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***Retrospective Study***

**Identification of multiple risk factors for colorectal cancer relapse after laparoscopic radical resection**

Luo J *et al*. CRC relapse risk factors identified

Jun Luo, Mei-Wen He, Ting Luo, Guo-Qing Lv

**Jun Luo, Mei-Wen He,** Department of Gastrointestinal Surgery, Peking University Shenzhen Hospital, Shenzhen 518036, Guangdong Province, China

**Ting Luo,** Department of Operating Room, Peking University Shenzhen Hospital, Shenzhen 518036, Guangdong Province, China

**Guo-Qing Lv,** Department of Gastrointestinal Surgery, Shenzhen Peking University-The Hong Kong University of Science and Technology Medical Center, Peking University Shenzhen Hospital, Shenzhen 518036, Guangdong Province, China

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**Corresponding author: Guo-Qing Lv, MS, Attending Doctor,** Department of Gastrointestinal Surgery, Shenzhen Peking University-The Hong Kong University of Science and Technology Medical Center, Peking University Shenzhen Hospital, No. 120 Lianhua Road, Futian District, Shenzhen 518036, Guangdong Province, China. 365973269@qq.com

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**Abstract**

BACKGROUND

Colorectal cancer (CRC) is a common life-threatening disease that often requires surgical intervention, such as laparoscopic radical resection. However, despite successful surgeries, some patients experience disease relapse. Identifying the risk factors for CRC relapse can help guide clinical interventions and improve patient outcomes.

AIM

To determine the risk factors that may lead to CRC relapse after laparoscopic radical resection.

METHODS

We performed a retrospective analysis using the baseline data of 140 patients with CRC admitted to our hospital between January 2018 and January 2020. All included participants were followed up until death or for 3 years. The baseline data and laboratory indicators were compared between the patients who experienced relapse and those who did not experienced relapse.

RESULTS

Among the 140 patients with CRC, 30 experienced relapse within 3 years after laparoscopic radical resection and 110 did not experience relapse. The relapse group had a higher frequency of rectal tumors with low differentiation and lymphatic vessel invasion than that of the non-relapse group. The expression of serum markers and the prognostic nutritional index were lower, whereas the neutrophil-to-lymphocyte ratio, expression of cytokeratin 19 fragment antigen 21-1, vascular endothelial growth factor, and Chitinase-3-like protein 1 were significantly higher in the relapse group than those in the non-relapse group. The groups did not differ significantly based on other parameters. Logistic regression analysis revealed that all the above significantly altered factors were independent risk factors for CRC relapse.

CONCLUSION

We identified multiple risk factors for CRC relapse following surgery, which can be considered for the clinical monitoring of patients to reduce disease recurrence and improve patient survival.

**Key Words:** Colorectal cancer; Laparoscopic surgery; Relapse; Risk factors

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**Core Tip:** This study aimed to identify the risk factors for colorectal cancer (CRC) relapse after laparoscopic radical resection by comparing the baseline data and laboratory indicators of 140 patients with CRC, of whom 30 patients experienced relapse within 3 years. Rectal tumors with low differentiation and lymphatic vessel invasion were associated with higher relapse rates. Lower CD4+/CD8+ ratio, immunoglobulins (Ig) IgA, IgG, IgM, albumin-globulin ratio, and prognostic nutritional index and higher neutrophils to lymphocytes ratio, cytokeratin 19 fragment antigen 21-1, vascular endothelial growth factor, and Chitinase-3-like protein 1 were also identified as independent risk factors for CRC relapse following surgery. These findings suggested that monitoring these factors could reduce the risk of disease recurrence and improve patient outcomes.

**INTRODUCTION**

Colorectal cancer (CRC) is a prevalent digestive tract cancer associated with lifestyle and living conditions. The lack of specific symptoms at the early stage of the disease leads to a low early detection rate. Thus, many patients are diagnosed at an advanced stage, and their prognoses are often unsatisfactory[1,2]. Treatments for CRC have progressed rapidly, and the overall principle is to adopt surgical intervention supplemented by comprehensive standardized treatments, such as radiotherapy and targeted therapy. Endoscopic technology has gradually replaced traditional laparotomy and is the first choice and main intervention for the treatment of CRC[3,4]. Although patients with CRC receive timely consolidation treatment with adjuvant therapies, such as chemoradiotherapy and molecular targeted therapy after surgery, the risk of postoperative relapse remains high, leading to a high mortality rate[5,6]. Approximately 30% of patients with CRC who have undergone laparoscopic radical surgery show a risk of metastasis or relapse after surgery, and the 5-year survival rate of such patients is only approximately 19%. Liver metastasis presents a major clinical challenge. Therefore, exploring the factors that may lead to postoperative relapse is necessary to enhance the vigilance of patients at high risk of relapse and guide more appropriate clinical interventions, ultimately reducing the risk of postoperative relapse and enhancing patient prognosis[7,8]. A search for clinical literature related to the exploration of factors that may affect relapse after laparoscopic radical resection in patients with CRC revealed varying factors, such as patient age, tumor stage, and tumor size, with no firm consensus[9-11]. Therefore, in this study, we compared and analyzed the baseline data of included participants to identify the influencing factors that may lead to relapse in patients with CRC after laparoscopic radical resection to guide future interventions and reduce the risk of relapse in patients with CRC after surgery.

**MATERIALS AND METHODS**

***Participants***

Baseline data were collected from 140 patients (80 male and 60 female) with CRC admitted to Peking University Shenzhen Hospital between January 2018 and January 2020. The inclusion criteria were as follows: (1) Patients with CRC who met the diagnostic requirements of the “Clinical Guideline for Diagnosis and Treatment of Tumor”[12] and were confirmed using biopsy; (2) those who underwent successful laparoscopic radical resection; and (3) those with baseline data and complete laboratory test results.

The exclusion criteria were as follows: (1) Patients with other cancerous lesions; (2) those with metastasis diagnosed before or during the surgery; (3) those who received targeted therapy, chemoradiotherapy, and other adjuvant treatments before the surgery; (4) those with reduced compliance due to psychological disorders; and (5) presence of acute or chronic diseases, such as impaired liver and kidney function, pulmonary, cardiovascular, cerebrovascular, and hematological diseases, or coagulation disorders, intestinal diseases including intestinal obstruction and intestinal perforation, and acute and chronic infections or active inflammation that may affect the prognosis of the patient.

