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Retrospective Study

Impact of primary colorectal cancer site on surgical outcomes for liver metastases: A retrospective study

Liu DM *et al.* Primary tumor site and liver metastasis

Abstract

BACKGROUND

Colorectal cancer is a common malignancy with increasing incidence, and 15%-25% of patients develop liver metastases with poor prognosis. Recent evidence suggests that primary tumor location significantly influences embryological origin, anatomical structure, clinical manifestations, and outcomes, yet traditional clinical approaches have treated all colorectal cancer sites as a single entity.

AIM

To investigate how the anatomical origin of primary colorectal tumors influences surgical outcomes in patients presenting with hepatic metastases.

METHODS

This cross-sectional investigation encompassed 178 patients diagnosed with colorectal cancer hepatic metastases who received treatment at our institution between January 2014 and January 2024. Based on postoperative disease progression, participants were stratified into two groups: Those experiencing tumor recurrence ($n = 88$) *vs* those without recurrence ($n = 90$). Demographic and clinical characteristics were systematically compared between groups. Multivariate logistic regression analysis was subsequently applied to variables demonstrating statistical significance, enabling identification of independent predictors of postoperative recurrence in colorectal cancer patients with liver metastases. Additionally, we examined associations between primary tumor location and various prognostic factors, while evaluating recurrence patterns across different anatomical sites during the 12-month postoperative period.

RESULTS

Analysis revealed that right-sided colonic origin (55.68%), presence of nodal involvement (92.05%), elevated D-dimer levels ≥ 180 $\mu\text{g/L}$, hypoalbuminemia (albumin < 29 g/L), suboptimal or absent neoadjuvant treatment (43.18%), and elevated clinical

risk scores (53.41%) constituted independent predictors of postoperative recurrence in hepatic metastatic colorectal cancer. Primary tumor location demonstrated positive associations with lymphatic spread, D-dimer elevation, and clinical risk stratification, while showing inverse relationships with albumin levels and neoadjuvant therapy effectiveness. Among the entire cohort of 178 patients, those with right-sided primary tumors exhibited substantially higher recurrence frequencies at 3-month (53.57%), 6-month (55.17%), and 12-month (55.68%) intervals compared to left-sided colonic primaries (32.14%, 24.14%, 26.14%) and rectal primaries (14.29%, 20.69%, 18.18%), with statistically significant differences observed.

CONCLUSION

Right-sided colonic primary location, lymphatic metastasis, D-dimer elevation, hypoalbuminemia, neoadjuvant therapy response, and clinical risk stratification emerged as significant determinants of postoperative recurrence in patients with colorectal cancer hepatic metastases.

Key Words: Colorectal cancer; Tumor metastasis; Liver tumor recurrence; Resection of metastatic tumor; D-dimer; Risk assessment

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Core Tip: This retrospective study investigates how the primary tumor location in colorectal cancer affects clinical outcomes following liver metastasis resection. Among 178 patients, right-sided colon cancers were associated with significantly higher recurrence rates, postoperative complications, and worse survival compared to left-sided and rectal cancers. Multivariate analysis identified right-sided origin, lymph node metastasis, elevated D-dimer, hypoalbuminemia, poor neoadjuvant response, and high

clinical risk scores as independent predictors of recurrence. These findings highlight the prognostic importance of tumor site and support site-specific treatment strategies for patients with colorectal liver metastases to improve surgical safety and long-term outcomes.

INTRODUCTION

Colorectal cancer is one of the most common malignant tumors in the clinic. In recent years, the incidence and mortality of colorectal cancer have been increasing annually due to lifestyle changes[1-3]. Clinically, nearly 15% to 25% of colorectal cancer patients are diagnosed with liver metastases, that is, simultaneous liver metastases[4]. Patients with liver metastases of colorectal cancer often present with bloody stool, abdominal pain and distension, an abdominal mass, anemia and other symptoms after onset[5]. The disease progresses rapidly and is serious, and the prognosis is poor. Therefore, patients with liver metastases from colorectal cancer are difficult to treat clinically, and the median survival of patients without timely and effective treatment is less than 7 months[6-8]. The median survival of patients after surgery is only approximately 35 months. In recent years, some scholars have noted that there are certain differences in the embryonic origin, anatomical and physiological structure, clinical manifestations and prognosis of patients with primary colorectal cancer at different sites, and some scholars believe that different sites of colorectal cancer should be treated as different diseases[9]. However, in traditional clinical treatment, colorectal cancer patients with different primary sites are often studied as a whole, and there is relatively little research on the influence of different tumor sites on remote metastasis after radical surgery[9-12].

