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Multi-modality treatment of colorectal liver metastases

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Abstract

Liver metastases synchronously or metachronously occur in approximately 50% of colorectal cancer patients. Multimodality comprehensive treatment is the best therapeutic strategy for these patients. However, the optimal pattern of multimodality therapy is still controversial, and it raises several significant concerns. Liver resection is the most important treatment for colorectal liver metastases. The definition of resectability has shifted to focus on the completion of R0 resection and normal liver function maintenance. The role of neoadjuvant and adjuvant chemotherapy still needs to be clarified. The management of either progression or complete remission during neoadjuvant chemotherapy is challenging. The optimal sequencing of surgery and chemotherapy in synchronous colorectal liver metastases patients is still unclear. Conversional chemotherapy, portal vein embolization, two-stage resection, and tumor ablation are effective approaches to improve resectability for initially unresectable patients. Several technical issues and concerns related to these methods need to be further explored. For patients with definitely unresectable liver disease, the necessity of resecting the primary tumor is still debatable, and evaluating and predicting the efficacy of targeted therapy deserve further investigation. This review discusses different patterns and important concerns of multidisciplinary treatment of colorectal liver metastases.

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Key words: Colorectal cancer; Liver metastases; Multimodality therapy

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INTRODUCTION

Colorectal cancer is one of the most commonly diagnosed cancers, and it is ranked the third most common globally and fourth in China. Approximately 40% of colorectal cancer patients die of cancer recurrence and metastasis. The liver is the most frequent metastatic site of colorectal cancer. Approximately 15%-25% of colorectal cancer patients have synchronous liver metastases, and 20%-25% of patients with colorectal cancer develop metachronous hepatic metastases.

In recent decades, the 5-year overall survival (OS) after curative liver resection of colorectal liver metastases (CRLM) has increased to 35%-58%. This improvement is largely due to advancements in CRLM multimodality treatment. Generally, CRLM can be categorized into three subsets: clearly resectable, potentially resectable, or definitely unresectable. This review discusses patterns and key issues of multidisciplinary treatment of these three different CRLM subsets with a focus on the
interactive influence of different therapeutic approaches.

CLEARLY RESECTABLE COLORECTAL LIVER METASTASES

Shifting definition of CRLM resectability

Liver lesions numbering more than three, an estimated resection margin < 1 cm, the presence of extrahepatic disease, or no expected sufficient remnant liver volume used to be deemed as contraindications for CRLM liver resection. According to this definition, only 10%-20% of CRLM patients were resectable. However, this definition has changed in recent years. The report by Malik et al has indicated that patients with 4-7 or > 7 CRLMs still had a favorable outcome after liver resection (5-year OS 34.8% and 24.2%, respectively). In the past, it was widely accepted that at least a 1-cm resection margin must be achieved for CRLM resection. However, several studies have indicated that the actual clearance margin did not affect survival as long as R0 resection could be achieved. The presence of extrahepatic metastases is also no longer considered an absolute contraindication for liver resection. Some cancer centers have reported that the 5-year OS after combined resection of lung and liver metastases is approximately 30%.[13,14] The CRLM resectability criteria have shifted to focus on whether R0 resection for all tumors can be achieved and if a sufficient volume of residual liver can be preserved. The requirement for residual liver volume can be different for patients receiving intensive chemotherapy. Although at least 20% of total liver volume should be preserved for a healthy liver, it is recommended that at least 30%-60% should be preserved for livers impaired by chemotherapy-associated steatosis or hepatitis.[15]

Advantages and disadvantages of perioperative chemotherapy

The combination of surgery and chemotherapy is the most effective multidisciplinary therapeutic paradigm for CRLM with a curative intent. There are two patterns of perioperative chemotherapy for resectable CRLM: preoperative and postoperative chemotherapy. Postoperative chemotherapy is also known as adjuvant chemotherapy, although it is still debatable whether the alternative term adjuvant therapy should be used instead. Preoperative chemotherapy has become a common practice and is intended to reduce the high risk of recurrence after resection of metastases. Preoperative chemotherapy is also called neoadjuvant chemotherapy in the setting of resectable liver metastases. The role of preoperative chemotherapy is more controversial than postoperative chemotherapy because it can give rise to major concerns. Generally, the paradigm of preoperative chemotherapy plus liver resection plus postoperative chemotherapy has become the most prevalent treatment modality in real practice.