***Methods***

We retrospectively analyzed the baseline data of the enrolled patient cohort.

***Diagnostic criteria for relapse***

The diagnostic criteria included patients followed up effectively until death or up to 3 years (until January 31, 2023). Relapse was determined as the detection of pathological lesions similar to the primary lesions regrowing around the sites of the primary lesion, intestinal anastomosis, peri-intestinal tissue, mesentery, and lymph node regions through clinical imaging (B-scan ultrasonography, abdominal radiography, computed tomography) and further confirmation by tissue biopsy for patients suspected of relapse.

***Baseline data collection***

The following baseline data were collected: Sex; age (≥ 60 years); tumor node metastasis (TNM)[13] stage (stage I–II, stage III–IV); degree of differentiation (with reference to the Edmondson-Stener classification of tumor pathological grade[14] (stage I: Highly differentiated carcinoma, stage II: Moderately differentiated carcinoma; stage III and IV: Poorly differentiated carcinoma); maximum tumor diameter (≥ 5 cm); location of the lesion (rectum, left/right hemicolon); lymphovascular invasion (present, absent); pathological type (glandular cancer, mucinous adenocarcinoma, Indian cell carcinoma); depth of invasion (T1 + T2, T3 + T4); serum tumor and immune indicators including lymphocytes (CD4+/CD8+), immunoglobulins (Ig) IgA, IgG, IgM, neutrophils to lymphocytes ratio (NLR), albumin-globulin ratio (AGR), cytokeratin 19 fragment antigen 21-1 (CYFRA 21-1), vascular endothelial growth factor (VEGF), prognostic nutritional index (PNI), and the inflammatory biomarker Chitinase-3-like protein 1 (YKL-40).

***Detection of serum indicators***

Fasting peripheral blood was collected in anticoagulation tubes and used for the following assays: Absolute neutrophil count and absolute lymphocyte count (ALC) using the XE-2100 blood cell analyzer (SYSMEX Corporation, Japan; NLR = PLT/ALC); enzyme-linked immunosorbent assay detection of immunoglobulins, VEGF and YKL-40, Huamei, and Zhenke Biotechnology, China, respectively); total serum protein and albumin detection by an auto chemistry analyzer (BK-400, Jinan Olebo Electronic Commerce, China; globulin = total protein-albumin, AGR = albumin/globulin); CYFRA 21-1 detection by electrochemical luminescence; PNI determination by calculating the albumin concentration and lymphocyte counts using the AU680 automatic biochemical analyzer [Beckman Coulter, United States; PNI = albumin (mg/L) + 5 × lymphocyte counts (× 109/L)].

***Statistical analysis***

Data analysis was conducted using SPSS 25.0 software. The Shapiro-Wilk test was used to determine the normality of the measurement data. Measurement data conforming to a normal distribution were expressed as mean ± SD. The independent sample *t*-test was used for inter-group comparison; count data were presented as *n* (%) and analyzed using the *χ*2 test was used. Logistic regression analysis was used to analyze the risk factors for relapse in patients with CRC after laparoscopic radical resection, maintaining an inspection level of α=0.05.

**RESULTS**

***Relapse status of patients after radical resection of CRC***

Among the 140 patients with CRC included in the study, 30 experienced relapse within 3 years after laparoscopic radical resection, whereas 110 did not experience relapse, resulting in the relapse rate being 21.43% (30/140) and non-relapse rate being 78.57% (110/140). We analyzed baseline data of the relapsed and non-relapsed groups.

***Comparison of baseline data between the two groups***

The relapse and non-relapse groups were comparable in terms of their baseline characteristics. However, significant differences between the two groups were observed in the degree of tumor differentiation, lesion location, lymphatic vessel invasion, and several serum indicators. Most patients in the relapse group exhibited rectal tumors characterized by low differentiation and lymphatic vessel invasion. However, patients in the non-relapse group predominantly presented tumors in the left/right hemicolon, with higher differentiation and lack of lymphatic invasion (Table 1). The CD4+/CD8+ ratio and levels of IgG, IgA, IgM, AGR, and PNI were lower, whereas the expression of NLR, CYFRA21-1, VEGF, and YKL-40 was higher in the relapse group than those in the non-relapse group, and the differences were statistically significant (*P* < 0.05).

***Logistic regression analysis of relapse after laparoscopic radical resection of CRC***

To determine whether the factors that were significantly different between patients in the relapse and non-relapse groups were significant risk factors for relapse after laparoscopic radical resection, we performed logistic regression analysis with relapse after surgery being treated as the dependent variable (1 = relapse, 0 = non-relapse) and indicators with significant differences from Table 1 as the independent variables (Table 2 presents the assignment). The results demonstrated that the degree of differentiation (low differentiation); location of the lesion (rectum); lymphatic vessel invasion (present); low expression of serum CD4+/CD8+, IgG, IgA, IgM, AGR, and PNI; and high expression of serum NLR, CYFRA21-1, VEGF, and YKL-40 were independent risk factors for relapse in patients with CRC after laparoscopic radical surgery (OR> 1, *P* < 0.05; Table 3).

**DISCUSSION**

Laparoscopic radical resection can significantly improve overall patient outcomes and reduce the impact of open surgery on immune function. However, the risk of relapse remains high in patients with CRC after radical resection. Our present study supports this conclusion, as our results are consistent with the observed relapse rate of 21.43% observed in a cohort of 140 patients. The results negatively impact patients’ quality of life and overall survival rate. Therefore, for patients with CRC, early detection of relapse after surgery and exploration of the risk factors that may lead to relapse are particularly crucial for guiding further treatment, prolonging survival time, and improving the quality of life[15,16].

This study demonstrated that patients with rectal tumors with a low degree of differentiation and lymphatic vessel invasion were at higher risk of postsurgical relapse than that of patients with more differentiated tumors located within the colon and without lymphatic vessel invasion. Other immune/tumor-related risk factors for relapse included lower expression of CD4+/CD8+, IgG, IgA, IgM, AGR, and PNI and higher expression of NLR, CYFRA21-1, VEGF, and YKL-40. Logistic regression analysis indicated that all variables were independent risk factors for CRC relapse after laparoscopic radical resection.

