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***Retrospective Study***

**Prognostic value of lymph node metastasis in patients with T1-stage colorectal cancer in multiplecenters in China**

Sun ZQ *et al*. Clinical predictors of survival after resection

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**Abstract**

***AIM***

To explore the features and prognostic value of lymph node metastasis in patients with T1-stage colorectal cancer (CRC).

***METHODS***

In all, 321 cases of T1-stage CRC were selected from 10132 total patients with CRC who received surgical therapy in 6 large-scale hospitals in China and were retrospectively analyzed. Univariate and multivariate analyses were performed to analyze the risk factors of lymphatic metastasis. A survival analysis was then performed to analyze the prognostic value of lymph node metastasis.

***RESULTS***

The occurrence rate of T1 stage was 3.17% (321/10132); of these patients, the lymph node metastasis rate was 8.41% (27/321), and the non-lymph node metastasis rate was 91.59% (294/321). A univariate analysis showed that preoperative serum CEA, preoperative serum CA199, preoperative serum CA724, vascular invasion and degree of differentiation were associated with lymph node metastasis in T1-stage CRC (all *P* < 0.05). A multivariate analysis indicated that preoperative serum CA724, vascular invasion and degree of differentiation were closely related to lymph node metastasis (all *P* < 0.05). A log-rank survival analysis showed that age, preoperative serum CEA, preoperative serum CA199, vascular invasion, degree of differentiation and lymph node metastasis (*χ*2 = 24.180, *P <* 0.001) were predictors of the 5-year overall survival (OS) (all *P <* 0.05). A COX regression analysis demonstrated that preoperative serum CA199 and lymph node metastasis (HR = 5.117; *P <* 0.05; 95%CI: 0.058-0.815) were independent prognostic indicators of the 5-year OS of patients with T1-stage CRC (both *P <* 0.05).

***CONCLUSION***

The morbidity of T1-stage CRC was 3.17% for all CRC cases. Preoperative serum CA724, vascular invasion and degree of differentiation were independent risk factors for lymph node metastasis. Lymph node metastasis was an independent prognostic factor for OS of patients with T1-stage CRC.

**Key words:**Colorectal cancer; Lymph node metastasis; T1 stage; Prognosis

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**Core tip:** The high morbidity of patients with colorectal cancer (CRC) is caused by the likelihood of recurrence and metastasis. This study focused on the features and prognostic value of lymph node metastasis in patients with T1-stage CRC. According to the statistical analysis, we found a very low morbidity in patients with T1-stage CRC. Moreover, our findings confirm that preoperative serum CA724, vascular invasion and degree of differentiation were independent risk factors for lymph node metastasis, which was demonstrated to be an independent prognostic factor for the 5-year overall survival of patients with T1-stage CRC.

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**INTRODUCTION**

Colorectal cancer (CRC) is one of the most common malignancies worldwide[[1](#_ENREF_1)]. With economic development and changes in dietary history, CRC has shown a steady increasing incidence and is now the fifth leading cause of cancer-related death in China[[2](#_ENREF_2),[3](#_ENREF_3)]. Due to adverse treatment-related side effects and the poor prognosis of this disease, which results from easy recurrence and metastasis, oncotherapy for CRC has posed a dilemma[[4](#_ENREF_4)]. In addition, lymph node metastasis is the main type of metastasis in advanced CRC. The occurrence rate of T1-stage CRC has been reported to be approximately 3.51％[[5](#_ENREF_5),[6](#_ENREF_6)]. When the tumor is completely removed, patients with T1-stage CRC generally have a good prognosis. However, because metastasis does not often occur in lymph nodes in T1-stage CRC, lymph node metastasis is often overlooked during the process of diagnosis and treatment. Nevertheless, lymph node metastasis is one of the most essential prognostic risk factors. Chock *et al* reported that the incidence of lymph node metastasis was 5.6% in T1-stage CRC[[7](#_ENREF_7)], whereas Gao *et al*[[8](#_ENREF_8)] demonstrated that the occurrence of lymph node metastasis was 5.5% in T1-stage CRC. Zheng reported that elevated serum levels of tumor markers indicate a high risk of cancer recurrence and poor survival, yet the relationship between tumor markers and lymph node metastasis in T1-stage CRC remains unknown[[9](#_ENREF_9)].Our study found that the incidence of lymph node metastasis was 8.41% in T1-stage CRC. What is the detailed prognostic value of lymph node metastasis in T1-stage CRC? This question has received increased attention in clinical practice, but as of now, no definite answer has been provided.