Survival benefit of perioperative chemotherapy: Adjuvant chemotherapy for stage III colorectal cancer patients has been widely accepted based on solid evidence for survival benefit. Although postoperative chemotherapy after liver metastases resection is also accepted by many oncologists, there have been few prospective randomized clinical studies that have investigated the adjuvant chemotherapy survival benefit after liver resection, and the sample size of these studies has been limited due to difficult accrual. In the Fédération Francophone de la Cancérologie digestive (FFCD) ACHBT TH AURC 9002 clinical trial, CRLM patients receiving adjuvant chemotherapy of 5-fluorouracil (5-FU) and leucovorin (LV) after R0 liver resection had a significantly better 5-year disease-free survival (DFS) compared with the observation group (33.5% vs 26.7%, P = 0.028). There was also a trend toward better OS in the adjuvant chemotherapy group, although this was not statistically significant (51.1% vs 41.1%, P = 0.13).[16] This study was prematurely stopped due to slow accrual. A pooled data analysis combined with another study (i.e., European Organisation for Research and Treatment of Cancer/National Cancer Institute of Canada Clinical Trials Group/Interdisciplinary Group for Cancer Care Evaluation trial), which had a similar design and stopped ahead of schedule for the same reason, was performed but also could not demonstrate a statistically significant improvement in OS (P = 0.095).[17]

Although the most fascinating benefit of preoperative chemotherapy is the conversion of unresectability to resectability, the role of neoadjuvant chemotherapy in patients with initially resectable CRLM is still controversial. The most important concern about neoadjuvant chemotherapy is whether it can bring about a survival benefit. The only published randomized prospective clinical trial to investigate the role of neoadjuvant chemotherapy in CRLM patients, EORTC 40983,[18] indicated that patients with initially resectable CRLM undergoing liver resection plus six cycles of preoperative FOLFOX4 and six cycles of postoperative FOLFOX4 chemotherapy had a better 3-year progression-free survival (PFS) compared to those receiving liver resection alone. However, there was a significant defect in this study: patients in the control group did not undergo chemotherapy after hepatic resection. Therefore, it is difficult to determine whether the PFS improvement is brought about by preoperative chemotherapy, postoperative chemotherapy or both. To investigate the exact role of neoadjuvant chemotherapy, we still need to wait for the results of ongoing clinical studies to compare survival directly in patients undergoing postoperative chemotherapy alone with those undergoing both preoperative and postoperative chemotherapy.

Management of disappearing CRLM: A potential drawback of neoadjuvant chemotherapy in resectable CRLM patients is missing the optimal timing of liver resection because of complete response of liver tumors during chemotherapy. Approximately 4% of patients achieved a radiographic complete response (CR) to chemotherapy, and 9% had a pathological CR.[19,20] Radiographic CR does...
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not always mean true hepatic metastases remission. Viable cancer cells can be pathologically found in 80%-100% of patients with a radiographic CR and undergoing resection according to the prior sites[21]. If these radiographically disappearing liver metastases are kept in place without resection, 41%-75% will have recurrence in situ[21-23]. Nevertheless, it is not always easy to perform liver resection according to the previous site of disappearing liver metastases. To avoid such an intractable condition, it is recommended that the evaluation of liver lesions be repeated every 2 mo during preoperative chemotherapy[7,23-25].

Resection of CRLM progressing during neoadjuvant chemotherapy: A second potential risk of neoadjuvant chemotherapy is disease progression. Liver tumor progression may add to the difficulty of liver resection and even deprive patients of the opportunity for hepatic resection. The EORTC 40983 clinical study[18] reported that 7% of initially resectable CRLM patients had progressive disease (PD) during neoadjuvant chemotherapy, and 4% did not complete liver resection due to prior liver disease progression or the presence of new extrahepatic metastases. Another issue concerning liver metastases progression is whether they should be resected even if it is possible. Adam et al[26] have suggested that liver PD during chemotherapy indicates poor prognosis after resection and should be considered as a contraindication to liver resection. They reported a dismal 5-year OS (8%) and DFS (3%) after liver resection in patients with tumor progression during neoadjuvant chemotherapy. However, other studies have indicated that the response to neoadjuvant chemotherapy has no prognostic value. Reports from Neumann et al[27] and Gallagher et al[28] have indicated no difference in survival after liver resection among three groups of CRLM patients with PD, stable disease (SD) or objective response to neoadjuvant chemotherapy.