The complex rectal lymphatic drainage system may be a possible reason for the higher relapse rate in patients with rectal tumors. The absence of a serosa in the lower rectal cancer tube may allow lesions to easily adhere to the surrounding tissues, increasing the difficulty of complete surgical removal and the risk of postoperative relapse[17]. The degree of tissue differentiation has a significant effect on the biological behavior of tumors. A lower degree of differentiation indicates that the tumor tissue has strong regenerative ability; a fast growth rate due to rapid cell division and proliferation; and high migration and invasiveness into surrounding tissues, lymphatic vessels, and capillaries, contributing to a high probability of postoperative relapse[18,19].

As an important immune organ, the lymph node is the switch that activates the immune response in the body. Because of the abundant lymphatic and blood vessels in the mesorectum, cancer cells can easily invade these circulatory systems, forming circulating tumor cells that are resistant to apoptosis and attacks from the immune system and many other environmental factors, eventually invading new tissues to form metastases, thereby increasing the relapse rate of patients after surgery[20,21]. The body’s immune function is essential for monitoring and inhibiting tumor progression, and T cells and their subsets are particularly associated with the progression of malignant diseases. CD8+ T cells can directly act as effector cells to kill tumor cells, whereas CD4+ T cells mainly inhibit inflammatory factors, secrete specific cytokines to assist other immune cells, regulate the body’s immune function against tumors, and increase the body’s immune tolerance to achieve antitumor immunity. Thus, changes in the CD8+/CD4+ ratio directly affect the ability of the body to resist tumor cells[22-24]. Regulatory T cells contribute to the immune escape mechanisms of cancer lesions. When the CD4+/CD8+ ratio is high, many regulatory T cells infiltrate the tumor and elicit a significant immunosuppressive effect contributing to tumor occurrence, progression, and metastasis. When the CD4+/CD8+ ratio is increased for various reasons, it indicates that the immune function is in an inhibitory state with decreased immunity and increased tolerance, and the antitumor immune response is also damaged, leading to the proliferation and progression of cancerous lesions and a directly increase in the risk of postoperative relapse. When a patient experiences relapse after surgery, many soluble immunosuppressive factors are produced during tumor regeneration and progression. These hinder the maturation of CD4+ cells, inhibit the immune system, and promote disease progression. This vicious cycle leads to poor patient prognosis[25-27]. Immunoglobulins, such as IgG, IgA, and IgM, are important immune system components. They mainly activate the complement system by specifically binding to antigens, accelerating cell lysis, and enhancing antibody regulation to achieve antitumor immune effects. Abnormal immunoglobulin expression is a manifestation of impaired humoral immune function. Decreased IgG, IgA, and IgM expression indicates decreased mucosal defense and weakened complement-mediated phagocytosis. Thus, the reduced phagocytic removal of cancer cells potentially increases the risk of postoperative relapse in patients[28-30].

The AGR and NLR are markers of inflammation that indicate systemic inflammatory response and immunosuppressive function of the body. Inflammatory responses are triggered when the body is infected or exposed to other stimuli. However, unregulated inflammation can cause significant damage to the body, and a chronic inflammatory state impedes immune infiltration and increases angiogenesis, providing an ideal environment for the growth and reproduction of cancer cells and promoting the generation and spread of cancerous lesions. Relapsing tumors aggravate the inflammatory response in the body and form a negative feedback loop that increases the risk of postoperative relapse in patients[31-33].

In addition to the AGR, a combination of albumin and lymphocyte count readouts in the form of PNI may be a useful marker in cancer biology. Lymphocytes are important components of the immune system and are involved in protein recovery and nutrient transport; therefore, PNI can highlight the nutritional status of an individual. Reduced PNI values indicate decreased lymphocyte counts and albumin levels, along with possible inflammation and malnutrition in the body. This can lead to treatment intolerance and a decline in antitumor immune function, increasing cancer cell proliferation and the risk of postoperative relapse[34-36].

The protein antigen CYFRA21-1 is mainly present in the lymph nodes, bone marrow, and epithelium of healthy individuals. When cells become cancerous, proteases are activated, and normal colorectal epithelial tissues are damaged. When cells die, the activated protease accelerates the dissolution rate, a large amount of CYFRA21-1 is released into the blood, and the expression of CYFRA21-1 in serum is increased. Thus, high expression of CYFRA21-1 indicates extensive cell death or damage. We should be aware of the reinvasion of cancer lesions, which indicates that patients have a high risk of relapse[37-39].

Many vascular stimulatory factors can stimulate cancer cells to release many angiogenic factors that promote angiogenesis within tumors. VEGF has a strong induction effect that can accelerate tumor abnormalities and rapid growth. High levels of serum VEGF can promote the abnormal proliferation of tumor cells, accelerate the transformation of cancer cells into solid tumors, stimulate their migration and invasion into surrounding tissues and organs, destroy normal colorectal epithelial tissues and cells, accelerate neoangiogenesis, change the microenvironment, and increase the chance of relapse[40-42].

YKL-40 is a secretory glycoprotein mainly produced by chondrocytes, neutrophils, and other cells under the influence of inflammation. YKL-40 has many biological functions and signals through multiple pathways involved in angiogenesis, cell proliferation and differentiation, and immune and inflammatory responses. High YKL-40 expression may accelerate colorectal epithelial-mesenchymal transition (EMT) by upregulating vimentin and N-cadherin and downregulating E-cadherin. Because EMT is an important process for tumor migration and invasion, increased YKL-40 expression may increase the risk of relapse in patients with CRC after radical surgery[43,44].

**CONCLUSION**

In this study, we highlighted several risk factors associated with relapse in patients with CRC after surgery, which will enable the adoption of targeted interventions in clinical practice based on the combination of risk factors present. These factors can serve as monitoring strategies for identifying high-risk patients and detecting early disease recurrence. Direct interventions to reduce abnormal expression of these serum indicators may also reduce the risk of relapse after radical surgery. However, owing to the retrospective nature of this study and the limited sampling within a single center, the reproducibility and generalizability of our conclusions requires validation through further exploration. In addition, the results of this study revealed that the TNM stage is not a risk factor for postoperative recurrence in patients with CRC, which is inconsistent with the findings of Ma*et al*[45]. However, this study did not elaborate on the reasons for these inconsistent results. Further research is needed to determine the impact of the TNM stage on postoperative recurrence in patients with CRC.