In this study, 321 cases of T1-stage CRC were selected from 10,132 total patients with CRC who received surgical therapy in 6 large-scale hospitals in China and were retrospectively analyzed. A statistical analysis was employed to analyze the features of lymph node metastasis and to evaluate its related risk factors and prognostic value in patients with T1-stage CRC. These data will provide a theoretical basis for more effective treatments for patients with T1-stage CRC.

**MATERIALS AND METHODS**

***Research subjects***

In all, 321 cases of T1-stage CRC were screened from 10132 total patients with CRC who received surgical therapy in 6 large-scale hospitals in China (the First Affiliated Hospital of Zhengzhou University, the Affiliated Tumor Hospital of Xinjiang Medical University, Sun Yat-sen Memorial Hospital of Sun Yat-sen University, the First Affiliated Hospital of Xinjiang Medical University, the Third Xiangya Hospital of Central South University and the Affiliated Hospital of Traditional Chinese Medicine of Xinjiang Medical University) from June 2001 to June 2011. These cases consisted of 172 males and 149 females. The mean patient age was 61.37 ± 13.41 years. Prior to participation, a diagnosis of CRC was confirmed by histopathology for all patients. The tumor-node-metastasis (TNM) stage was determined according to the American Joint Committee on Cancer/International Union Against Cancer TNM staging system for colorectal cancer (2010, 7th edition). No patient received preoperative chemotherapy, radiotherapy or immunotherapy. The following exclusion criteria were used: cases with incomplete clinical data, those that were inappropriate for statistical analysis, cases that were combined with other malignant tumors and cases that were treated by endoscopic resection.

All tissues were approved by the Ethics Review Committees of the First Affiliated Hospital, Zhengzhou university before they were used for research purposes. All the patients who provided clinical material signed an informed consent.

***Patient follow-up***
After surgery, the patients were assessed once a month for the first 6 mo, once every 3 mo from 6 mo to 2 years, once every 6 mo from 2 years to 5 years, and finally, once a year after 5 years. Follow-ups were conducted either by outpatient or inpatient review or by telephone. Forty patients did not participate in the follow-up analyses because they did not communicate with the physicians after surgery. In addition, 16 patients developed dysthymia and were unable to cooperate for the remainder of the study, 2 patients committed suicide, and 21 patients did not participate in the follow-up for unknown reasons. Therefore, the total follow-up rate in the study was 75.39%.

***Chemotherapy and radical surgery***

According to the NCCN Guidelines, colorectal cancer with lymph node metastasis is defined as stage III disease, but postoperative chemotherapy should be performed in patients with colorectal cancer with lymph node metastasis, regardless of T stage. FOLFOX6 was used as the first-line adjuvant or neoadjuvant therapy regimen for CRC patients with stage III disease. CapeOX was used as either a first- or second-line adjuvant or neoadjuvant chemotherapy regimen for patients with stage III CRC, those with drug resistance or those with postoperative recurrence. FOLFIRI was used as the chemotherapy regimen for CRC patients with postoperative recurrence, metastasis or drug resistance.

Radical surgery was performed according to complete mesocolic excision for patients with colon cancer and total mesorectal excision for patients with rectal cancer. All the patients received scheduled surgery (*i.e.*, not emergency surgery). More than 12 lymph nodes were removed during surgery.