Impact of chemotherapy-induced hepatotoxicity on the outcome of hepatic resection: Another important concern related to neoadjuvant chemotherapy is whether the hepatotoxicity caused by preoperative chemotherapy increases the perioperative morbidity and mortality of liver surgery. There are two types of chemotherapy-associated hepatotoxicity: non-alcoholic fatty liver disease (i.e., macrovesicular steatosis/steatohepatitis) and vascular sinusoidal obstruction. All three commonly used chemotherapeutic agents for colorectal cancer, 5-FU, oxaliplatin and irinotecan, can induce steatosis with an incidence rate of 30%-40%[29-31]. Steatohepatitis is less common in patients with chemotherapy. Approximately 3.6%-8%[27,32] of patients have chemotherapy-associated steatohepatitis, which is relatively more common in patients receiving irinotecan as compared with those receiving 5-FU[23]. Vascular sinusoidal obstruction is associated with the use of oxaliplatin, and is present in 10%-52% of patients undergoing preoperative oxaliplatin therapy[23-25].

The impact of chemotherapy induced hepatic toxicity on the short-term outcome of patients receiving liver resection is still uncertain. A slightly increased morbidity was noted in patients undergoing six cycles of preoperative FOLFOX4 chemotherapy as compared with those without preoperative chemotherapy in the EORTC 40983 study[18]. Nevertheless, there was no difference in the perioperative mortality between these two groups. The study of Kooby et al[33] has demonstrated an increase in infection-related complications associated with moderate to severe steatosis in patients undergoing hepatic resection after chemotherapy, but no association with major surgical complications or mortality for preoperative chemotherapy was shown. However, Vauthey et al[34] have reported that, after the use of irinotecan, patients with steatohepatitis had a significantly higher 90-d postoperative mortality compared with those without steatohepatitis (15% vs 2%, P = 0.001). Therefore, it is recommended that irinotecan should be used cautiously in patients with known steatosis or steatohepatitis or those with a high risk for steatosis, such as those with obesity, hypertension or diabetes.

Management of resectable synchronous CRLM

Optimal sequencing of colorectal surgery, liver resection and perioperative chemotherapy: Approximately 15%-25% of patients have synchronous liver metastases at the diagnosis of colorectal cancer[1-3]. The optimal timing of primary tumor and liver metastases resection in synchronous resectable CRLM patients is still controversial. There are three approaches for the sequence of surgical treatment for primary tumor and liver disease: (1) simultaneous resection of primary cancer and liver metastases; (2) resection of primary colorectal tumor first followed by liver resection; and (3) hepatectomy first followed by primary cancer resection. The clinical decision usually depends on many factors, including surgical exposure, colectomy and hepatectomy complexity, surgeon expertise and patient comorbidity[35].

Based on the observation of the possible increased morbidity and mortality using a combination of hepatectomy and colectomy[36-39], a staged approach (i.e., liver resection following primary tumor resection and optional chemotherapy) was widely performed in the past. However, simultaneous resection of the primary cancer and the liver metastases has been increasingly adopted in recent years due to more recent reports that perioperative morbidity and mortality of simultaneous resection are comparable to that of staged resection[40-42]. No significant difference in 5-year survival was found between these two groups in a systemic analysis[43]. However, Reddy et al[43] have reported that patients undergoing simultaneous major hepatectomy (i.e., resection of three or more liver segments) had a significantly higher mortality (8.3% vs 1.4%) and severe morbidity (36.1% vs 17.6%) than those receiving staged resection. Therefore, simultaneous major hepatectomy is not highly recommended at present due to the potentially increased risk of severe complications. A new paradigm has been proposed more recently that is called the “liver-first” strategy[44], and includes first, liver resection, with or without preoperative...
chemotherapy, followed by optional chemotherapy after hepatectomy, and finally, primary tumor resection. This approach may be suitable for borderline resectable liver metastases, which may lose the time frame of resection if delayed. Mentha et al\textsuperscript{[44]} have reported 20 CRLM patients undergoing such a sequential resection with a resection rate of 80% and 4-year OS of 56%. However, there are some potential defects in the design of this approach. For patients with obstructive symptoms caused by the primary tumor, primary-tumor-directed treatment is more urgent and should be performed first. Another potential disadvantage of this approach is that the primary tumor may progress and require emergency surgery during this process. A decision-making analysis has demonstrated that it is least probable to complete all intended sequential treatment for the liver-first approach among the above three treatment sequences\textsuperscript{[45]}.