In conclusion, we identified many risk factors for CRC relapse following laparoscopic radical resection, including tumors located in the rectum with low differentiation and lymphatic vessel invasion; low serum expression of CD4+/CD8+, IgG, IgA, IgM, AGR, and PNI; and high serum expression of NLR, CYFRA21-1, VEGF, and YKL-40. Monitoring these risk factors will help enhance vigilance regarding the risk of CRC relapse after laparoscopic radical surgery.

**ARTICLE HIGHLIGHTS**

***Research background***

Colorectal cancer (CRC) is a prevalent and life-threatening disease that often necessitates surgical intervention, such as laparoscopic radical resection. However, despite successful surgical procedures, a subset of patients experiences relapse. The identification of risk factors associated with CRC relapse is crucial for guiding clinical interventions and enhancing patient outcomes. This study aimed to conduct a comparative analysis of baseline data and laboratory indicators in CRC patients to determine the risk factors contributing to relapse following laparoscopic radical resection. A retrospective analysis was performed on 140 CRC patients, of which 30 experienced relapse within three years after surgery. The study revealed that tumors located in the rectum with low differentiation and lymphatic vessel invasion were associated with higher relapse rates. Additionally, specific serum markers, including CD4+/CD8+ ratio, immunoglobulins (Ig) IgA, IgG, IgM, albumin-globulin ratio (AGR), neutrophils to lymphocytes ratio (NLR), cytokeratin 19 fragment antigen 21-1 (CYFRA 21-1), vascular endothelial growth factor (VEGF), and the inflammatory biomarker Chitinase-3-like protein 1 (YKL-40), were identified as independent risk factors for CRC relapse. These findings underscore the importance of monitoring these factors to reduce the risk of disease recurrence and improve patient outcomes.

***Research motivation***

CRC is a significant health burden with the potential for relapse even after successful surgical intervention. The identification of risk factors associated with CRC relapse is crucial to guide clinical interventions and enhance patient outcomes. This study aimed to analyze the baseline data and laboratory indicators of CRC patients who underwent laparoscopic radical resection, with the objective of determining the risk factors contributing to relapse. The findings highlighted several key factors, including tumor location, differentiation, lymphatic vessel invasion, as well as serum markers such as CD4+/CD8+ ratio, IgG, IgA, IgM, AGR, NLR, CYFRA21-1, VEGF, and YKL-40. Understanding these risk factors can aid in identifying high-risk patients and implementing proactive measures for monitoring and intervention, ultimately reducing the risk of relapse and improving the long-term survival prospects for CRC patients.

***Research objectives***

This study aimed to compare baseline data and laboratory indicators of CRC patients who underwent laparoscopic radical resection to identify risk factors associated with CRC relapse. The objectives were to determine the differences in tumor characteristics, analyze serum markers, assess statistical significance, identify independent risk factors using logistic regression, and provide insights for clinical monitoring and interventions to reduce relapse risk and improve patient outcomes.

***Research methods***

This study utilized a retrospective analysis of baseline data from 140 CRC patients admitted to the hospital between January 2018 and January 2020. The included subjects were followed up until death or a maximum of three years. Comparative analysis was conducted to compare the baseline data and laboratory indicators between patients who experienced relapse and those who did not. Tumor characteristics, including location, differentiation, and lymphatic vessel invasion, were assessed. Serum markers, such as CD4+/CD8+ ratio, IgG, IgA, IgM, AGR, NLR, CYFRA21-1, VEGF, and YKL-40, were measured and compared between the relapse and non-relapse groups. Statistical analyses were performed to determine the significance of the observed differences. Logistic regression was employed to identify independent risk factors associated with CRC relapse after laparoscopic radical surgery. The research methods aimed to provide valuable insights into the identification and monitoring of risk factors for disease recurrence and improving patient survival outcomes.

***Research results***

Out of the 140 CRC patients included in the study, 30 cases (21.43%) experienced relapse within three years after laparoscopic radical resection, while 110 patients (78.57%) did not relapse. The relapse group exhibited a higher frequency of tumors located in the rectum with low differentiation and lymphatic vessel invasion compared to the non-relapse group. Significant differences were observed in the levels of several serum markers. The relapse group showed lower expressions of CD4+/CD8+ ratio, IgG, IgA, IgM, AGR, and PNI. Conversely, the relapse group had higher levels of NLR, CYFRA21-1, VEGF, and YKL-40. Logistic regression analysis confirmed that all these altered factors were independent risk factors for CRC relapse following laparoscopic radical surgery, with odds ratios greater than 1 and statistically significant values (*P* < 0.05). These findings emphasize the importance of monitoring these factors for reducing disease recurrence and improving patient survival outcomes.

***Research conclusions***

Based on our comparative analysis of baseline data and laboratory indicators in CRC patients who underwent laparoscopic radical resection, we have identified several important conclusions. Firstly, tumors located in the rectum with low differentiation and lymphatic vessel invasion are associated with a higher risk of relapse after surgery. Additionally, lower levels of CD4+/CD8+ ratio, IgG, IgA, IgM, AGR, and PNI, along with higher levels of NLR, CYFRA21-1, VEGF, and YKL-40, serve as independent risk factors for CRC relapse following surgery. These findings highlight the significance of monitoring these factors to guide clinical interventions and reduce the risk of disease recurrence. By focusing on these risk factors, healthcare professionals can enhance patient surveillance and develop strategies to improve survival outcomes in CRC patients undergoing laparoscopic radical resection.

***Research perspectives***

The identification of multiple risk factors for CRC relapse following laparoscopic radical surgery provides valuable insights into improving patient outcomes. Moving forward, prospective studies should focus on validating these findings in larger patient populations and diverse healthcare settings. Further investigations can explore the molecular mechanisms underlying the identified risk factors to gain a deeper understanding of their roles in disease recurrence. Additionally, the development of predictive models incorporating these risk factors could aid in personalized treatment strategies and postoperative surveillance. Long-term follow-up studies are warranted to assess the impact of monitoring these factors on long-term survival and quality of life in CRC patients. Furthermore, intervention studies targeting modifiable risk factors may offer potential avenues for reducing disease relapse rates. Overall, continued research efforts in this field will contribute to optimizing clinical management and ultimately enhancing the prognosis of CRC patients undergoing laparoscopic radical resection.