***Statistical analysis***

All statistical analyses were performed with SPSS version 18.0. Graphs were constructed with the GraphPad Prism software. The univariate analysis was performed using the *χ*2 test to analyze lymph node metastasis and clinicopathological parameters. Kaplan-Meier survival curves and the log-rank test were used to compare the group with lymph node metastasis and the group without lymph node metastasis. The multivariate survival analysis was performed using the Cox regression model to determine the relative risk (RR) and 95% confidence intervals (CIs). Statistical significance was defined as *P <* 0.05.

**RESULTS**

***Univariate analysis of the correlation between lymph node metastasis and the clinicopathological parameters of patients with T1-stage colorectal cancer***

In all, 321 patients with T1-stage CRC were divided into the lymph node metastasis group (27 cases) and the non-lymph node metastasis group (294 cases). The occurrence rate of lymph node metastasis was 8.41%. The univariate analysis showed that lymph node metastasis was associated with preoperative CEA, preoperative CA199, preoperative CA724, vascular invasion and degree of differentiation (*P* < 0.05 for all parameters; Table 1). Lymph node metastasis was not associated with gender, age, smoking status, absolute granulocyte count, the D-dimer value, preoperative hemoglobin level, tumor location, tumor size, general tumor type or tumor tissue type (all *P* > 0.05).

***Multivariate analysis of the correlation between lymph node metastasis and the clinicopathological parameters of patients with T1-stage colorectal cancer***

The multivariate analysis showed that lymph node metastasis was associated with preoperative CA724, vascular invasion and degree of differentiation (*P* < 0.05 for all parameters; Table 2). Lymph node metastasis was not associated with gender, age, smoking status, preoperative CEA, preoperative CA199, absolute granulocyte count, the D-dimer value, preoperative hemoglobin level, tumor location, tumor size, general tumor typeor tumor tissue type (all *P* > 0.05).

***Univariate analysis of the correlation between the clinicopathological parameters and the 5-year overall survival (OS)***

As shown in Table 3, the univariate survival analysis demonstrated that age, preoperative CEA, preoperative CA199, vascular invasion, degree of differentiation and lymph node metastasis (*χ*2 = 24.180, *P* < 0.001) were associated with the 5-year OS (all *P* < 0.05). Gender, smoking status, preoperative CA724, absolute granulocyte count, the D-dimer value, preoperative hemoglobin level, tumor location, tumor size, general tumor type and tissue type were not associated with the 5-year OS (all *P* > 0.05). The Kaplan-Meier curve showed that the 5-year OS of patients in the lymph node metastasis group was lower than that of patients in the non-lymph node metastasis group for patients with T1 stage CRC (Figure 1).

***Cox regression analysis of the correlation between the clinicopathological parameters and the 5-year overall survival***

The multivariate survival analysis showed that the preoperative CA199 level and lymph node metastasis (RR: 5.117, *P* < 0.05, 95%CI: 0.058-0.815) were associated with the 5-year OS (both *P* < 0.05, Table 4). Moreover, gender, age, smoking status, preoperative CEA level, preoperative CA724 level, absolute granulocyte count, D-dimer value, preoperative hemoglobin level, tumor location, tumor size, general tumor type, tissue type, vascular invasion and degree of differentiation were not associated with the 5-year OS (all *P* > 0.05).

**DISCUSSION**

CRC is the third most common cancer and the third leading cause of cancer-related death worldwide[[10](#_ENREF_10)]. The 5-year overall survival (OS) rate of patients with colon cancer is 64.9% and is 66.5% for those with rectal cancer. T1 stage is generally early-stage CRC and has a good prognosis, but if lymph node metastasis occurs, the prognosis is usually poor. Therefore, lymph node metastasis has garnered increased attention in recent years. According to previous studies, the proportion of lymph node metastasis in patients with T1-stage CRC was reported to be 5.6% and 5.5%, which is relatively low[[11](#_ENREF_11),[12](#_ENREF_12)]. In this study, the proportion of lymph node metastasis in patients with T1-stage CRC was 8.41%. The factors that affect lymph node metastasis of T1 colorectal cancer are multifaceted and are also interrelated with each other. Lymph node metastasis is the main basis for clinic pathological staging of CRC for the prediction of the prognosis of patients and for the determination of the appropriate regimen of postoperative adjuvant therapy. Therefore, it is necessary to study the risk factors that are correlated with lymph node metastasis of CRC, as well as their influence on the prognosis of T1-stage CRC<Bosch, 2013 #12;Frattini, 2004 #13;Kawachi, 2015 #14}<Bosch, 2013 #15;Frattini, 2004 #16;Kawachi, 2015 #17}[[13-15](#_ENREF_13)].

