Journal on Surgery
www.journalonsurgery.org

Review Article

ISSN: 2691-7785

Open Access, Volume 4

Advancements in the Treatment of Recurrent Metastatic Colorectal Cancer

Jiawen Fan; Dinghua Yang*

Department of General Surgery, Nanfang Hospital, The First School of Clinical Medicine, Southern Medical University, Guangzhou, 510515, P.R. China.

Abstract

Radical resection is the main approach for achieving a cure in patients with recurrent liver metastasis of colorectal cancer. However, due to the limited liver volume and the tolerance of late-stage tumor patients, it is not possible to perform repeated resections infinitely. Therefore, the scope and timing of repetitive liver resection become critically important. In the opposing contradiction between the residual liver volume (FLR) and tumor burden, finding the most beneficial treatment plan for patients is the mission of precision medicine. The treatment of colorectal cancer liver metastasis emphasizes a Multidisciplinary Team (MDT) approach, aiming to achieve disease-free survival or prolong the patient's survival.

Keywords: Colorectal-liver metastasis; MDT; Treatment mode.

Introduction

Colorectal Cancer (CRC) is the third most common cancer worldwide. The liver is the most common target organ for colorectal cancer metastasis, and liver metastasis is the main cause of death in colorectal cancer patients. Approximately 40-50% of colorectal cancer patients develop liver metastasis throughout the course of the disease. Even with R0 tumor resection surgery, over 50% of patients will still experience recurrence within 2 years post-operation, with a high recurrence rate of 50-80% [1]. Nowadays, the number or location of liver metastases is no longer a surgical contraindication, as long as all metastases can be completely removed and the residual liver volume (FLR) is sufficient. Multidisciplinary approaches to Colorectal Liver Metastasis (CRLM) resection have not only made significant technological advancements but also bring significant survival benefits to patients. However, the highly elevated risk of post-operative recurrence, tumor heterogeneity, and significant differences in patient prognosis pose significant challenges to clinical surgeons in making surgical decisions.

In addition to surgical resection, there are more options available for selection, including intervention, chemotherapy, targeted therapy, immunotherapy, and liver transplantation. These options can help patients reduce tumor size and lower the risk of tumor recurrence before surgery, as well as maintain a "No Evidence of Disease (NED)" status after surgery. Therefore, we need to have a deeper understanding of the disease characteristics and individual-specific manifestations of liver metastasis from colorectal cancer in order to achieve personalized precision treatment and improve patients' survival time and quality of life.

Mechanism of recurrent liver metastasis of colorectal cancer

The recurrence of colorectal cancer liver metastasis is mainly caused by two reasons: either the development of undetected small metastatic lesions or the re-metastasis of the primary colorectal cancer lesion. It is generally believed that recurrence occurring within 2 years is caused by the development of small metastatic lesions, while recurrence after more than 3 years may be due to re-metastasis.

Manuscript Information: *Received: Apr 13, 2024; Accepted: Apr 30, 2024; Published: May 07, 2024*

Correspondance: *Dinghua Yang, Department of General Surgery, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, 510515, P.R. China. Tel: +86-020-61641702; Email: yangdinghua@smu.edu.cn*

Citation: *Fan J, Yang D. Advancements in the Treatment of Recurrent Metastatic Colorectal Cancer. J Surgery. 2024; 4(1): 1163.*

If viewed from a molecular perspective, the recurrence mechanism of liver metastasis in colon cancer is a complex process involving multiple factors. Studies have shown that the upregulation of MMP7, TROP2, and survivin expression is associated with the survival, disease recurrence, and liver metastasis of colon cancer [2]. In addition, it has been found that recruitment of myeloid cell subsets (CD11b/Gr1mid) through CCL2/CCR2 can promote the development of colorectal cancer liver metastasis [3]. Furthermore, inhibition of miR-15b has been demonstrated to reduce cell migration and metastasis of colorectal cancer [4]. The tumor microenvironment also plays a crucial role in the progression and metastasis of colon cancer. It has been discovered that interleukin-8 (IL-8) and its receptor CXCR2 in the tumor microenvironment can promote the growth, progression, and metastasis of colon cancer [5]. In addition, hepatic stellate cells have been shown to promote liver metastasis of colon cancer cells through the SDF-1/CXCR4 axis [6]. In terms of treatment strategies, TSU68 has been identified as an inhibitor that can prevent liver metastasis of colon cancer xenografts by modulating the pre-metastatic niche. Furthermore, it has been found that Cinobufacini inhibits invasion and metastasis of colon cancer by suppressing the Wnt/β-catenin signaling pathway and EMT. Overall, understanding the potential mechanisms underlying colon cancer liver metastasis recurrence is crucial for developing effective treatment strategies. Further research is needed to investigate the roles of specific molecules and pathways involved in this process in order to improve patient prognosis.