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**REFERENCES**

1 **Fedewa SA**, Siegel RL, Jemal A. Are temporal trends in colonoscopy among young adults concordant with colorectal cancer incidence? *J Med Screen* 2019; **26**: 179-185 [PMID: 31296103 DOI: 10.1177/0969141319859608]

2 **Vuik FE**, Nieuwenburg SA, Bardou M, Lansdorp-Vogelaar I, Dinis-Ribeiro M, Bento MJ, Zadnik V, Pellisé M, Esteban L, Kaminski MF, Suchanek S, Ngo O, Májek O, Leja M, Kuipers EJ, Spaander MC. Increasing incidence of colorectal cancer in young adults in Europe over the last 25 years. *Gut* 2019; **68**: 1820-1826 [PMID: 31097539 DOI: 10.1136/gutjnl-2018-317592]

3 **Saesen R**, Lacombe D, Huys I. Design, organisation and impact of treatment optimisation studies in breast, lung and colorectal cancer: The experience of the European Organisation for Research and Treatment of Cancer. *Eur J Cancer* 2021; **151**: 221-232 [PMID: 34023561 DOI: 10.1016/j.ejca.2021.04.012]

4 **Huang XM**, Huang JJ, Du JJ, Zhang N, Long Z, Yang Y, Zhong FF, Zheng BW, Shen YF, Huang Z, Qin X, Chen JH, Lin QY, Lin WJ, Ma WZ. Autophagy inhibitors increase the susceptibility of KRAS-mutant human colorectal cancer cells to a combined treatment of 2-deoxy-D-glucose and lovastatin. *Acta Pharmacol Sin* 2021; **42**: 1875-1887 [PMID: 33608672 DOI: 10.1038/s41401-021-00612-9]

5 **Hung P**, Deng S, Zahnd WE, Adams SA, Olatosi B, Crouch EL, Eberth JM. Geographic disparities in residential proximity to colorectal and cervical cancer care providers. *Cancer* 2020; **126**: 1068-1076 [PMID: 31702829 DOI: 10.1002/cncr.32594]

6 **Nigro O**, Chini C, Proserpio I. Molecularly targeted therapy for advanced gastrointestinal noncolorectal cancer treatment: how to choose? Past, present, future. *Anticancer Drugs* 2021; **32**: 593-601 [PMID: 33929995 DOI: 10.1097/CAD.0000000000001071]

7 **Fedewa SA**, Siegel RL, Goding Sauer A, Bandi P, Jemal A. Colorectal cancer screening patterns after the American Cancer Society's recommendation to initiate screening at age 45 years. *Cancer* 2020; **126**: 1351-1353 [PMID: 31850529 DOI: 10.1002/cncr.32662]

8 **Burr NE**, Plumb A, Sood R, Rembacken B, Tolan DJM. CT colonography remains an important test for colorectal cancer. *Gut* 2022; **71**: 217-218 [PMID: 33753420 DOI: 10.1136/gutjnl-2021-324399]

9 **Holt J**, Schwalb H, Elbourne H, Te Marvelde L, Reid C. Risk factors for recurrence in colorectal cancer: a retrospective analysis in a regional Australian hospital. *ANZ J Surg* 2021; **91**: 2482-2486 [PMID: 34595825 DOI: 10.1111/ans.17209]

10 **Wada Y**, Shimada M, Morine Y, Ikemoto T, Saito Y, Baba H, Mori M, Goel A. A transcriptomic signature that predicts cancer recurrence after hepatectomy in patients with colorectal liver metastases. *Eur J Cancer* 2022; **163**: 66-76 [PMID: 35042069 DOI: 10.1016/j.ejca.2021.12.013]

11 **Cañellas-Socias A**, Cortina C, Hernando-Momblona X, Palomo-Ponce S, Mulholland EJ, Turon G, Mateo L, Conti S, Roman O, Sevillano M, Slebe F, Stork D, Caballé-Mestres A, Berenguer-Llergo A, Álvarez-Varela A, Fenderico N, Novellasdemunt L, Jiménez-Gracia L, Sipka T, Bardia L, Lorden P, Colombelli J, Heyn H, Trepat X, Tejpar S, Sancho E, Tauriello DVF, Leedham S, Attolini CS, Batlle E. Metastatic recurrence in colorectal cancer arises from residual EMP1(+) cells. *Nature* 2022; **611**: 603-613 [PMID: 36352230 DOI: 10.1038/s41586-022-05402-9]

12 **CMA.** Guidelines for clinical diagnosis and treatment. Tumor fascicle. *People’s Health Publishing House* 2009; 93-94, 708

13 **German AI,** Wittekind C. TNM system:on the 7th edition of TNM classification of malignant tumors. *Patholog E* 2010; **31**: 331-332

14 **Pirisi M**, Leutner M, Pinato DJ, Avellini C, Carsana L, Toniutto P, Fabris C, Boldorini R. Reliability and reproducibility of the edmondson grading of hepatocellular carcinoma using paired core biopsy and surgical resection specimens. *Arch Pathol Lab Med* 2010; **134**: 1818-1822 [PMID: 21128781 DOI: 10.5858/2009-0551-OAR1.1]

15 **Fang S**, Guo S, Du S, Cao Z, Yang Y, Su X, Wei W. Efficacy and safety of berberine in preventing recurrence of colorectal adenomas: A systematic review and meta-analysis. *J Ethnopharmacol* 2022; **282**: 114617 [PMID: 34509605 DOI: 10.1016/j.jep.2021.114617]

16 **Kato Y**, Shigeta K, Okabayashi K, Tsuruta M, Seishima R, Matsui S, Sasaki T, Koseki Y, Kitagawa Y. Lymph node metastasis is strongly associated with lung metastasis as the first recurrence site in colorectal cancer. *Surgery* 2021; **170**: 696-702 [PMID: 33902923 DOI: 10.1016/j.surg.2021.03.017]

17 **Lu YY,** Yin T. Logistic analysis of influencing factors of recurrence and metastasis of colorectal cancer. *Linchuang Xiaohuabing Zazhi* 2022; **34**: 454-456

18 **Ye XH,** Wang XY. Analysis of the factors influencing recurrence and metastasis after chemotherapy for advanced colorectal cancer. *Shiyong Aizheng Zazhi* 2020; **35**: 330-334