Some studies have reported that tumor markers had certain clinical value in the detection of postoperative recurrence and metastasis of colorectal cancer as well as in the judgment of prognosis[[16-18](#_ENREF_16)]. In our study, a univariate analysis showed that preoperative CEA, preoperative CA199 and preoperative CA724 were associated with lymph node metastasis, while amultivariate analysis showed that preoperative CA724was an independent risk factor for lymph node metastasis. CA724 has been reported to be a marker for gastrointestinal and ovarian cancer and was shown to be a better indicator for the diagnosis of gastric cancer compared with the levels of CA199 and CEA. Our study found that the CA724 level was a good indicatorof lymph node metastasis, which has not been previously reported in T1-stage CRC.

Previous studies have reported that the degree of differentiation of tumor cells of rectal cancer was closely related to lymph node metastasis[[19](#_ENREF_19), [20](#_ENREF_20)]. Our study demonstrated that the degree of differentiation was an independent risk factor for lymph node metastasis of T1-stage CRC. The reason for this may be that when the degree of differentiation is relatively high, the tumor cells are still in a more primitive stage, and the possibility that they may invade the lymph nodes is much lower. Poorly differentiated or undifferentiated carcinomas have a strong ability to invade the surrounding tissues, especially the lymphatic vessels. Derwinger *et al*[[21](#_ENREF_21)] showed that the degree of differentiation of colorectal cancer was significantly associated with lymph node metastasis. In our study, the rate of lymph node metastasis in patients with highly/moderately and poorly differentiated T1-stage CRC was 7.5% and 28.6%, respectively. In addition, a univariate survival analysis showed that the degree of tumor differentiation was a prognostic factor in patients with T1-stage CRC.

Most studies have reported that vascular invasion was an essential risk factor for lymph node metastasis in CRC[[22](#_ENREF_22), [23](#_ENREF_23)]. Similarly, our study verified that vascular invasion was a positive independent risk factor for lymph node metastasis in T1-stage CRC[[23](#_ENREF_23)]. A univariate survival analysis showed that vascular invasion was associated with the 5-year OS of patients with T1-stage CRC. However, according to the multivariate analysis, no correlation was observed between lymph node metastasis and the 5-year OS in T1-stage CRC, which may have been due to the limited case number.

In clinical practice, lymph node metastasis is a significant indicator of clinical evaluation of rectal cancer recurrence and the survival of patients, and is also the primary method used to determine the therapeutic schedule of patients with rectal cancer[[24-27](#_ENREF_24)]. When the tumor is confined to the mucosal layer, no lymph node metastasis occurs because the layer has no lymphatic vessels. When lymphatic vessels are distributed in the submucosa, lymph node metastasis is likely to occur when the tumor invades the submucosa. When the tumor invades the deep intestinal wall, the lymph node metastasis rate will increase significantly[[28](#_ENREF_28),[29](#_ENREF_29)]. In our study, the lymph node metastasis rate of this group of patients with T1-stage CRC was 8.41%, which is mostly consistent with previous reports[[7](#_ENREF_7),[8](#_ENREF_8)]. In this study, the survival analysis of patients with lymph node metastasis of T1-stage CRC showed that patients without lymph node metastasis had a significantly higher 5-year survival rate than those with lymph node metastasis. Furthermore, our study verified that lymph node metastasis was an independent prognostic factor in patients with T1-stage CRC, which was also consistent with previous reports[[30](#_ENREF_30)]. With the development of several new technologies, such as endoscopic mucosal resection, endoscopic submucosal dissection and transanal endoscopic microsurgery, studies on local resection for the treatment of early rectal cancer have gradually increased<De, 2016 #53;Backes, 2016 #54}[[31-33](#_ENREF_31)]. The biggest drawback of local resection is its failure to dissect the lymph nodes in relevant drainage areas. Left metastatic lymph nodes are an important reason for postoperative recurrence, which is also the reason why caution should be taken if local resection is selected[[34-36](#_ENREF_34)]. Consequently, if it is not clear whether preoperative lymph node metastasis is present in T1-stage CRC, radical surgery may be the most suitable choice. Moreover, the intraoperative dissection of lymph nodes should be standardized.

