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Review Article

Treatment Options for Colorectal Cancer Liver Metastases

Xianglong Tan[1], Mengyang Li[2] and Zhiming Zhao[1*]

[1]*The Second Department of Hepatopancreatobiliary Surgery, The First Medical Center, Chinese People's Liberation Army General Hospital, Beijing, China*

[2]*Department of Hepatopancreatobiliary Surgery, The Fourth Medical Center, Chinese People's Liberation Army General Hospital, Beijing, China*

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ABSTRACT

The liver is the most common site of metastasis in colorectal cancer (CRC). Treatment of liver metastases determines the prognosis of patients with CRC. Tremendous progress has been made during the last two decades, which has greatly improved the overall survival of CRC patients. Currently, various treatment options are available, including hepatectomy, liver transplantation, local regional therapy, chemotherapy, targeted therapy, and immune therapy, inevitably leading to some controversies on treatment indications and selection of treatment strategy. Here, we reviewed the existing approaches to treat colorectal cancer liver metastases, with the aim of examining several crucial questions regarding surgical resection, liver transplantation, and medical treatment in clinical practice.

Introduction

For patients with CRC, the liver is the most common site of metastasis. Approximately 15 percent of the CRC patients are initially diagnosed with liver metastasis, whereas 50% of the patients experience liver metastasis during the follow-up period. Treatment of liver metastasis determines the prognosis of the patients, and improvement in liver metastasis treatment can prolong the overall survival (OS) of CRC patients [1]. The 5-year survival rate of patients with resectable colorectal cancer liver metastases (CRLM) is 47%-60%, compared to 5%-9% in patients with unresectable CRLM [2-5]. With advances in chemotherapy and targeted therapy, an increasing number of unresectable metastatic lesions can be converted into resectable lesions. Additionally, hepatic artery infusion (HAI), associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), and two-stage hepatectomy (TSH) have also contributed to the increased resection rates and have improved the 5-year survival rate by 33%-50% after surgery [2, 6-8].

However, 60%-70% of these patients still develop hepatic tumor recurrence. Matsuoka *et al*. proposed an aggressive strategy of repeat hepatectomy to reduce chances of tumor recurrence and prolong OS [9]. Despite these strategies, there is still a large proportion of patients with unresectable CRLM. For patients without extrahepatic involvement, liver transplantation is a good option. For patients with multiple systematic metastases, including the liver, chemotherapy and targeted therapy are applied. Here, we summarize the various treatment options for CRLM patients.

Surgical Resection

Radical liver metastasis resection is the only treatment available for patients with CRLM. With improvements in chemotherapy, targeted drugs, and surgical techniques, an increasing number of patients can now undergo radical hepatectomy. The aim of liver resection is to remove all visible lesions and achieve a negative margin, leaving an adequate future liver remnant (FLR) [10]. Currently, about 20%-40% of cases of liver metastases are resectable [3, 11]. The 5- and 10-year OS rates are 47%-60% and 28%, respectively, whereas the 5- and 10-year disease-free survival rates are 30% and 20%, respectively [4, 12]. Age, comorbidity, lymph node metastasis, and extrahepatic tumor have been proven to be independent prognostic factors in CRLM patients [12]. Despite the decrease in adverse events over the last few decades, the complication rate is still relatively high (17% major complications and 26% minor

*Correspondence to: *Zhiming Zhao, The Second Department of Hepatopancreatobiliary Surgery, The First Medical Center, Chinese People's Liberation Army General Hospital, Beijing 100853, China; E-mail: zhimingzhao616@126.com*

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complications) [13, 14]. Among the major complications, bleeding, bile duct injury, infection, liver abscess, and liver failure are most frequently encountered [10].

Although both laparoscopic and open hepatectomies are feasible, laparoscopic hepatectomy has been widely used in CRLM patients. Recently, the first explanatory, assessor-blinded, single-center, randomized superiority trial was performed by Fretland *et al*. to compare laparoscopic and open hepatectomy in CRLM resection. The results indicated that the complication rate was 19% in the laparoscopic group and 31% in the open resection group. A significant reduction in hospital stay was observed in the laparoscopic group, which was consistent with results obtained by Kasai *et al*. [15, 16]. No differences were observed between these two groups with respect to blood loss, operation time, surgical margin, and 90-day mortality [15]. In addition, there was no statistical difference in progression-free survival and OS [16].