19 **Yamada H**, Kondo S, Okushiba S, Morikawa T, Katoh H. Analysis of predictive factors for recurrence after hepatectomy for colorectal liver metastases. *World J Surg* 2001; **25**: 1129-1133 [PMID: 11571947 DOI: 10.1007/BF03215859]

20 **Li C,** Li JH, Huo BL. Effect of lateral lymph node dissection on prognosis, recurrence and metastasis in patients with low rectal cancer. *Xiandai Xiaohua Ji Jieru Zhenliao* 2020; **25**: 1596-1600 [DOI: 10.3969/j.issn.1672-2159.2020.12.009]

21 **Luo ZW,** Chen X, Zhang YF, Huang Z, Chen QC, Zhao H, Zhao JJ, Li ZY, Zhou JG, Cai JQ. Influencing factors for the early recurrence of synchronous colorectal cancer liver metastases. *Zhonghua Gandan Waike Zazhi* 2020; **26**: 741-747 DOI: [10.3760/cma.j.cn113884-20200811-00426]

22 **Øgaard N**, Reinert T, Henriksen TV, Frydendahl A, Aagaard E, Ørntoft MW, Larsen MØ, Knudsen AR, Mortensen FV, Andersen CL. Tumour-agnostic circulating tumour DNA analysis for improved recurrence surveillance after resection of colorectal liver metastases: A prospective cohort study. *Eur J Cancer* 2022; **163**: 163-176 [PMID: 35074652 DOI: 10.1016/j.ejca.2021.12.026]

23 **Eugène J**, Jouand N, Ducoin K, Dansette D, Oger R, Deleine C, Leveque E, Meurette G, Podevin J, Matysiak T, Bennouna J, Bezieau S, Volteau C, Thomas WEA, Chetritt J, Kerdraon O, Fourquier P, Thibaudeau E, Dumont F, Mosnier JF, Toquet C, Jarry A, Gervois N, Bossard C. The inhibitory receptor CD94/NKG2A on CD8(+) tumor-infiltrating lymphocytes in colorectal cancer: a promising new druggable immune checkpoint in the context of HLAE/β2m overexpression. *Mod Pathol* 2020; **33**: 468-482 [PMID: 31409873 DOI: 10.1038/s41379-019-0322-9]

24 **Whiteside SK**, Grant FM, Gyori DS, Conti AG, Imianowski CJ, Kuo P, Nasrallah R, Sadiyah F, Lira SA, Tacke F, Eil RL, Burton OT, Dooley J, Liston A, Okkenhaug K, Yang J, Roychoudhuri R. CCR8 marks highly suppressive Treg cells within tumours but is dispensable for their accumulation and suppressive function. *Immunology* 2021; **163**: 512-520 [PMID: 33838058 DOI: 10.1111/imm.13337]

25 **Xue J**, Yu X, Xue L, Ge X, Zhao W, Peng W. Intrinsic β-catenin signaling suppresses CD8(+) T-cell infiltration in colorectal cancer. *Biomed Pharmacother* 2019; **115**: 108921 [PMID: 31078045 DOI: 10.1016/j.biopha.2019.108921]

26 **Rostamzadeh D**, Haghshenas MR, Daryanoosh F, Samadi M, Hosseini A, Ghaderi A, Mojtahedi Z, Babaloo Z. Altered frequency of CD8(+) CD11c(+) T cells and expression of immunosuppressive molecules in lymphoid organs of mouse model of colorectal cancer. *J Cell Physiol* 2019; **234**: 11986-11998 [PMID: 30623416 DOI: 10.1002/jcp.27856]

27 **Giannini R**, Zucchelli G, Giordano M, Ugolini C, Moretto R, Ambryszewska K, Leonardi M, Sensi E, Morano F, Pietrantonio F, Cremolini C, Falcone A, Fontanini G. Immune Profiling of Deficient Mismatch Repair Colorectal Cancer Tumor Microenvironment Reveals Different Levels of Immune System Activation. *J Mol Diagn* 2020; **22**: 685-698 [PMID: 32173570 DOI: 10.1016/j.jmoldx.2020.02.008]

28 **Nuccetelli M**, Pieri M, Gisone F, Sarubbi S, Ciotti M, Andreoni M, Bernardini S. Evaluation of a new simultaneous anti-SARS-CoV-2 IgA, IgM and IgG screening automated assay based on native inactivated virus. *Int Immunopharmacol* 2021; **92**: 107330 [PMID: 33412393 DOI: 10.1016/j.intimp.2020.107330]

29 **Demers-Mathieu V**, Huston RK, Markell AM, McCulley EA, Martin RL, Dallas DC. Impact of pertussis-specific IgA, IgM, and IgG antibodies in mother's own breast milk and donor breast milk during preterm infant digestion. *Pediatr Res* 2021; **89**: 1136-1143 [PMID: 32599609 DOI: 10.1038/s41390-020-1031-2]

30 **Orth-Höller D**, Eigentler A, Stiasny K, Weseslindtner L, Möst J. Kinetics of SARS-CoV-2 specific antibodies (IgM, IgA, IgG) in non-hospitalized patients four months following infection. *J Infect* 2021; **82**: 282-327 [PMID: 32956726 DOI: 10.1016/j.jinf.2020.09.015]

31 **Kong JC**, Su WK, Ng CW, Guerra GR, Chakraborty J, Lutton N, Morris B, Gourlas P. Colorectal cancer in younger adults from a Bi-National Colorectal Cancer Audit registry. *ANZ J Surg* 2021; **91**: 367-374 [PMID: 32856368 DOI: 10.1111/ans.16250]

32 **Ying HQ**, Deng QW, He BS, Pan YQ, Wang F, Sun HL, Chen J, Liu X, Wang SK. The prognostic value of preoperative NLR, d-NLR, PLR and LMR for predicting clinical outcome in surgical colorectal cancer patients. *Med Oncol* 2014; **31**: 305 [PMID: 25355641 DOI: 10.1007/s12032-014-0305-0]

33 **Qiu L,** Tan CL, Liu H. Clinical value of preoperative combined serum tumor markers NLR and PLR in evaluating the prognosis of colorectal cancer patients. *Zhongguo Putong Waike Zazhi* 2020; **29**: 1533-1538 [DOI:10.7659/j.issn.1005-6947.2020.12.017]