In conclusion, through statistical analysis, we verified that the occurrence rate of T1 stage out of all the cases of CRC was 3.17%; The lymph node metastasis rate was 8.41%, and the non-lymph node metastasis rate was 91.59%. The preoperative serum CA724 level, vascular invasion and degree of differentiation were independent risk factors for lymph node metastasis in patients with T1-stage CRC. Lymph node metastasis was an essential prognostic factor in patients with T1-stage CRC. An accurate assessment of the lymph node metastasis status is essential for decision-making regarding effective intraoperative therapeutic strategies for T1-stage CRC.

**ARTICLE HIGHLIGHTS**

***Research background***

The background, present status and significance of the study should be described in detail. Lymph node metastasis is the primary type of metastasis seen in advanced colorectal cancer (CRC). The occurrence rate of T1-stage CRC has been reported to be approximately 3.51%[[5](#_ENREF_5),[6](#_ENREF_6)].When the tumor is completely removed, patients with T1-stage CRC generally have a good prognosis. However, since lymph node metastasis rarely occurs in T1-stage CRC, lymph node metastasis is often overlooked during the process of diagnosis and treatment. Nevertheless, lymph node metastasis is one of the most essential prognostic factors. In this study, we explored the features and prognostic value of lymph node metastasis, which will provide a theoretical basis for more effective treatments for patients with T1-stage CRC.

***Research motivation***

The main topic of this study is the exploration of whether lymph node metastasis in patients with T1-stage colorectal cancer is valuable for patient survival in multiplecenters in China. The key is to find the risk factors for lymph node metastasis of CRC. The significance is the confirmation of the prognostic value of lymph node metastasis in patients with T1-stage CRC.

***Research objectives***

Studies have reported that lymph node metastasis is an essential prognostic factor for patients with colorectal cancer (CRC) and that lymph node metastasis seldom occurs in T1-stage CRC. However, the definitive prognostic value of lymph node metastasis of T1-stage CRC remains elusive. The main objective was to explore the features and prognostic value of lymph node metastasis in patients with T1-stage CRC.

***Research methods***

The current research was a case-control study.

***Research results***

The occurrence rate of T1 stage CRC was 3.17％ (321/10,132); of these cases, the lymph node metastasis rate was 8.41% (27/321), and the non-lymph node metastasis rate was 91.59% (294/321). The univariate analysis showed that preoperative serum CEA, preoperative serum CA199, preoperative serum CA724, vascular invasion and degree of differentiation were associated with lymph node metastasis in T1-stage CRC (all *P* < 0.05). A multivariate analysis indicated that preoperative serum CA724, vascular invasion and degree of differentiation were closely related to lymph node metastasis (all *P* < 0.05). The log-rank survival analysis showed that age, preoperative serum CEA, preoperative serum CA199, vascular invasion, degree of differentiationand lymph node metastasis (*χ*2 = 24.180, *P* < 0.001) were prognostic factors for the 5-year overall survival (OS) (all *P* < 0.05). A COX regression analysis demonstrated that preoperative serum CA199 and lymph node metastasis (HR = 5.117; *P*, 0.024; 95%CI: 0.058-0.815) were independent prognostic factors for the 5-year OS of patients with T1-stage CRC (both *P* < 0.05).