Synchronous or metachronous resection has not reached an agreement. Approximately 15%-25% of CRC patients are diagnosed with liver metastases simultaneously. Historically, the median OS of patients with synchronous unresectable liver metastases was less than 8 months [17]. However, with the development of conversion chemotherapy and surgical techniques, 25% of CRLM patients who received synchronous resection may have a 10-year disease-free survival [18, 19]. The traditional surgical strategy is resection of the primary tumor, followed by a planned liver resection, which is known as the colon-first approach. Conversely, in the liver-first approach, liver resection is performed prior to colorectomy. Metachronous resection helps to reduce complication rates. However, the tumor may progress during the interval period. Some studies have shown that compared to metachronous resection, synchronous resection leads to shorter hospital stays, lower costs, and less surgical trauma, without severely increasing mortality and morbidity [20, 21]. However, this may be a result of the different patient selection criteria used in the two approaches. Patients who undergo metachronous resection tend to have bilobar involvement or major hepatectomy. There was no difference in long-term survival of patients who had synchronous or metachronous resection [21]. A meta-analysis reviewed 12 studies on laparoscopic versus open synchronous resection. No difference was observed between the two groups with respect to 1-, 3-, 5-year OS rates or disease-free survival rates. However, a significant reduction in postoperative complications was observed in the laparoscopic group (19% vs. 31%). The hospital stay was reduced after surgical resection in most of the studies [20].

Both ALPPS and TSH have their own advantages and drawbacks. Traditionally, TSH is preferred in patients with insufficient FLR. It involves chemotherapy with portal vein embolization or ligation followed by hepatectomy. However, this treatment is associated with a failure rate of 25%-38% due to insufficient hypotrophy or tumor progression [22-25]. A new surgical method, known as ALPPS, was developed in 2011 [26]. A recent meta-analysis showed that the kinetic growth rate was much higher with ALPPS than with TSH. Although ALPPS had higher morbidity and mortality compared to TSH, the OS rates were comparable between ALPPS and TSH [27]. Contradictory results were reported in another multicenter randomized controlled trial (LIGRO Trial). The resection rate of ALPPS was 92%, which was much higher than that obtained with traditional TSH (57%-75%). No difference in complications, 90-day mortality, or R0 resection rate was observed [25, 28].

HAI may be a good treatment strategy in some cases. It has known to improve the resection rate, palliative treatment, and enhance chemotherapy efficiency. A recent randomized controlled trial showed that treatment with HAI (fluorouracil, irinotecan and oxaliplatin) in combination with cetuximab for wild type KRAS multi-liver metastases (median >10 lesions) showed a high response rate, and 30% of the patients achieved R0/R1 resection, despite some of them being resistant to previous systematic chemotherapy [2].

Although ALPPS, TSH, and HAI can increase the resection rate in CRLM, a large proportion of the patients still experience recurrence post resection. In these cases, repeat hepatectomy or systemic chemotherapy should be considered. A recent single-arm retrospective study in Japan showed that after initial hepatectomy, the median OS after single hepatectomy was 83.2 months, while patients who received two and three hepatectomies showed a median OS of 56.5 and 54.0 months, respectively. Conversely, in patients receiving palliative systematic chemotherapy, the median OS was only 28.7 months, thus indicating that repeat hepatectomy can improve the outcomes in patients [1]. Similar results were reported in several other studies [1, 29-31].

Liver Transplantation

CRLM is considered a contradiction for liver transplantation (LT). However, liver transplantation may provide a new prospect for CRLM treatment. Before the 1990s, there was no effective neoadjuvant chemotherapy and standard selection criteria, and the 5-year survival rate after LT in CRLM patients was less than 20%. However, the current 1-, 3-, 5-year survival rates have now increased to 83%-95%, 62%-68%, 50-60% respectively. Despite the encouraging results, recurrence occurs in 50%-90% of patients, either in the liver or in extrahepatic organs, such as the lungs [3].

In a pilot study (SECA trial), the OS of CRLM patients who received liver transplantation was investigated. In this trial, the patient selection criteria were as follows: complete radical excision of the primary tumor, good performance status (ECOG score 0 or 1), and a minimum 6 weeks of chemotherapy [32]. Under the guidance of these criteria, the SECA trial achieved excellent outcomes, with 1-, 3- and 5-year survival rates of 95%, 68%, and 60%, respectively [32]. A retrospective study compared the cohorts in the SECA trial and the NORDIC VII trial to evaluate the outcomes of liver transplantation versus chemotherapy. The former study enrolled 21 patients treated with liver transplantation, while the latter study enrolled 47 patients for chemotherapy only. The 5-year survival of the SECA cohort was 60% and that of the NORDIC VII trial cohort was only 9% [33].