34 **Ying HQ**, Liao YC, Sun F, Peng HX, Cheng XX. The Role of Cancer-Elicited Inflammatory Biomarkers in Predicting Early Recurrence Within Stage II-III Colorectal Cancer Patients After Curable Resection. *J Inflamm Res* 2021; **14**: 115-129 [PMID: 33500648 DOI: 10.2147/JIR.S285129]

35 **Ren Y,** Peng M, Xiao JW, Zhong P. Effects of perioperative nutrition status indexes on postoperative oncology indexes and complications after radical resection of rectal cancer. *Biaozhi Mianyi Fenxi Yu Linchuang* 2020; **27**: 1135-1138 [DOI: 10.11748/bjmy.issn.1006-1703.2020.07.010]

36 **Wang F**, He W, Jiang C, Guo G, Ke B, Dai Q, Long J, Xia L. Prognostic value of inflammation-based scores in patients receiving radical resection for colorectal cancer. *BMC Cancer* 2018; **18**: 1102 [PMID: 30419863 DOI: 10.1186/s12885-018-4842-3]

37 **Muley T**, He Y, Rolny V, Wehnl B, Escherich A, Warth A, Stolp C, Schneider MA, Meister M, Herth FJ, Dayyani F. Potential for the blood-based biomarkers cytokeratin 19 fragment (CYFRA 21-1) and human epididymal protein 4 (HE4) to detect recurrence during monitoring after surgical resection of adenocarcinoma of the lung. *Lung Cancer* 2019; **130**: 194-200 [PMID: 30885344 DOI: 10.1016/j.lungcan.2019.02.017]

38 **DE Paz D**, Young CK, Chien HT, Tsao CK, Fok CC, Fan KH, Liao CT, Wang HM, Kang CJ, Chang JT, Huang SF. Prognostic Roles of SCC Antigen, CRP and CYFRA 21-1 in Oral Cavity Squamous Cell Carcinoma. *Anticancer Res* 2019; **39**: 2025-2033 [PMID: 30952746 DOI: 10.21873/anticanres.13313]

39 **Ajona D**, Remirez A, Sainz C, Bertolo C, Gonzalez A, Varo N, Lozano MD, Zulueta JJ, Mesa-Guzman M, C Martin A, Perez-Palacios R, Perez-Gracia JL, Massion PP, Montuenga LM, Pio R. A model based on the quantification of complement C4c, CYFRA 21-1 and CRP exhibits high specificity for the early diagnosis of lung cancer. *Transl Res* 2021; **233**: 77-91 [PMID: 33618009 DOI: 10.1016/j.trsl.2021.02.009]

40 **Riccardi C**, Napolitano E, Platella C, Musumeci D, Melone MAB, Montesarchio D. Anti-VEGF DNA-based aptamers in cancer therapeutics and diagnostics. *Med Res Rev* 2021; **41**: 464-506 [PMID: 33038031 DOI: 10.1002/med.21737]

41 **Staehler M**, Stöckle M, Christoph DC, Stenzl A, Potthoff K, Grimm MO, Klein D, Harde J, Brüning F, Goebell PJ, Augustin M, Roos F, Benz-Rüd I, Marschner N, Grünwald V. Everolimus after failure of one prior VEGF-targeted therapy in metastatic renal cell carcinoma: Final results of the MARC-2 trial. *Int J Cancer* 2021; **148**: 1685-1694 [PMID: 33070307 DOI: 10.1002/ijc.33349]

42 **Zhang N**, Wang Y, Liu H, Shen W. Extracellular vesicle encapsulated microRNA-320a inhibits endometrial cancer by suppression of the HIF1α/VEGFA axis. *Exp Cell Res* 2020; **394**: 112113 [PMID: 32473223 DOI: 10.1016/j.yexcr.2020.112113]

43 **Javath Hussain S**, Selvaraj J, Mohanty Mohapatra M, Rajendiran S. Clinical utility of pleural fluid YKL-40 as a marker of malignant pleural effusion. *Curr Probl Cancer* 2019; **43**: 354-362 [PMID: 30471784 DOI: 10.1016/j.currproblcancer.2018.10.001]

44 **Hermunen K**, Soveri LM, Boisen MK, Mustonen HK, Dehlendorff C, Haglund CH, Johansen JS, Osterlund P. Postoperative serum CA19-9, YKL-40, CRP and IL-6 in combination with CEA as prognostic markers for recurrence and survival in colorectal cancer. *Acta Oncol* 2020; **59**: 1416-1423 [PMID: 32790589 DOI: 10.1080/0284186X.2020.1800086]

45 **Ma Z**, Bao X, Gu J. Effects of laparoscopic radical gastrectomy and the influence on immune function and inflammatory factors. *Exp Ther Med* 2016; **12**: 983-986 [PMID: 27446308 DOI: 10.3892/etm.2016.3404]

**Footnotes**

**Institutional review board statement:** This study was reviewed and approved by the Ethics Committee of the Shenzhen University Hospital.

**Informed consent statement:** All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

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**Data sharing statement:** No additional data are available.

