 (23.53)	21 (63.64)		
< 5 cm	13 (76.47)	12 (36.36)		
CEA (ng/mL)			9.102	0.003
< 200	13 (76.47)	14 (42.42)		
≥ 200	4 (23.53)	19 (57.58)		
KRAS/NRAS			3.950	0.047
Wild type	16 (94.12)	21 (63.64)		
Mutation	1 (5.89)	12 (36.36)		
BRAF V600E			4.685	0.030
Wild type	17 (100.0)	23 (69.70)		
Mutation	0 (0)	10 (30.30)		
Chemotherapy regimen			3.212	0.073
mFOLFOX	13 (76.47)	15 (45.45)		
FOLFIRI	4 (23.53)	18 (54.55)		
Combined targeted drugs			4.063	0.044
Cetuximab	12 (70.59)	11 (33.33)		
Bevacizumab	3 (17.65)	14 (42.42)		

NED, no evidence of disease; CEA, Carcino-Embryonic Antigen.

Table 2 Logistic regression analysis of multiple factors influencing the achievement of NED through conversion therapy

Factor	β	SE	Wald	P	OR	95% CI
Number of liver metastases	2.371	1.197	3.923	0.048	10.704	1.025–111.765
Combined targeted drugs	1.558	0.839	3.446	0.063	4.750	0.917–24.620
Constant	-2.520	1.183	4.538	0.033	0.080	

NED, no evidence of disease.

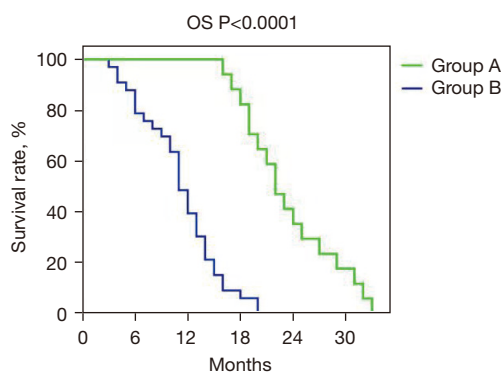


Figure 4 Kaplan-Meier analysis of the overall survival of the two patient groups. (Group A) The patient group undergoing resection/ablation of liver metastases after conversion therapy; (Group B) the patient group with progressive/inconspicuous liver metastases after conversion therapy. OS, overall survival.

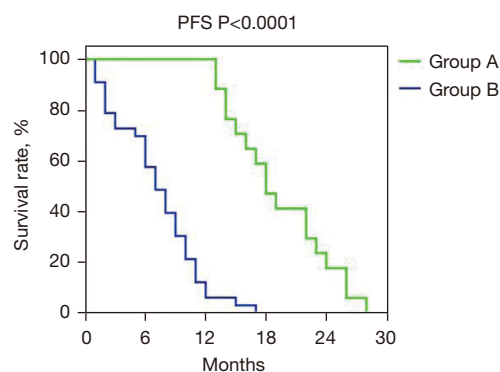


Figure 6 Kaplan-Meier analysis of the progression-free survival of the two patient groups. (Group A) The patient group undergoing resection/ablation of liver metastases after conversion therapy; (Group B) the patient group with progressive/inconspicuous liver metastases after conversion therapy. PFS, progression-free survival.

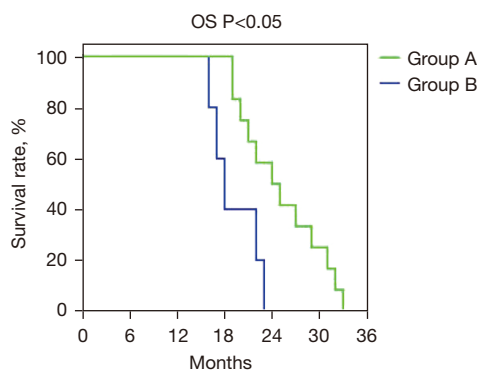


Figure 5 Kaplan-Meier analysis of the overall survival of the two patient groups. (Group A) The patient group undergoing surgical resection of liver metastases after conversion therapy; (Group B) the patient group undergoing (radiofrequency/microwave) ablation of liver metastases after conversion therapy. OS, overall survival.

ablation was 13–18 months with a median of 14 months, which was significantly different between surgical resection group and ablation group ($P < 0.01$; see *Figure 7*).

Analysis of factors affecting the survival of patients whose CRLM was initially evaluated as unresectable

Fifty CRLM patients were divided into two groups based on the median OS (i.e., OS < 14 months and OS ≥ 14 months). The results of the monofactor analysis revealed that the number and maximum diameter of liver metastases, the serum CEA level, and BRAF V600E mutations were factors affecting the OS of CRLM patients (see *Table 3*). More specifically, the results of the logistic multifactor analysis showed that BRAF V600E mutations alone were the primary determinant affecting OS (see *Table 4*).