Classic prediction model

The existing prediction models for liver metastasis of colorectal cancer are mainly based on patients' clinical pathological features, such as CRS model (clinical risk score) [7], preoperative and postoperative BPI score [8], Nordlinger score [9], Iwatsuki score [10], etc.

The CRS model proposed by FONG was used to analyze the clinical, pathological, and prognostic data of 1001 patients with metastatic colorectal cancer who underwent consecutive liver resections from July 1985 to October 1998. Multivariate analysis revealed that seven factors were significantly independent predictors of poor long-term prognosis: positive resection margin (P=0.004), extrahepatic disease (P=0.003), positive lymph nodes at the primary site (P=0.02), disease-free interval from primary cancer to metastasis <12 months (P=0.03), >1 liver tumor (P=0.0004), largest liver tumor >5 cm (P=0.01), and carcinoembryonic antigen level >200 ng/ml (P=0.01). When the last five criteria were used in the preoperative scoring system, each criterion was assigned one point, and the total score highly predicted the outcome (P<0.0001). Patients who met two criteria may have a favorable outcome. Patients who met three, four, or five criteria should be considered for experimental adjuvant trials.

Tumor behavior and Histopathological Growth Patterns (HGP)

The "behavior of tumors" has not received much attention in scientific research, mainly because tumor behavior is difficult to identify and quantify, and there are no standardized guidelines to incorporate tumor behavior into predictive models. However, in clinical treatment, different behaviors of tumors such as compression, obstruction, infiltration destruction, metastasis, and physical exhaustion demonstrate intricate connections with prognosis, and are closely related to the quality of patient survival.

Histopathological Growth Patterns (HGPs) of liver metastasis cancer tissue refers to a way of qualitatively distinguishing tumor behavior at the interface between colorectal cancer cells and liver parenchymal cells. In simple terms, different pathological growth patterns reflect the interaction between the tumor and the host, and are associated with patient prognosis. The histopathological growth patterns are mainly divided into three modes: desmoplastic - there is a thick stromal band containing connective tissue, lymphocytes, and blood vessels between the colorectal metastatic tumor and the liver parenchymal cells, separating the tumor cells from the liver cells and causing physical encapsulation and fibrosis; pushing - tumor cell growth compresses and collapses the surrounding liver cells, but does not invade the liver cell plates, the tumor cells come into contact with the liver cells but do not merge; replacement - tumor cells grow in a way that mimics the structure of liver cells, infiltrating the liver tissue and replacing some of the liver cells to form a liver cell-like structure. Among them, the replacement HGP recurrence pattern is associated with multi-organ recurrence and a poorer Recurrence-Free Survival rate (RFS) and Overall Survival rate (OS); while the desmoplastic HGP even if there is recurrence, it only occurs within the liver, with the best prognosis [11].

In the microstructure of tumors, Hypervascular Growth Pattern (HGP) tends to rely on neovascularization to supply the tumor's demands, making it more sensitive to anti-angiogenic drugs. In contrast, Expanding and Replacing HGPs depend on pre-existing blood vessels to nourish the tumor, resulting in less effectiveness of anti-angiogenic drugs [12]. Surrounding the Hypervascular Growth Pattern (HGP), there is a ring of firm and inflammatory cell-rich stroma, which can reduce the positive margin rate during surgery. In Infiltrative or Expanding HGPs, there is an increased risk of positive margins and higher recurrence risk [13]. Replacing HGP is associated with Microvessel Density (MVD), with high MVD being a predictor of poor prognosis for primary Colorectal Cancer (CRC) and liver metastasis [14]. Therefore, the growth pattern can reflect tumor behavior and microenvironmental information, aiding in the design of more precise surgical strategies.