***Research conclusions***

The morbidity of T1-stage CRC was 3.17% out of all cases of CRC. Preoperative serum CA724, vascular invasion and degree of differentiation were independent risk factors for lymph node metastasis of T1-stage CRC. Lymph node metastasis was an independent prognostic factor of OS in patients with T1-stage CRC.

***Research perspectives***

T1-stage CRC is generally regarded as the early stage, easily leading to the neglect of metastasis, especially lymph node metastasis. However, a little part of these cases (8.41%) combined with lymph node metastasis and their prognosis will be much poorer than none ones. We also analysed high risk factors of lymph node metastasis of T1-stage CRC patients. Therefore, we must pay enough attention to lymph node metastasis status of T1-stage CRC patients to guide clinic therapy. Future researches should be focused on greater verifying study to expand further clinical samples. In addition, the mechanism study of lymph node metastasis in T1-stage CRC patients should be further explored. Clinical multi-center prospective cohort study will be needed to further validate the conclusion. Moreover, high-throughput screening technology of transcriptome or proteome will be necessary for analysing the regulators of lymph node metastasis in T1-stage CRC patients in the future.

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**Figure 1 Kaplan-Meier curve of lymph node metastasis in colorectal cancer patients with T1 stage.** Overall survival of T1-stage CRC patients with non-lymph node metastasis (blue) and lymph node metastasis (red) pre-operative CEA levels compared to total (gray) CRC patients based on Kaplan-Meier curves and log-rank test. As shown, patients with low pre-CEA levels survived longer than those with high pre-CEA levels (log-rank test, *P <* 0.001).

**Table 1 Univariate analysis of correlation between lymph node metastasis with clinicopathological parameters of T1-stage colorectal cancer patients**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Clinicopathologic characteristics** | ***n*** | **Lymph node metastasis** | **χ2** | ***P* value** |
| **Yes** | **No** |
| Gender |  |  |  | 1.955 | 0.162 |
| Male 1138 | 172 | 11 | 161 |  |  |
| Female  | 149 | 16 | 133 |  |  |
| Age |  |  |  | 0.436 | 0.509 |
| ≥ 60 | 174 | 13 | 161 |  |  |
| < 60 | 147 | 14 | 133 |  |  |
| Smoking |  |  |  | 0.766 | 0.382 |
| No | 279 | 22 | 257 |  |  |
| Yes | 42 | 5 | 37 |  |  |
| Preoperative CEA (ng/mL) |  |  |  | 5.994 | 0.014 |
| < 5 | 284 | 20 | 264 |  |  |
| ≥ 5 | 37 | 7 | 30 |  |  |
| Preoperative CA199 (ng/mL) |  |  |  | 5.015 | 0.025 |
| < 9 | 173 | 9 | 164 |  |  |
| ≥ 9 | 148 | 18 | 130 |  |  |
| Preoperative CA724 (ng/mL) |  |  |  | 12.275 | 0.000 |
| < 2 | 163 | 5 | 158 |  |  |
| ≥ 2 | 158 | 22 | 136 |  |  |
| Granulocyte absolute value |  |  |  | 0.771 | 0.380 |
| < 2.2 | 32 | 4 | 28 |  |  |
| ≥ 2.2 | 289 | 23 | 266 |  |  |
| D-dimer |  |  |  | 2.227 | 0.136 |
| < 0.21 | 158 | 17 | 141 |  |  |
| ≥ 0.21 | 163 | 10 | 153 |  |  |
| Preoperative hemoglobin |  |  |  | 1.504 | 0.220 |
| < 132 | 154 | 16 | 138 |  |  |
| ≥ 132 | 167 | 11 | 156 |  |  |
| Vascular invasion |  |  |  | 18.421 | 0.000 |
| No | 313 | 23 | 290 |  |  |
| Yes | 8 | 4 | 4 |  |  |
| Tumor location |  |  |  | 1.184 | 0.277 |
| Rectum | 170 | 17 | 153 |  |  |
| Colon | 151 | 10 | 141 |  |  |
| Tumor size (cm) |  |  |  | 1.526 | 0.217 |
| < 3 | 190 | 19 | 171 |  |  |
| ≥ 3 | 131 | 8 | 123 |  |  |
| Differentiated degree |  |  |  | 7.723 | 0.005 |
| High/Moderate | 307 | 23 | 284 |  |  |
| Low | 14 | 4 | 10 |  |  |
| Tumor general type |  |  |  | 0.219 | 0.640 |
| Ulcer | 238 | 19 | 219 |  |  |
| Non-ulcer | 83 | 8 | 75 |  |  |
| Tumor tissue type |  |  |  | 2.293 | 0.130 |
| Non-adenocarcinoma | 9 | 2 | 7 |  |  |
| Adenocarcinoma | 312 | 25 | 287 |  |  |