Discussion

Precise evaluation

According to China's 2021 guidelines for CRLM diagnosis and comprehensive therapy, imaging tests (e.g., liver ultrasound and enhanced abdominal CT) should be performed in addition to rectal MRI, transrectal ultrasonography, CT evaluation, clinical staging, and

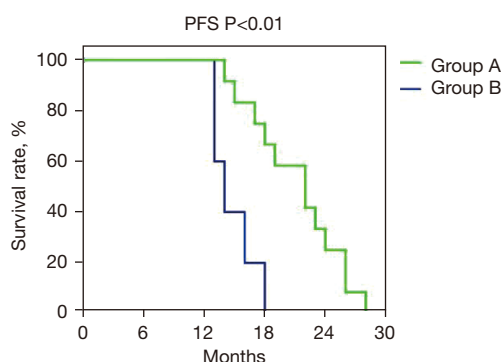


Figure 7 Kaplan-Meier analysis of the progression-free survival of the two patient groups. (Group A) The patient group undergoing resection of liver metastases after conversion therapy; (Group B) the patient group undergoing (radiofrequency/microwave) ablation of liver metastases after conversion therapy. PFS, progression-free survival.

routine tests of serum CEA, CA199, and other tumor markers to diagnose liver metastases in patients with pathologically confirmed colorectal cancer. For patients with suspected but unconfirmed liver metastases, additional methods, such as a serum AFP tumor marker test, liver ultrasound contrast, liver MRI plain scan, and enhanced tests should be conducted to undertake a comprehensive and precise evaluation of the sites, sizes, and the number of liver metastases, and determine the presence of synchronous metastases (7,10). Additionally, CRLM patients should undergo genetic testing to analyze the mutational status of KRAS, NRAS, BRAF, Microsatellite Instability (MSI), and human epidermal growth factor receptor 2 (HER2).

Development of therapeutic measures under the guidance of MDT

MDT for colorectal tumors should comprise professional senior experts specializing in general (tumor and liver) surgery, medical oncology, gastroenterology, radiotherapy, pathology, nutrition, imaging, endoscopy, and psychotherapy and care (11). These specialists should work together to set therapeutic goals, develop treatment measures, and determine the time for subsequent visits based on each patient's medical condition, age, basic condition, psychological state, family, society status, and other influencing factors. The advantages are reflected in more accurate staging assessment, better connection of treatment, reduction of confusion and delay, full

consideration of patients' quality of life and health economic and social effects, the best survival benefits, so as to achieve personalized and precise treatment (12-14).

In relation to the diagnosis of CRLM patients, the first step is to evaluate whether the liver metastases and the primary lesions can be resected in a single operation. This decision should be made based on the sites, number, and sizes of liver metastases. For patients whose CRLM is initially evaluated as unresectable, it is recommended that conversion therapy regimens be developed based on CRS scoring, the results of genetic testing, the sites of the primary lesions, and the patient's general condition, such as any underlying disease, nutrition, physical condition, and immune function, as all aspects of survival and the quality of life of patients who achieve NED status after treatment for liver metastases are considerably higher than those of patients who do not achieve it. For CRLM patients who may achieve NED status, conversion therapy is of particular importance. Additionally, the early shrinkage of metastatic lesions is an important indicator of favorable prognosis (15,16).

MDT mode has been widely applied in clinical practice. Many international guidelines and expert recommendations emphasize the importance of multidisciplinary diagnosis and treatment, and also, MDT has been included in the guidelines in China, suggesting that all CRLM patients should participate in MDT diagnosis and treatment mode (17,18). The overall prognosis of CRLM can be improved by making an individualized and most appropriate comprehensive treatment plan to maximize the benefit of patients.

Treatment for resectable liver metastases of colorectal cancer

For resectable liver metastases, preoperative chemotherapy could help shrink the tumor, test biological behavior, and reduce recurrence rate; but it may also cause liver injury and delay surgery. There is still controversy whether neoadjuvant chemotherapy should be performed and how to select patients from chemotherapy before surgery.