Multi-Disciplinary Treatment (MDT) medical model

MDT is a multidisciplinary collaborative diagnostic and therapeutic mode aimed at providing diagnostic and therapeutic advice for diseases involving important organs or complex systems. The "Guidelines for Diagnosis and Comprehensive Treatment of Colorectal Liver Metastasis in China," the "NCCN Guidelines," and the "ESMO Guidelines" all recommend the use of MDT treatment mode for colorectal cancer liver metastasis patients [15]. MDT requires the participation of experts from various disciplines such as surgery, imaging, oncology, and interventional medicine. By rigorously evaluating tumor staging, typing, and prognosis based on clinical symptoms, laboratory tests, pathology, and molecular biology, as well as utilizing various treatment methods from different disciplines, personalized treatment plans that best suit the patient can be formulated. In addition to standardized treatment, the MDT model also emphasizes individualized treatment, aiming to achieve optimal treatment plans and maximize patient survival benefits by providing accurate diagnosis and treatment based on patient prognosis.

Interventional therapy can be used to solve some clinically complex, dangerous, complication-prone, and ineffective problems, and provide the opportunity for radical surgery for some patients who cannot undergo surgical resection at the initial diagnosis. Interventional therapy plays an important role as part of comprehensive treatment in the treatment of liver metastasis from colorectal cancer. It includes two approaches: intravascular and percutaneous. According to the 'Guidelines for the Diagnosis and Comprehensive Treatment of Liver Metastasis from Colorectal Cancer in China (2023 edition)', for liver metastasis patients who are eligible for surgical resection, adjunctive hepatic artery infusion chemotherapy can be applied to reduce or delay recurrence. For patients who are not eligible for surgical resection, interventional therapy, including hepatic artery infusion chemotherapy and drug-eluting microsphere arterial chemoembolization, combined with targeted therapy, immunotherapy, and other systemic treatments, can help reduce tumor burden for surgical resection, or control tumor growth, improve quality of life, and prolong survival.

Chemotherapy can play a role in improving the surgical resection rate and disease-free survival rate of colorectal cancer liver metastases before, during the disease-free period, and after resection. XELOX and mFOLFOX6 regimens are the most common standardized chemotherapy regimens in clinical practice, both of which can reduce the recurrence rate and mortality rate in patients. The drugs used in the mFOLFOX6 regimen include oxaliplatin, folinic acid, and fluorouracil, which are improved based on the FOLFOX regimen and are the preferred treatment for colorectal cancer in clinical practice. Compared with the FOLFOX regimen, the FOLFIRI chemotherapy regimen replaces oxaliplatin with irinotecan, significantly reducing neurotoxicity and other adverse events. The CAPEOX chemotherapy regimen consists of capecitabine and oxaliplatin, which is convenient to use and has better patient tolerance, making it more suitable for elderly and frail patients or patients receiving chemotherapy in outpatient settings.

The current first-line and second-line treatment for liver metastasis of colorectal cancer mainly consists of chemotherapy ± targeted therapy, while the third-line treatment mainly includes small molecule Tyrosine Kinase Inhibitors (TKIs) and monotherapy chemotherapy, etc. However, in patients with Microsatellite Instability/High Mismatch Repair protein deficiency (MSI-H/dMMR), the efficacy of chemotherapy with or without targeted therapy is limited for this type of patients. The success of the KEYNOTE-177 study has made immunotherapy the standard first-line treatment for this type of patients, changing the treatment pattern of colorectal cancer. With the continuous progress of research, MSI-H/dMMR colorectal cancer patients have now become a clearly defined population with immunotherapy advantages.

As a PD-1 antibody, Toripalimab has unique pharmaceutical characteristics. Its antibody binding fragment (Fab fragment) can specifically bind to PD-1, preventing off-target effects and exhibiting higher affinity and lower dissociation rate. Additionally, the Fc fragment has been genetically engineered to eliminate Antibody-Dependent Cell-mediated Phagocytosis (ADCP effect), avoiding T cell consumption and further enhancing the anti-tumor efficacy of the drug.

Summary and outlook

With the development of minimally invasive surgery and the acceptance of the concept of "No Evidence of Disease (NED)" survival, the treatment approach for advanced tumor diseases with high recurrence rates, such as colorectal cancer liver metastases, is gradually shifting towards comprehensive management and long-term management. For advanced and elderly patients, preserving liver function, reducing chemotherapy side effects, and maintaining quality of life may bring more survival advantages than radical resection. If a new biomarker can be identified, or a more advanced evaluation scheme can be established to differentiate between patient subtypes and apply different treatment strategies to patients with easy recurrence and difficult recurrence, it may comprehensively prolong the survival of colorectal cancer liver metastasis patients.