**Table 2 Multivariate analysis of the correlation between lymph node metastasis with clinicopathological parameters of T1-stage colorectal cancer patients**

|  |  |  |  |
| --- | --- | --- | --- |
| **Clinicopathologic characteristics** | **HR** | ***P* value** | **95%CI** |
| **Lower bound** | **Upper bound** |
| GenderMales *vs* Females | 1.636 | 0.201 | 0.698 | 5.518 |
| Age< 60 *vs* ≥ 60 | 0.063 | 0.801 | 0.357 | 2.218 |
| SmokingNo *vs* Yes  | 0.880 | 0.348 | 0.529 | 6.077 |
| Preoperative CEA< 5 *vs* ≥ 5 | 1.188 | 0.276 | 0.603 | 5.904 |
| Preoperative CA199< 9 *vs* ≥ 9  | 2.765 | 0.096 | 0.869 | 5.541 |
| Preoperative CA724< 2 *vs* ≥ 2 | 5.461 | 0.019 | 1.232 | 10.783 |
| Granulocyte absolute value< 2.2 *vs* ≥ 2.2  | 0.004 | 0.951 | 0.285 | 3.797 |
| D-dimer< 0.21 *vs* ≥ 0.21  | 1.398 | 0.237 | 0.651 | 5.652 |
| Preoperative hemoglobin< 132 *vs* ≥ 132  | 0.437 | 0.508 | 0.249 | 1.992 |
| Location size (cm)< 3 cm *vs* ≥ 3 cm  | 2.090 | 0.148 | 0.185 | 1.290 |
| Vascular invasionNo *vs* Yes  | 8.461 | 0.004 | 2.358 | 81.596 |
| Tumor locationRectum *vs* Colon | 0.264 | 0.607 | 0.485 | 3.444 |
| Differentiated degreeHigh/Media *vs* Low Tumor general type Non-ulcer *vs* UlcerTissue typeNon-adenocarcinoma*vs* Adenocarcinoma | 4.2040.6860.897 | 0.0400.4070.344 | 1.0570.5560.043 | 11.9564.2392.989 |