According to current domestic and foreign studies, the clinical benefit of direct surgery may outweigh the benefit of neoadjuvant tumor reduction in patients with obviously resectable liver metastases with overall good prognostic factors (CRS score <2). For patients with the number of metastases >3, the maximum diameter ≥ 5 cm, the primary tumor with lymph node metastasis, serum CEA level increased and not receiving chemotherapy in the past 12 months, the clinical benefit of

Table 3 Analysis of factors influencing survival in patients whose CRLM was initially evaluated as potentially resectable

Parameter	<14 m (n=23), n (%)	≥14 m (n=27), n (%)	χ^2	P
Gender			1.817	0.178
Male	17 (73.91)	15 (55.56)		
Female	6 (26.09)	12 (44.44)		
Age (years)			0.038	0.845
36–60	10 (43.48)	11 (40.74)		
61–79	13 (56.52)	16 (59.26)		
Site of primary lesions			2.158	0.142
Left hemicolon	2 (8.70)	6 (22.22)		
Right hemicolon	6 (26.09)	9 (33.33)		
Rectum and colon	15 (65.22)	12 (44.44)		
Number of liver metastases			8.459	0.004
≥3	23 (100.0)	17 (62.96)		
<3	0 (0)	10 (37.04)		
Maximum diameter of liver metastases			6.522	0.011
≥5 cm	16 (69.57)	9 (33.33)		
<5 cm	7 (30.43)	18 (66.67)		
CEA (ng/mL)			9.522	0.002
<200	7 (30.43)	20 (74.07)		
≥200	16 (69.57)	7 (25.93)		
KRAS/NRAS			0.435	0.509
Wild type	16 (69.57)	21 (77.78)		
Mutation	7 (30.43)	6 (22.22)		
BRAFV600E			4.232	0.040
Wild type	15 (65.22)	25 (92.59)		
Mutation	8 (34.78)	2 (7.41)		
Chemotherapy regimen			2.710	0.100
mFOLFOX	10 (43.48)	18 (66.67)		
FOLFIRI	13 (56.52)	9 (33.33)		
Combined targeted drugs			0.484	0.486
Cetuximab	9 (39.13)	14 (51.85)		
Bevacizumab	9 (39.13)	9 (33.33)		

CRLM, Colorectal Cancer Liver Metastasis; CEA, Carcino-Embryonic Antigen.

Table 4 Logistic multifactor analysis of patients whose CRLM was initially evaluated as potentially resectable

Item	β	SE	Wald	P	OR	95% CI
KARS/NARS	-3.908	2.061	3.594	0.058	0.020	0.000–1.141
BRAF V600E	-4.110	1.834	5.024	0.025	0.016	0.000–0.597
Constant	50.076	13,900.835	0.000	0.997	5.597	

CRLM, Colorectal Cancer Liver Metastasis.

neoadjuvant chemotherapy may be greater than that with not neoadjuvant chemotherapy (19,20).

The challenges involved in providing comprehensive therapy to patients whose CRLM was initially evaluated as unresectable

It is currently believed that complete surgical resection of liver metastases (CRLM) is the only possible treatment option for patients with colorectal cancer. For CRLM patients who were initially assessed as unresectable, the prognosis of patients who underwent resection after transformation was nearly identical to that of those who underwent the initial resection. Translational therapy is a method of transforming the initial unresectable foci into surgically resectable foci through preoperative systematic or local therapy for suitable patients to shrink the tumor. A number of studies have shown that the response rate of patients to preoperative chemotherapy drugs is significantly positively correlated with the conversion rate (21,22). Therefore, according to the characteristics of patients with metastasis, individualized treatment with high response rate can improve the success rate of conversion therapy.

Multiple center studies have demonstrated that chemotherapy combined with targeted drugs improve the rate of conversion therapy (23,24). The chemotherapy regimens commonly used for CRLM patients include FOLFIRI, FOLFOX, and FOLFOXIRI. The use of targeted drugs should be directed at the sites of primary lesions and the mutation status of KRAS and NRAS. In terms of primary lesions of the left hemicolon (including the rectum) with wild-type KRAS/NRAS, cetuximab is more effective against EGFR than VEGF given the OS and the objective remission rates. Conversely, for CRLM patients whose primary lesions are in the right hemicolon, cetuximab is less effective against EGFR than VEGF in terms of OS (25,26). For CRLM patients with the BRAF V600E mutation, given the poor prognosis of these patients, FOLFOXIRI could be used in combination with cetuximab

to inhibit VEGF (27-30).

For CRLM patients that undergo successful conversion therapy, the surgical resection of liver metastases is still the best approach. Apart from surgery, topical destruction therapies (e.g., radiofrequency ablation and microwave ablation) against some types of tumors can also lead to the thorough destruction of metastatic lesions (31,32). Thus, the above-mentioned therapies can be considered for patients for whom surgical resection poses a substantial difficulty, for those for whom the postoperative residual liver volume is expected to be insufficient, and for those whose physical tolerance is poor, as this will enable more patients to achieve NED and improve the 5-year survival rate. Additionally, given the radiofrequency and microwave ablation therapies available for such patients, a MDT led by surgeons should be established to develop a comprehensive and individualized treatment plan based on MDT discussions and evaluations.