The role of minimally invasive surgery: It is difficult to perform a one-stage resection of primary and liver disease for rectal cancer liver metastases due to surgical exposure and lengthy incisions. In such a condition, laparoscopic surgery, particularly robot-assisted laparoscopic surgery, is advantageous to perform a simultaneous resection of liver metastases and rectal cancer. This type of surgery has been reported to be safe and feasible in a pilot study by Patriot\textsuperscript{[46]} et al. An important concern about the laparoscopic hepatic resection is the oncologic outcome. It has been reported that the laparoscopic approach had a positive resection margin rate (5.6%) and 5-year OS (50%); comparable with open surgery for CRLMs. In a French study\textsuperscript{[47]} comparing CRLM patients undergoing laparoscopic hepatic resection or open resection, the 5-year OS and DFS were similar in these two groups, whereas the laparoscopic surgery group even had a lower rate of positive resection margin than the open surgery group (13% vs 28%, $P = 0.04$).

**UNRESECTABLE COLORECTAL LIVER METASTASES WITH POTENTIAL CONVERTIBILITY**

Some CRLM patients are initially unresectable but have the potential to become resectable through conversion therapeutic strategies including chemotherapy, embolization, two-staged operation or the combination of ablation therapy.

**Conversion chemotherapy**

It is estimated that 80%-90% of CRLMs are considered unresectable at diagnosis. Due to the development of new chemotherapy agents and targeted therapeutic agents, chemotherapy can convert a considerable portion of initially unresectable CRLM into resectable disease, which is called conversion chemotherapy\textsuperscript{[48-50]}. It was first reported in 1996 by Bismuth et al\textsuperscript{[49]} that preoperative chemotherapy, using oxaliplatin plus 5-FU/LV, enabled 16% (53/330) of initially unresectable CRLM patients to gain the chance of undergoing liver resection with a 5-year OS of 40%. In 2001, Adam et al\textsuperscript{[51]} reported that 13.6% (95/701) of initially unresectable CRLM patients underwent liver metastases resection after systemic chemotherapy and achieved a 5-year OS of 34%. Intensified chemotherapy such as FOLFOXIRI (i.e., oxaliplatin, 5-FU/LV and irinotecan) has been shown to have high response and conversion rates (19%)\textsuperscript{[48]}; however, it has not been generally recommended thus far due to its considerable toxicity. In recent years, the addition of targeted agents such as cetuximab to chemotherapy has been shown to further improve the conversion rate to 30%-40%\textsuperscript{[52]}. In the CELIM study\textsuperscript{[53]}, 106 patients with initially unresectable CRLM underwent cetuximab plus FOLFOX6 or cetuximab plus FOLFIRI and achieved an objective response rate of 68% and 57%, a liver resection rate of 40% and 38%, and a R0 liver resection rate of 38% and 30%, respectively.

**Portal vein embolization and two-stage operation**

Preserving at least 20% of future liver remnant is a major obstacle when performing an extended hemihepatectomy for extensive liver metastases. In this situation, Portal vein embolization (PVE) can be helpful to induce hypertrophy of the contralateral liver to fulfill the minimal liver volume requirement\textsuperscript{[54]}. Generally, PVE is usually used before extended right hepatectomy and is seldom used for extended left hepatectomy because the right posterior sector generally provides > 30% of the liver volume. Even after preoperative chemotherapy or PVE, some patients cannot become eligible for complete CRLM resection through a single hepatectomy. PVE combined with a two-stage resection may be helpful in such circumstances. In 2000, Adam et al\textsuperscript{[55]} first proposed the two-stage resection strategy when they reported the initial results from 13 patients undergoing two-stage hepatectomy with a 3-year survival rate of 35%. An updated result of a 5-year OS of 42% in 41 patients receiving two-staged resection was reported in 2006\textsuperscript{[56]}. However, > 30% (18/59) of patients could not complete the second hepatectomy, mostly because of disease progression ($n = 17$). Additionally, the second hepatectomy has a significant higher postoperative mortality (7%) and morbidity (59%) than the first hepatectomy (0% and 20%, respectively).