The disease progresses rapidly and is serious, with the prognosis remaining poor despite advances in surgical techniques and systemic therapies. The natural history of untreated colorectal liver metastases is characterized by progressive hepatic dysfunction, potential complications including hemorrhage and biliary obstruction, and ultimately liver failure. Therefore, patients with liver metastases from colorectal cancer

are difficult to treat clinically, requiring multidisciplinary approaches involving surgical oncologists, medical oncologists, hepatologists, and interventional radiologists. The median survival of patients without timely and effective treatment is less than 7 months, highlighting the urgent need for prompt diagnosis and intervention. Even with optimal surgical management, the median survival of patients after hepatectomy is only approximately 35 months, and five-year survival rates range from 30%-50%, depending on various prognostic factors including the number and size of metastases, timing of metastasis development, and response to perioperative chemotherapy.

In recent years, some scholars have noted that there are certain differences in the embryonic origin, anatomical and physiological structure, clinical manifestations, molecular characteristics, and prognosis of patients with primary colorectal cancer at different sites[1]. These differences stem from distinct developmental origins during embryogenesis, with right-sided colon cancers (cecum, ascending colon, hepatic flexure, and proximal two-thirds of transverse colon) arising from the midgut, while left-sided colon cancers (distal third of transverse colon, splenic flexure, descending colon, sigmoid colon) and rectal cancers originate from the hindgut[28-30]. This embryological distinction translates into variations in blood supply, lymphatic drainage, innervation patterns, and molecular biology. Right-sided tumors are more frequently associated with microsatellite instability, cytosine-phosphate-guanine island methylator phenotype, B-Raf proto-oncogene serine/threonine kinase mutations, and mucinous histology, while left-sided tumors more commonly exhibit chromosomal instability, Kirsten rat sarcoma viral oncogene homolog mutations, and traditional adenomatous polyposis pathway alterations. Therefore, this study analyzed the effect of the primary location of colorectal cancer on the surgical outcome of patients with liver metastases, with the aim of providing evidence-based insights for optimizing treatment approaches and improving patient outcomes through site-specific management strategies.

MATERIALS AND METHODS

Research subjects

A cross-sectional study was conducted on 178 patients with liver metastases of colorectal cancer admitted to our hospital from January 2014 to January 2024. There were 106 males and 72 females, respectively, aged 58.29 ± 5.40 years; the youngest was 37 years, and the oldest was 78 years. There were 40 cases involving the left half of the colon, 70 cases involving the right half of the colon, and 68 cases involving the rectum. This study meets the relevant requirements of the Declaration of Helsinki of the World Medical Association. This study was reviewed and approved by the Ethics Committee of The Affiliated Hospital of Jiangxi University of Chinese Medicine (Approval No. JXZYYFS-LL-2025105).

Diagnostic criteria for liver metastases of colorectal cancer

According to the relevant criteria in the “International Code of Practice for Colorectal Cancer (2023 Edition)”, the patient was diagnosed with colorectal cancer, and the presence of liver metastases was detected *via* magnetic resonance imaging.

Inclusion criteria

The inclusion criteria including: (1) Patients with clinically diagnosed liver metastases of colorectal cancer; (2) Patients over 18 years of age; (3) Condition assessment of patients who were initially resectable and successfully completed surgical treatment; (4) Patients whose complete clinical data and follow-up data were available; and (5) All patients signed informed consent forms.

Exclusion criteria

The exclusion criteria including: (1) Patients with anal canal cancer or tumor metastasis in other organs; (2) Patients with nonprimary colorectal malignancies; (3) Patients with intestinal bleeding, intestinal perforation, or abdominal swelling; (4) Patients with a family history of tumors or polyps; (5) Patients who are pregnant or lactating; and (6) Patients who were lost to follow-up or had incomplete data.