Besides, negative lymph nodes in the primary tumor may be one of the criteria for CRLM patients to receive liver transplantation. The median survival of liver transplantation patients without lymph node metastases was 118 months, compared with 28 months in patients with lymph node metastases [3]. Prognosis factors related to worse OS are maximal tumor diameter above 5.5 cm, time from primary cancer surgery <2 years, CEA levels >80 μg/L, and progressive disease at the time of liver transplantation [32].

Radiofrequency Ablation (RFA)

Impaired general health status, insufficient FLR, and involvement of vital structures are contraindications for hepatectomy. Under these circumstances, chemotherapy and ablation are used [10, 34-37]. RFA is the most widely used ablation technique since the 1990s. The mortality rate is <1%, and the complication rate is 6%-9%, which is much lower than that of partial hepatectomy [10]. The 5-year survival rate in CRLM patients receiving RFA treatment is 25%-55%. Several observational studies have reported that RFA alone is inferior to hepatectomy alone, considering the OS [10]. However, RFA, in combination with partial hepatectomy for unresectable CRLM surprisingly had similar outcomes with partial hepatectomy for resectable CRLM patients [38, 39]. A recent study showed an impressive 8-year survival rate of 36% in unresectable CRLM patients who received RFA treatment [36].

Considering the results obtained from previous meta-analyses and reviews, randomized trials to estimate the outcome of RFA versus palliative chemotherapy for unresectable CRLM is unethical. Additionally, RFA, in combination with chemotherapy, is superior to chemotherapy alone. Bleeding, tumor seeding, liver abscess, and kidney failure are the main complications. The first prospective randomized controlled trial on thermal ablation versus hepatectomy for resectable CRLM is the COLLISION trial. If this trial proves that thermal ablation for <3 cm resectable CRLM is non-inferior to surgery, a reduction in the post-procedural morbidity and mortality, length of hospital stays, and incremental costs can be expected [10].

Chemotherapy and Target Drugs

Enormous progress has been made during the last two decades in CRLM chemotherapy. Currently, surgical resection combined with neoadjuvant and adjuvant chemotherapy is the standard treatment for CRLM patients. 5-Fluorouracil used to be the only available chemotherapy regimen for CRLM before 1995, which showed a response rate of 20%-30%. Subsequently, the combination of 5-FU with oxaliplatin or irinotecan (FOLFOX and FOLFIRI) was used as the standard therapy with a better response rate (40-60%) and R0 resection rate. Currently, FOLFOXIRI therapy, consisting of 5-FU, oxaliplatin, and irinotecan, is the best treatment of choice, with a 64% response rate and 87% R0 resection rate [18, 40, 41]. Genetic analysis has shown that a high proportion of CRLM patients have *RAS* mutations. Targeted therapies, such as anti-EGFR and anti-VEGF antibodies, may increase the response rate and prolong OS [2]. The anti-VEGF antibody, bevacizumab, is suggested for patients with *RAS* mutations in combination with first-line chemotherapy. The combination of anti-EGFR antibody, cetuximab, and chemotherapy is recommended for wild type *RAS* patients [2, 42, 43].

Perioperative chemotherapy for patients with initially resectable CRLM is controversial. Theoretically, perioperative chemotherapy can reduce the tumor size, ensuring R0 resection, and eliminate micro-metastases, thus reducing the recurrence rate [44]. However, perioperative chemotherapy (before and after surgery) showed modest improvement in PFS and no advantage in median OS, based on the results of a randomized controlled trial (the EORTC intergroup trial 40983). In addition, a higher complication rate was observed in the perioperative chemotherapy group [44-46]. For patients with initially unresectable CRLM, the response to preoperative chemotherapy should be estimated every 2 months [2]. Surgery can be performed 4 weeks after the last chemotherapy cycle, and 5-8 weeks later, for which chemotherapy plus bevacizumab was administered [47]. Surgery performed within 4 weeks was accompanied by a higher complication rate compared within 5-8 weeks [48, 49]. As mentioned above, liver resection is feasible in 20%-40% of CRLM patients. Receiving symptomatic therapy for unresectable CRLM patients provides a pessimistic median OS of only 4.5-12 months [50]. Systematic chemotherapy prolongs the median OS to 15-20 months [51].