References

1. Cervantes A, Adam R, Roselló S, et al. Metastatic colorectal cancer: Esmo Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of Oncology. 2023; 34(1): 10-32. doi:10.1016/j.annonc.2022.10.003.

2. Fang YJ, Lu ZH, Wang GQ, et al. Elevated expressions of MMP7, TROP2, and survivin are associated with survival, disease recurrence, and liver metastasis of colon cancer. Int J Colorectal Dis. 2009; 24(8): 875-884. doi:10.1007/s00384-009-0725-z.

3. Zhao L, Lim SY, Gordon-Weeks AN, et al. Recruitment of a myeloid cell subset (CD11b/Gr1 mid) via CCL2/CCR2 promotes the development of colorectal cancer liver metastasis. Hepatology. 2013; 57(2): 829-839. doi:10.1002/hep.26094.

4. Li J, Chen Y, Guo X, et al. Inhibition of miR-15b decreases cell migration and metastasis in colorectal cancer. Tumour Biol. 2016; 37(7): 8765-8773. doi:10.1007/s13277-015-4396-9.

5. Lee YS, Choi I, Ning Y, et al. Interleukin-8 and its receptor CXCR2 in the tumour microenvironment promote colon cancer growth, progression and metastasis. Br J Cancer. 2012; 106(11): 1833-1841. doi:10.1038/bjc.2012.177.

6. Matsusue R, Kubo H, Hisamori S, et al. Hepatic stellate cells promote liver metastasis of colon cancer cells by the action of SDF-1/CXCR4 axis. Ann Surg Oncol. 2009; 16(9): 2645-2653. doi:10.1245/s10434-009-0599-x.

7. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: Analysis of 1001 consecutive cases. Ann Surg. 1999; 230(3): 318-321. doi:10.1097/00000658-199909000-00004.

8. Rees M, Tekkis PP, Welsh FKS, O'Rourke T, John TG. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: A multifactorial model of 929 patients. Ann Surg. 2008; 247(1): 125-135. doi:10.1097/SLA.0b013e31815aa2c2.

9. Nordlinger B, Guiguet M, Vaillant JC, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Française de Chirurgie. Cancer. 1996; 77(7): 1254-1262.

10. Iwatsuki S, Dvorchik I, Madariaga JR, et al. Hepatic resection for metastatic colorectal adenocarcinoma: A proposal of a prognostic scoring system. J Am Coll Surg. 1999; 189(3): 291-299. doi:10.1016/s1072-7515(99)00089-7.

11. van Dam PJ, van der Stok EP, Teuwen LA, et al. International consensus guidelines for scoring the histopathological growth patterns of liver metastasis. Br J Cancer. 2017; 117(10): 1427-1441. doi:10.1038/bjc.2017.334.

12. Van den Eynden GG, Majeed AW, Illemann M, et al. The multifaceted role of the microenvironment in liver metastasis: Biology and clinical implications. Cancer Res. 2013; 73(7): 2031-2043. doi:10.1158/0008-5472.CAN-12-3931.

13. Viganò L, Branciforte B, Laurenti V, et al. The Histopathological Growth Pattern of Colorectal Liver Metastases Impacts Local Recurrence Risk and the Adequate Width of the Surgical Margin. Ann Surg Oncol. 2022; 29(9): 5515-5524. doi:10.1245/s10434-022-11717-8.

14. Vermeulen PB, Colpaert C, Salgado R, et al. Liver metastases from colorectal adenocarcinomas grow in three patterns with different angiogenesis and desmoplasia. J Pathol. 2001; 195(3): 336-342. doi:10.1002/path.966.

15. Chinese College of Surgeons, Section of Gastrointestinal Surgery, Branch of Surgery, Chinese Medical Association, Section of Colorectal Surgery, Branch of Surgery, Chinese Medical Association, et al. [China guideline for diagnosis and comprehensive treatment of colorectal liver metastases (version 2023)]. Zhonghua Wei Chang Wai Ke Za Zhi. 2023; 26(1): 1-15. doi:10.3760/cma.j.cn441530-20221229-00542.