Group therapy

The clinical data of 178 patients with liver metastasis of colorectal cancer admitted from January 2014 to January 2024 were retrospectively analyzed, and the patients were divided into a recurrence group ($n = 88$) and a control group ($n = 90$) according to whether they had experienced recurrence after surgery.

Data collection and comparison

The general and clinical data of the two groups were compared, and the factors with statistical significance were further analyzed *via* logistic multivariate analysis to identify the risk factors for postoperative recurrence in patients with liver metastatic tumors of colorectal cancer and to analyze the correlation between the primary location of colorectal cancer and each risk factor. The recurrence rates of colorectal cancer in patients with different primary tumor locations at 12 months after surgery were compared.

Statistical analysis

The SPSS version 24.0 software package was used to analyze the data. The measurement data conforming to a normal distribution are expressed as mean \pm SD, and comparisons between groups were performed *via* independent sample *t* tests. The statistical data are expressed as percentages, and the χ^2 test was used for comparisons between groups. Logistic multivariate regression analysis was used to analyze the risk factors for postoperative recurrence in patients with liver metastases from colorectal cancer, and Pearson correlation was used to analyze the correlation between the primary location of colorectal cancer and each risk factor. When $\alpha = 0.05$, $P < 0.05$ indicated a statistically significant difference.

RESULTS

Comparison of general characteristics between the two groups

Compared with those in the control group, the proportions of the right half of the colon, poorly differentiated region, lymph node metastasis, extraserous/muscular infiltration, infiltrating ulcerative pathology, and resection margin of liver metastasis < 1 cm were significantly greater in the recurrence group (all $P < 0.05$; Table 1).

Comparison of clinical data between the two groups

Compared with those in the control group, the levels of carcinoembryonic antigen, D-dimer, soluble intercellular adhesion molecule, white blood cells, platelets, and fibrinogen increased, the level of albumin decreased, and the proportion of patients with ineffective/no neoadjuvant chemotherapy and a high clinical risk score increased. The differences were statistically significant (all $P < 0.05$; Table 2).

Analysis of risk factors for postoperative recurrence in patients with liver metastases from colorectal cancer

This forest plot demonstrates six independent risk factors for postoperative recurrence in 178 patients with colorectal cancer liver metastases. All factors show 95% confidence intervals that do not cross the odds ratio (OR) = 1.0 reference line, indicating that these factors significantly increase the risk of recurrence. The strongest risk factors are D-dimer ≥ 180 $\mu\text{g/L}$ and high clinical risk score, both with OR values of 3.67, suggesting these two factors increase recurrence risk by nearly 4-fold. Elevated D-dimer reflects a hypercoagulable state in patients, which facilitates tumor cell metastasis; the high clinical risk score integrates multiple tumor characteristics and can accurately identify high-risk patients. Important risk factors include positive lymph node metastasis and invalid/not performed neoadjuvant chemotherapy, both with OR values of 3.52. Lymph node metastasis indicates that the tumor has acquired the ability for distant spread, while ineffective chemotherapy reflects the drug-resistant characteristics of the tumor; both are traditional important prognostic indicators. Moderate risk factors include hypoalbuminemia (< 29 g/L , OR = 2.30) and right colon primary site (OR = 1.74). Decreased albumin reflects malnutrition and impaired immune function; right

colon cancer has special molecular biological characteristics with relatively poor prognosis (Figure 1A).

Correlation analysis between primary location and risk factors for colorectal cancer

It shows a strong positive correlation with lymph node metastasis, with a correlation coefficient of 0.86. This suggests that an increase in D-dimer levels is likely associated with an increased risk of lymph node metastasis. The correlation coefficient is 0.37, indicating a moderate positive correlation between albumin levels and lymph node metastasis. Although this relationship is not as strong as that of D-dimer, it still suggests that albumin levels may have some association with the risk of lymph node metastasis. The correlation coefficient is -0.54, demonstrating a moderate negative correlation with lymph node metastasis. This implies that better outcomes from neoadjuvant chemotherapy are associated with a lower likelihood of lymph node metastasis. These insights could be significant for clinical decision-making and the development of treatment strategies (Figure 1B).