**Table 3** **Univariate analysis of the correlation between clinicopathological parameters and 5-year overall survival**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Clinicopathologic characteristics** | ***n*** | **OS%** | **χ2** | ***P* value** |
| Gender |  |  | 1.225 | 0.268 |
| Male 1138 | 172 | 90.9% |  |  |
| Female  | 149 | 90.1% |  |  |
| Age |  |  | 6.103 | 0.013 |
| ≥ 60 | 174 | 86.5% |  |  |
| < 60 | 147 | 95.5% |  |  |
| Smoking |  |  | 0.429 | 0.513 |
| No | 279 | 91.0% |  |  |
| Yes | 42 | 87.5% |  |  |
| Preoperative CEA |  |  | 13.594 | 0.000 |
| < 5 | 284 | 92.7% |  |  |
| ≥ 5 | 37 | 78.4% |  |  |
| Preoperative CA199 |  |  | 7.229 | 0.007 |
| < 9 | 173 | 94.7% |  |  |
| ≥ 9 | 148 | 85.7% |  |  |
| Preoperative CA724  |  |  | 0.012 | 0.912 |
| < 2 | 163 | 87.4% |  |  |
| ≥2 | 158 | 93.2% |  |  |
| Granulocyte absolute value |  |  | 1.613 | 0.204 |
| < 2.2 | 32 | 85.0% |  |  |
| ≥ 2.2 | 289 | 91.0% |  |  |
| D-dimer |  |  | 0.001 | 0.979 |
| < 0.21 | 158 | 88.8% |  |  |
| ≥ 0.21 | 163 | 91.9% |  |  |
| Preoperative hemoglobin |  |  | 0.907 | 0.341 |
| < 132 | 154 | 89.1% |  |  |
|  ≥ 132  | 167 | 91.7% |  |  |
| Vascular invasion |  |  | 12.955 | 0.000 |
| No | 313 | 91.6% |  |  |
| Yes | 8 | 40.0% |  |  |
| Tumor location |  |  | 1.121 | 0.290 |
| Rectum | 170 | 89.8% |  |  |
| Colon | 151 | 91.9% |  |  |
| Tumor size |  |  | 0.210 | 0.647 |
| < 3 | 190 | 90.0% |  |  |
| ≥ 3 | 131 | 91.2% |  |  |
| Differentiated degree |  |  | 6.825 | 0.009 |
| High/Media | 307 | 91.3% |  |  |
| Low | 14 | 78.6% |  |  |
| Tumor general type |  |  | 3.149 | 0.207 |
| Protrude | 228 | 91.8% |  |  |
| Infiltration | 10 | 100.0% |  |  |
| Ulcer | 83 | 86.2% |  |  |
| Tumor tissue type |  |  | 1.828 | 0.176 |
| Non-adenocarcinoma | 9 | 75.0% |  |  |
| Adenocarcinoma | 312 | 91.3% |  |  |
| Lymph node metastasisNoYes | 29427 | 93.2%65.2% | 24.180 | .000 |

**Table 4** **COX regress analysis of the correlation between clinicopathological parameters and 5-year overall survival**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **RR** | ***P* value** | **95%CI** |
| **Lower bound** | **Upper bound** |
| GenderMale *vs* Female | 1.784 | 0.182 | 0.695 | 6.816 |
| Age< 60 *vs* ≥ 60 | 3.805 | 0.051 | 0.995 | 9.034 |
| Smoking No *vs* Yes | 0.590 | 0.442 | 0.413 | 7.565 |
| Preoperative CEA< 5 *vs* ≥ 5 | 1.121 | 0.290 | 0.580 | 6.206 |
| Preoperative CA199< 9 *vs* ≥ 9  | 6.452 | 0.011 | 1.411 | 14.481 |
| Preoperative CA724< 2 *vs* ≥ 2 | 0.935 | 0.333 | 0.201 | 1.725 |
| Granulocyte absolute value< 2.2 *vs* ≥ 2.2 | 0.040 | 0.841 | 0.171 | 8.761 |
| D-dimer< 0.21 *vs* ≥ 0.21 | 2.373 | 0.123 | 0.777 | 8.217 |
| Preoperative hemoglobin(< 132 *vs* ≥ 132) | 0.577 | 0.448 | 0.198 | 2.042 |
| Tumor size< 3 cm *vs* ≥ 3 cm | 0.581 | 0.446 | 0.261 | 21.193 |
| Vascular invasionNo *vs* Yes | 0.343 | 0.558 | 0.468 | 4.076 |
| Tumor locationRectum *vs* Colon | 0.210 | 0.647 | 0.310 | 2.068 |
| Differentiated degree High/Media *vs* Low | 1.031 | 0.310 | 0.435 | 13.792  |
| Tumor general typeUlcer *vs* Non-ulcer | 2.338 | 0.126 |  0.811 |  5.471 |
| Tumor tissue typeNon-adenocarcinoma *vs* Adenocarcinoma  | 0.783 | 0.376 | 0.068 | 2.755 |
| Lymph node metastasisNo *vs* Yes | 5.328 | 0.021 | 1.264 | 17.592 |