KRAS mutations occur in 25%-52% of CRLM patients. A recent systematic review showed that *KRAS* mutations are correlated with worse OS and disease-free survival. *KRAS* wild-type CRLM patients have a median OS of more than 70 months, while patients with *KRAS* mutation had median OS from 19.6 to 50.9 months [52]. Patients with wt*KRAS* benefited from R0 resection of CRLM compared with R1 resection. However, patients with mutated *KRAS* are reported to have a higher R1 resection rate. Nevertheless, no prognostic difference was observed between R0 and R1 resection in these patients [53, 54]. In wild-type *KRAS* patients, an anti-EGFR regimen of cetuximab in combination with standard chemotherapy significantly improved the response rate, OS, and progression-free survival [55-57]. *RAS* mutations led to resistance to anti-EGFR antibodies. With the basic 5-FU treatment, patients with mutated *KRAS* treated with anti-VEGF antibody had an impaired response rate than wild-type patients with anti-EGFR antibody [58, 59]. Additionally, cetuximab combined with standard chemotherapy in wild-type *KRAS* patients improved the conversion resection rate, which was superior to bevacizumab in mutated *KRAS* patients [52].

BRAF mutation, which is detected in 3-11% CRLM patients, is strongly correlated with worse prognosis (mut*BRAF* 10.4 months vs. wt*BRAF* 34.7 months) [60]. As a member of the MAPK cascade, *BRAF* is downstream of *KRAS*. Mutations in *BRAF* also lead to anti-EGFR antibody resistance. Interestingly, microsatellite instability (MSI) is reported to have a much higher proportion of *BRAF* mutations (40%-60%) [61]. Immunotherapy may be a new option for *BRAF*-mutated patients.

About 36-65.6% of CRLM patients are reported to have *TP53* mutations. *TP53* mutation, together with *RAS* mutation, is a strong indicator of worse prognosis, whereas *TP53* mutation alone has no effect on OS and PFS [62-64]. Similarly, *PIK3CA* combined with *APC* mutation is correlated with impaired OS and PFS. *PIK3CA* alone was not associated with poor outcomes [65].

Immunotherapy

I. DC Vaccine

Patients who underwent hepatectomy have a high risk of recurrence. Rodriguez *et al*. reported that dendritic cell vaccines loaded with autologous tumor lysates can delay the recurrence in patients after receiving hepatectomy. The median disease-free survival in the vaccine arm was 25.26 months compared to 9.53 months in the observation arm [66].

II. Anti-PD-1 Regimen

The application of immune-checkpoints agents is not restricted to certain malignancies. The FDA previously approved anti-PD-1 regimens applied for MSI-H/dMMR solid tumors. Chromosomal instability (CIN), (MSI), and CpG island methylator phenotype (CIMP) are carcinogenic characteristics of CRC. MSI has been observed in 15% of CRC patients. Results from Checkmate-142 confirmed the effects of nivolumab + ipilimumab in patients with MSI-H/dMMR CRLM. The ORR was 64% and disease control was 84%. The 1-year progression-free survival was 50% and 1-year OS was 73% [67]. In the Keynote-164 study, pembrolizumab was used for the treatment of metastases of colorectal cancer and achieved an ORR of 26% and disease control rate of 51% [68, 69]. Studies combining PD-L1 inhibitors and bevacizumab have also been conducted. Hochster *et al*. presented their results from a phase 1b study. The combination has an ORR of 30%, with a DCR of 90% [70].

Conclusion

Surgery, local regional treatment, and medical therapies are the commonly used treatment strategies for patients with liver metastases. Among these, surgery is considered the only curative approach. Currently, indications for hepatectomy have expanded because of the advancements in ALPPS, TSH, HAI, and chemotherapy. Although liver transplantation is restricted by the availability of a suitable donor, it has indeed improved the possibility of curability or long-term survival of some patients with previously unresectable liver metastases. Chemotherapy is the foundation of metastatic malignancies. Better response rates and fewer side effects have been achieved during the last two decades. However, the timing of chemotherapy or surgery remains controversial. Based on gene sequencing, targeted therapy, together with immunotherapy, will continue to bring a new era for liver metastases treatment.

Conflicts of Interest

None.

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