Postoperative recurrence of colorectal cancer in patients with different primary tumor locations

The bar chart provides a visual representation of the distribution of case numbers across three distinct segments of the colon and rectum at three different time intervals: 3 months, 6 months, and 12 months. At the 3-month mark, the left colon had approximately 10 cases, which increased to around 15 cases by the 6-month mark, and further rose to about 25 cases at 12 months. This demonstrates a steady rise in case numbers over time for the left colon. In contrast, the right hemicolon started with about 15 cases at 3 months, saw a significant jump to approximately 35 cases at 6 months, and peaked at around 50 cases at 12 months. This segment experienced the most substantial increase in case numbers across all time points, indicating a potentially higher incidence or faster progression of conditions in this area. The rectum had the lowest initial case count of about 5 at 3 months, which doubled to around 10 cases at 6 months, and then

increased to about 15 cases at 12 months. Although the rectum showed an increase in case numbers, it remained the segment with the fewest cases throughout the observed period (Figure 2A).

Comparison of postoperative complication rates in patients with different primary sites

Significant differences were observed in the incidence of postoperative complications between the two groups. Among the statistically significant complications, the relapse group demonstrated a significantly higher postoperative infection rate compared to the control group (18.18% vs 7.78%, $\chi^2 = 4.23$, $P = 0.039$), and the postoperative bleeding rate was also markedly increased (11.36% vs 2.22%, $\chi^2 = 3.91$, $P = 0.048$). Furthermore, the average postoperative length of stay was prolonged in the relapse group compared to the control group (14.2 ± 3.8 days vs 11.5 ± 2.9 days, $F = 5.67$, $P = 0.004$), indicating slower postoperative recovery and requiring longer hospitalization in the relapse group. Regarding other postoperative complications, although the incidence rates were consistently higher in the relapse group compared to the control group, the differences did not reach statistical significance. The postoperative intestinal obstruction rate was 9.09% in the relapse group vs 4.44% in the control group ($\chi^2 = 2.10$, $P = 0.150$); the postoperative anastomotic leak rate was 7.95% vs 3.33% ($\chi^2 = 2.45$, $P = 0.120$); the postoperative deep vein thrombosis rate was 5.68% vs 2.22% ($\chi^2 = 1.00$, $P = 0.320$); and the postoperative pulmonary embolism rate was 4.55% vs 1.11% ($\chi^2 = 2.00$, $P = 0.160$). These findings suggest that patients in the relapse group exhibited an overall increased trend in postoperative complication risks, particularly demonstrating significant disadvantages in infection control, bleeding management, and postoperative recovery (Table 3).

Impact of primary site on overall survival and disease-free survival

The Kaplan-Meier survival analysis revealed that primary site significantly affected patients' long-term survival outcomes. The median overall survival for right-sided

colon cancer patients was 28.5 months, significantly shorter than that for left-sided colon cancer patients at 41.2 months and rectal cancer patients at 38.7 months (log-rank test, $\chi^2 = 8.42$, $P = 0.015$). Regarding disease-free survival, the median disease-free survival for right-sided colon cancer patients was 15.8 months, significantly shorter than that for left-sided colon cancer patients at 26.4 months and rectal cancer patients at 24.1 months (log-rank test, $\chi^2 = 7.93$, $P = 0.019$). Cox multivariate regression analysis showed that, using left-sided colon cancer as reference, right-sided colon cancer was an independent risk factor affecting overall survival (hazard ratio = 1.73, 95% confidence intervals: 1.12-2.67, $P = 0.013$; Figure 2B).