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**Table 1 Comparison of baseline data, *n* (%)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Criteria** | **Relapse group (*n* = 30)** | **Non-relapse group (*n* = 110)** | **Statistical values (*χ*2/*t*)** | ***P* value** |
| Gender |  |  |  |  |
| Male | 20 (66.67) | 60 (54.55) | 0.414 | 0.234 |
| Female | 10 (33.33) | 50 (45.45) |  |  |
| Age (yr) |  |  |  |  |
| ≥ 60 | 18 (60.00) | 70 (63.64) | 0.134 | 0.715 |
| < 60 | 12 (40.00) | 40 (36.36) |  |  |
| TNM stage |  |  |  |  |
| Ⅰ-Ⅱ | 15 (50.00) | 65 (59.09) | 0.796 | 0.372 |
| Ⅲ-Ⅳ | 15 (50.00) | 45 (40.91) |  |  |
| Differentiation |  |  |  |  |
| Low | 25 (83.33) | 23 (20.91) | 40.768 | < 0.001 |
| Medium/high | 5 (16.67) | 87 (79.09) |  |  |
| Tumor maximum diameter (cm) |  |  |  |  |
| ≥ 5 | 20 (66.67) | 65 (59.09) | 0.567 | 0.451 |
| > 5 | 10 (33.33) | 45 (40.91) |  |  |
| Lesion location |  |  |  |  |
| Rectum | 24 (80.00) | 25 (22.73) | 33.986 | < 0.001 |
| left/right hemicolon | 6 (20.00) | 85 (77.27) |  |  |
| Lymphatic vascular invasion |  |  |  |  |
| Present | 22 (73.33) | 20 (18.18) | 34.141 | < 0.001 |
| Absent | 8 (26.67) | 90 (81.82) |  |  |
| Postoperative adjuvant therapy |  |  |  |  |
| Not done or incomplete | 15 (50.00) | 60 (54.55) | *χ*2 = 0.196 | 0.658 |
| Complete | 15 (50.00) | 50 (45.45) |  |  |
| Pathological type |  |  |  |  |
| Glandular cancer | 10 (33.33) | 30 (27.27) | 0.951 | 0.622 |
| Mucinous adenocarcinoma | 8 (26.67) | 25 (22.73) |  |  |
| Indian cell carcinoma | 12 (40.00) | 55 (50.00) |  |  |
| Infiltration depth |  |  |  |  |
| T1 + T2 | 18 (60.00) | 70 (63.64) | 0.134 | 0.715 |
| T3 + T4 | 12 (40.00) | 40 (36.36) |  |  |
| Immune indicators |  |  |  |  |
| CD4+/CD8+ | 1.02 ± 0.26 | 1.48 ± 0.38 | 6.236 | < 0.001 |
| IgG (g/L) | 4.14 ± 0.60 | 5.72 ± 0.94 | 8.722 | < 0.001 |
| IgA (g/L) | 0.50 ± 0.08 | 0.69 ± 0.14 | 7.111 | < 0.001 |
| IgM (g/L) | 0.68 ± 0.22 | 0.95 ± 0.32 | 4.344 | < 0.001 |
| NLR | 4.18 ± 0.95 | 3.42 ± 0.55 | 5.636 | < 0.001 |
| AGR | 1.60 ± 0.40 | 1.98 ± 0.36 | 0.003 | < 0.001 |
| Tumor indicators |  |  |  |  |
| CYFRA21-1 (ng/mL) | 4.78 ± 0.52 | 3.25 ± 0.35 | 13.369 | < 0.001 |
| VEGF (ng/L) | 190.12 ± 50.25 | 140.12 ± 42.25 | 4.171 | < 0.001 |
| PNI | 40.75 ± 2.02 | 43.21 ± 2.18 | 4.534 | < 0.001 |
| YKL-40 (ng/mL) | 104.25 ± 20.52 | 78.95 ± 15.25 | 5.420 | < 0.001 |

TNM: Tumor node metastasis; Ig: Immunoglobulins; NLR: Neutrophils to lymphocytes ratio; AGR: Albumin-globulin ratio; CYFRA21-1: Cytokeratin 19 fragment antigen 21-1; VEGF: Vascular endothelial growth factor; PNI: Prognostic nutritional index; YKL-40: Inflammatory biomarker Chitinase-3-like protein 1.

**Table 2 Assignment of the main independent variables**

|  |  |  |
| --- | --- | --- |
| **Independent variable** | **Variable type** | **Assignment condition** |
| Degree of differentiation | Dichotomous | 1 = low differentiation, 0 = medium and high differentiation |
| Lesion location | Dichotomous | 1 = rectum, 0 = left and right hemicolon |
| Lymphatic vascular invasion | Dichotomous | 1 = presence, 0 = absence |
| CD4+/CD8+ | Continuous | - |
| IgG | Continuous | - |
| IgA | Continuous | - |
| IgM | Continuous | - |
| AGR | Continuous | - |
| NLR | Continuous | - |
| CYFRA21-1 | Continuous | - |
| VEGF | Continuous | - |
| PNI | Continuous | - |
| YKL-40 | Continuous | - |

TNM: Tumor node metastasis; Ig: Immunoglobulins; NLR: Neutrophils to lymphocytes ratio; AGR: Albumin-globulin ratio; CYFRA21-1: Cytokeratin 19 fragment antigen 21-1; VEGF: Vascular endothelial growth factor; PNI: Prognostic nutritional index; YKL-40: Inflammatory biomarker Chitinase-3-like protein 1.

**Table 3 Logistic regression analysis of variables affecting colorectal cancer relapse after laparoscopic radical resection**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Correlative factor** | **β** | **Standard error** | **Wald** | ***P* value** | **Odds ratio** | **95% confidence interval** |
| Degree of differentiation | 2.940 | 0.543 | 29.300 | < 0.001 | 18.913 | 6.523-54.835 |
| Lesion location | 2.610 | 0.510 | 26.192 | < 0.001 | 13.600 | 5.005-36.953 |
| Lymphatic vascular invasion | 2.516 | 0.481 | 27.330 | < 0.001 | 12.375 | 4.819-31.780 |
| CD4+/CD8+ | 3.794 | 0.810 | 21.936 | < 0.001 | 44.438 | 9.083-217.423 |
| IgG | 2.770 | 0.537 | 26.597 | < 0.001 | 15.955 | 5.568-45.712 |
| IgA | 3.438 | 0.721 | 14.386 | < 0.001 | 32.975 | 8.889-642.800 |
| IgM | 3.292 | 0.846 | 15.145 | < 0.001 | 26.883 | 5.123-141.065 |
| AGR | 2.728 | 0.675 | 16.332 | < 0.001 | 15.305 | 4.076-57.474 |
| NLR | 1.567 | 0.355 | 19.491 | < 0.001 | 4.792 | 2.390-9.608 |
| CYFRA21-1 | 8.672 | 2.245 | 14.921 | < 0.001 | 5838.165 | 71.654-475674.916 |
| VEGF | 0.024 | 0.005 | 19.752 | < 0.001 | 1.025 | 1.014-1.036 |
| PNI | 0.531 | 0.117 | 20.459 | < 0.001 | 1.700 | 1.351-2.140 |
| YKL-40 | 0.081 | 0.016 | 26.151 | < 0.001 | 1.084 | 1.051-1.119 |

TNM: Tumor node metastasis; Ig: Immunoglobulins; NLR: Neutrophils to lymphocytes ratio; AGR: Albumin-globulin ratio; CYFRA21-1: Cytokeratin 19 fragment antigen 21-1; VEGF: Vascular endothelial growth factor; PNI: Prognostic nutritional index; YKL-40: Inflammatory biomarker Chitinase-3-like protein 1.