**Ablation therapy**

The most commonly used approach for ablation therapy is radiofrequency ablation (RFA). Most previous studies have indicated that RFA is inferior to liver resection for CRLM with a high local recurrence rate\textsuperscript{[57]}. However, for patients who cannot undergo liver resection because of extensive liver metastases and inadequate remnant liver volume, RFA can play an important role when combined with liver resection. RFA is generally recommended for CRLM less than 3 cm\textsuperscript{[58-64]}. The local recurrence rate after RFA increases with tumor size in liver lesions > 3 cm\textsuperscript{[65]}. Several studies have reported a significantly higher local
failure rate after ablation for tumors > 5 cm when com-
pared to those 3cm-5 cm\textsuperscript{[64,66]}. There are three approaches for RFA, including per-
cutaneous, open and laparoscopic. Ablation through the 
open approach seems to be superior to the percutane-
ous or laparoscopic methods in terms of local failure 
rate\textsuperscript{[57,67,68]}. However, the reported local recurrence rate of 
each approach has actually varied and overlapped each 
other in a range of 6%-40% in different studies\textsuperscript{[85-87]}.

**DEFINITELY UNRESECTABLE CRLMs**

**Necessity of primary tumor resection**

For patients with incurable metastatic colorectal cancer 
who have symptoms related to intestinal obstruction, 
perforation or intractable bleeding, palliative primary 
tumor resection is generally required and advocated. 
However, for asymptomatic patients with unresectable 
metastases, the value of primary tumor resection is still 
questionable. Early studies have indicated that primary 
tumor resection may have potential benefits in preventing 
tumor-related symptoms such as obstruction, which may 
require emergency operations with a high risk of surgical 
mortality\textsuperscript{[79-83]}. However, this opinion may become out-
dated with the application of new efficient chemotherapy 
agents that have the ability to control intestinal symptoms 
well. Therefore, the US National Comprehensive Cancer 
Network guidelines recommend that colon resection 
should be considered only for impending obstruction risk 
or intractable bleeding. It is estimated that only 20%-30% 
of metastatic colorectal cancer patients are eligible for 
curative resection. Nevertheless, data from the US Sur-
veillance, Epidemiology, and End Results (SEER) data-
basis have demonstrated that 66% of stage IV colorectal 
cancer patients received primary tumor resection\textsuperscript{[81]}. In 
another study based on 9000 elderly metastatic colorectal 
cancer patients, 72% underwent primary tumor resection, 
whereas only 3.9% received metastasectomy and 20% had 
symptoms of bowel obstruction, perforation or bleed-
ing\textsuperscript{[82]}. It suggests that a considerable portion of unre-
sectable colorectal cancer patients receive intestinal resection 
without a clear and reasonable indication. The Memorial 
Sloan-Kettering Cancer Center reported 233 metastatic 
colorectal cancer patients receiving chemotherapy with 
the primary tumor left in place\textsuperscript{[83]}. Only 7% of the pa-
tients required palliative primary tumor resection during 
the disease course. Thus, the authors recommended che-
motherapy without prophylactic primary tumor resection 
as a standard management of metastatic colorectal cancer 
without obstruction or bleeding symptoms.

**Targeted therapy in combination with chemotherapy**

The survival benefit of adding targeted therapeutic agents 
such as bevacizumab, cetuximab and panitumumab to 
traditional chemotherapy in patients with unresectable 
metastatic colorectal cancer has been validated by several 
randomized clinical trials. The BEAT study\textsuperscript{[84]} collected 
1965 metastatic colorectal cancer patients undergoing 
bevacizumab combined with different types of chemother-
apy as the first-line therapy, and demonstrated that the 
PFS in patients receiving bevacizumab plus FOLFIRI, 
FOLOFOX or Xelox was > 10 mo and the OS ap-
proached or exceeded 24 mo. This study indicated that be-
vacizumab-based combination chemotherapy is efficient 
in metastatic colorectal cancer. The PFS and OS were 8.6 
and 18.0 mo, respectively, in patients receiving bevac-
izumab plus 5-FU, which is also comparable to a regimen 
including 5-FU plus oxaliplatin or 5-FU plus irinotecan.