DISCUSSION

At present, most clinical scholars regard colon cancer and rectal cancer as the same entity and treat them equally[13-15]. However, some scholars have studied 17641 cases of colorectal cancer patients and reported that the clinical manifestations, epidemiological characteristics and pathological characteristics of patients with left, right, and colon cancer after surgical treatment differ, possibly because of genetic differences in carcinogenesis and biological behavior differences[16-18]. Therefore, in recent years, some scholars believe that different regimens, such as neoadjuvant chemoradiotherapy for colorectal cancer patients and different drug targets and early local treatment regimens for colorectal cancer patients with different primary locations, should be used in staging procedures and neoadjuvant therapy to improve patient prognosis[19]. On the basis of the above differences in colorectal cancer patients with different primary locations, this study analyzed the effect of the primary location of colorectal cancer on the surgical outcome of patients with liver metastases, with the goal of providing guidance for future clinical treatment[20-22].

The arteriovenous system of the rectum is the main part of the rectal blood supply, which is supplied by the middle and upper rectal artery above the dentiform line and the arteriovenous supply below it[23-25]. The distinct vascular drainage patterns between colorectal segments contribute to different metastatic behaviors. Rectal tumors

drain *via* the middle and lower rectal veins into the systemic circulation, potentially leading to pulmonary metastases, while colonic tumors primarily drain through the portal system, favoring hepatic spread. Our analysis identified six independent risk factors for postoperative recurrence in liver metastatic colorectal cancer: Right-sided colonic origin, lymph node metastasis, D-dimer ≥ 180 $\mu\text{g/L}$, albumin < 29 g/L , ineffective/absent neoadjuvant chemotherapy, and elevated clinical risk scores (all $P < 0.05$).

Right-sided colon cancers exhibit distinct biological characteristics that contribute to their aggressive behavior. These tumors demonstrate greater cellular atypia, poorer differentiation, and increased propensity for invasion and distant metastasis compared to left-sided lesions[26-28]. The anatomical drainage pattern further influences metastatic distribution, as the superior mesenteric vein primarily perfuses the right hepatic lobe, while splenic venous flow targets the left lobe[29-32]. Therefore, the right lobe of the liver first contacts diseased cancer cells *via* blood flow during the metastasis of colorectal cancer. In addition, microsatellite instability is more common in the right half of the colon, so patients with right half of the colon are prone to liver metastasis, and the postoperative recurrence rate is also high. Lymph node metastasis refers to the invasion of tumor cells into lymph vessels and the growth of tumors centered on lymph nodes in the confluent area along with lymph fluid[33-35]. Therefore, patients with lymph node metastasis have a higher recurrence rate after surgery. D-dimer is an indicator commonly used to reflect the coagulation/fibrinolytic system in clinical practice. An abnormal increase in D-dimer levels indicates that the coagulation and fibrinolytic systems of patients are activated and that patients are in a state of blood hypercoagulation; thus, D-dimer levels are correlated with benign and malignant tumors. In this study, patients with D-dimer levels ≥ 180 $\mu\text{g/L}$ were prone to recurrence after surgery. It has become clinically clear that with the progression of cancer, the increased permeability of microvessels around colorectal tissue leads to an increase in albumin permeability and a decrease in albumin levels, promotes protein catabolic metabolism, reduces protein anabolic metabolism, causes a negative nitrogen balance

and affects prognosis[36-38]. Therefore, patients with an albumin concentration < 29 g/L in this study were indicated to have more severe disease. Metabolic disorders in the body have a high recurrence rate after surgery. Neoadjuvant chemotherapy is an adjuvant treatment before surgery, which can shrink the lesion, kill unexplored metastatic cells, and have a positive effect on subsequent surgery and other treatments[39-42]. However, patients who do not receive neoadjuvant chemotherapy or who have poor effects and high clinical risk scores may have relatively large lesions and unexplored metastatic cells in the body, so the postoperative recurrence rate is high. Further investigation revealed that the recurrence rate of 178 patients with liver metastases of colorectal cancer at 3 months, 6 months and 12 months after surgery was significantly greater in patients whose right colon was primary than in patients whose left colon and rectum were primary[43-45]. These results further suggest that the prognosis of patients with primary colorectal cancer in the right colon is poor and that the clinical recurrence rate is high.

CONCLUSION

In summary, the right colon, lymph node metastasis, D-dimer, albumin, neoadjuvant chemotherapy efficacy, and clinical risk score are all risk factors for postoperative recurrence in patients with liver metastatic colorectal cancer, and the recurrence rate is higher in patients whose right colon is the primary location.

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