In this study, 50 patients from 3 regional medical centers whose CRLM was initially evaluated as potentially resectable met the inclusion criteria and were thus enrolled in the study. The pathological characteristics of these patients were analyzed and their survival data were collected. Our results demonstrated that 34% (17/50) of the patients achieved NED status through surgical resection and microwave/radiofrequency ablation after undergoing conversion therapy. The results of the monofactor analysis indicated that the influencing factors were the number and maximum diameter of liver metastases, serum CEA level, KRAS/NRAS mutation status, and the use of targeted drugs. More specifically, the results of the logistic multifactor analysis suggested that the number of liver metastases alone was the primary determinant, and the use of targeted drugs also had a certain effect. Due to the small sample, some indicators failed to meet the modeling requirements. In general, the OS and PFS of patients who achieved NED following successful conversion therapy was considerably higher than those of patients who failed to achieve NED after conversion therapy. Additionally, surgical resection led to better OS and PFS than treatment

with microwave/radiofrequency ablation in CRLM patients. However, this finding might have been affected by the small number of cases included after stratification. Thus, further research based on a larger sample size and multicenter data needs to be conducted.

The results of Ma *et al.* from Peking University Cancer Hospital (33) demonstrated that radical surgical resection was successfully performed in 31.59% (24/76) of patients whose CRLM was initially evaluated as unresectable after they underwent conversion therapy which was slightly higher than 24% (12/50) of our study, and the median OS was significantly longer than that of the 52 patients whose conversion therapy was unsuccessful (20 and 15 months, respectively, $P=0.034$).

The results of the univariate analysis showed that the maximum diameter of liver metastases <6 cm and a number of metastases ≤ 4 were independent factors associated with successful conversion therapy. Nozawa *et al.* (34) examined 99 metastatic colorectal cancer patients who received chemotherapy, among whom, 23 patients (23.23%) underwent radical surgical resection after conversion therapy, but found no significant difference in the long-term survival rate between these patients and the 112 patients with resectable phase-IV colorectal cancer who underwent surgery for the first time. Additionally, Bolhuis *et al.* (35) analyzed phase-II/III randomized trials published after 2008 on first-line systemic conversion therapy in patients or subgroups of patients with CRLM, and found that the mutational tumor status of KRAS/BRAF hampered conversion therapy in patients with unresectable CRLM (i.e., the R0 resection rate). To summarize, the results of the above-mentioned clinical studies are consistent with the findings of our study.

Further, a stratification analysis was conducted on the CRLM patients based on the median OS. The results of the monofactor analysis indicated that the number and maximum diameter of liver metastases, serum CEA level, and BRAF V600E mutational status affected the OS of CRLM patients, and that among these, the BRAF V600E mutation was the primary factor. However, concerns remain due to the failure of the relatively small number of parameters to meet the modeling requirements. Thus, a further demonstration is still needed based on a large sample of clinical data.

Conclusions

The use of advanced examination methods to correctly

diagnose and treat CRLM is essential for patients whose CRLM is initially evaluated as unresectable. Developing precise therapeutic measures under the guidance of a MDT combines the advantages of different disciplines, and maximizes the chances of prolonging patient survival and improving their quality of life (36,37). However, the treatment of these patients still faces substantial challenges. Undoubtedly, substantial benefits can be obtained by radical resection and ablation therapy in the case of some patients; however, the success rate of conversion therapy of about 30% is relatively low (38,39). Improving this success rate of conversion therapy is the major difficulty facing current clinical research in the field of CRLM. Thus, more precise and effective regimens of conversion therapy need to be developed to improve the conversion rate and long-term survival of CRLM patients.

Acknowledgments

Funding: The study was supported by Special Tumor Research Project of National Cancer Center (No. NCC2017A23), the Hebei Funding Project for High-level Talents (No. A202101062), the Training Project for Excellent Clinical Medical Talents of Hebei Provincial Department of Finance (No. 361009), the 2015 Key Medical Science Project of Hebei Provincial Department of Science and Technology (No. 152777237), and the Science and Technology Mandatory Plan of Zhangjiakou, Hebei (No. 1712005D).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://apm.amegroups.com/article/view/10.21037/apm-22-87/rc>

Data Sharing Statement: Available at <https://apm.amegroups.com/article/view/10.21037/apm-22-87/dss>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://apm.amegroups.com/article/view/10.21037/apm-22-87/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures

performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committees of The First Affiliated Hospital of Hebei North University (approval ID 2021013), Hebei Tumor Hospital (approval ID 2017kf386) and Tianjin Hospital of ITCWM Nankai Hospital (approval ID 2022026). Individual consent for this retrospective analysis was waived.

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Cite this article as: Han L, Xue J, Wu X, Liang G, Wu Y, Guo F, Gao S, Sun G. Multidisciplinary approach to the diagnosis and treatment of patients with potentially resectable colorectal cancer liver metastasis: results of a multicenter study. *Ann Palliat Med* 2022;11(2):717-729. doi: 10.21037/apm-22-87