The efficacy of cetuximab greatly depends on the 
status of the KRAS gene. The CRITIn study\textsuperscript{[85]}, which 
compared cetuximab plus FOLFIRI with FOLFIRI alone 
in the initial treatment of metastatic colorectal cancer 
patients, indicated that cetuximab improved the response 
rate (57.3% vs 39.7%, \textit{P} < 0.0001), PFS (9.9 mo \textit{vs} 8.4 mo, 
\textit{P} = 0.0012) and OS (23.5 mo \textit{vs} 20.0 mo, \textit{P} = 0.0094) 
significantly in patients with wild-type KRAS. However, 
in a population subset with mutant KRAS, there was no 
significant difference in the response rate, PFS or OS be-
tween the two groups. The OPUS study\textsuperscript{[86]} even exhibited 
a worse response rate and PFS for the cetuximab plus 
FOLFOX4 group as compared with FOLFOX4 group 
in patients with mutant KRAS. The status of the \textit{BR-RA}F 
gene is another efficient predictor of cetuximab efficacy. 
Di Nicolantonio \textit{et al.}\textsuperscript{[87]} have reported that the \textit{BR-RA}F 
gene mutation rate in patients with wild-type \textit{KRAS} was 
approximately 14% (11\textsuperscript{-79}). None of the \textit{BR-RA}F 
mutant patients responded to cetuximab or panitumumab 
or cetuximab plus chemotherapy. The PFS of patients with 
wild-type \textit{BR-RA}F was better than their counterparts (\textit{P} < 
0.001). A considerable defect in the \textit{BR-RA}F gene as a pre-
dictor of treatment response is that the mutation rate is 
low. The incidence rate of mutant \textit{BR-RA}F is only 6.4%-14% 
in patients with wild-type \textit{KRAS}, and no \textit{BR-RA}F mutation 
has been reported in those with \textit{KRAS} mutations.

In the second or third-line treatment settings, the ad-
dition of cetuximab or bevacizumab to chemotherapy, or 
a single treatment with cetuximab, has also been proven 
to be effective\textsuperscript{[88,89]}. In a phase III clinical trial\textsuperscript{[89]}, 463 
metastatic colorectal cancer patients received either pani-
tumumab plus best supportive care (BSC) or BSC alone 
after chemotherapy failure. Patients with panitumumab 
plus BSC had an objective response rate of 8% and a sig-
ificantly better median PFS (96 d \textit{vs} 60 d) than those who 
received BSC alone. In another clinical trial\textsuperscript{[90]}, the combi-
nation of panitumumab with FOLFIRI as a second treat-
ment for metastatic colorectal cancer patients improved 
the PFS (5.9 mo \textit{vs} 3.9 mo, \textit{P} = 0.004) and objective re-
response rate (35% \textit{vs} 10%, \textit{P} < 0.001) in patients with wild-
type \textit{KRAS} compared to the regimen of FOLFIRI alone.

**CONCLUSION**

Multidisciplinary treatment has become the standard 
practice for CRLM management. Nevertheless, the op-
timal paradigm of multimodality treatment still needs to 
be further investigated. As the most effective treatment
method, surgical CRLM resection has been rendered an expanded indication in recent years. CRLM patients can be categorized into three subtypes: clearly initially resectable, potentially resectable, or definitely unresectable. For patients with initially resectable CRLM, the survival benefit of neoadjuvant chemotherapy is still unclear. The management of CRLM disappearing or progressing during neoadjuvant chemotherapy is challenging and controversial. The influence of chemotherapy-related toxicity on the outcome of liver resection needs to be further clarified. The optimal sequencing of primary tumor resection and liver lesions and perioperative chemotherapy deserves further investigation in patients with resectable synchronous CRLM. For patients who are initially unresectable but potentially convertible, chemotherapy, PVE, two-staged operation and ablation therapy are effective methods to convert unresectability into resectability. How to utilize these methods in a reasonable and better way needs to be further explored. For definitely unresectable CRLMs, it is still being debated whether the primary tumor should be resected. Targeted therapy, in addition to traditional chemotherapy, has been shown to improve the survival of unresectable CRLM patients. How to accurately predict the tumor response to targeted therapy is an important issue that should be further investigated in consideration of its high cost. A better understanding of these issues will greatly improve the effect of multidisciplinary treatment of CRLM patients.

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