Prognostic value of lymph node metastasis in patients with T1-stage colorectal cancer from multiple centers in China

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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 patients with CRC who received surgical therapy in six large-scale hospitals in China and were retrospectively analyzed. Univariate and multivariate analyses were performed to analyze the risk factors for 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). Univariate analysis showed that preoperative serum CEA, preoperative serum CA724, vascular invasion, and degree of differentiation were associated with lymph node metastasis in T1-stage CRC (P < 0.05 for all). Multivariate analysis indicated that preoperative serum CA724, vascular invasion, and degree of differentiation were closely related to lymph node metastasis (P < 0.05 for all). Log-rank survival analysis showed that age, preoperative serum CEA, preoperative serum CA199, vascular invasion, degree of differentiation, and lymph node metastasis were predictors of 5-year overall survival (OS) (P < 0.05 for all). COX regression analysis demonstrated that preoperative serum CA199 and lymph node metastasis (HR = 5.117; 95% CI: 0.058-0.815) were independent prognostic indicators of 5-year OS in patients with T1-stage CRC (P < 0.05 for both).

Conclusion
The morbidity of T1-stage CRC was 3.17% for all CRC cases. Preoperative serum CA724, vascular invasion, and degree of differentiation are independent risk factors for lymph node metastasis. Lymph node metastasis is an independent prognostic factor for OS in 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 5-year OS in patients with T1-stage CRC.

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Introduction
Colorectal cancer (CRC) is one of the most common malignancies worldwide\[1\]. With economic development and changes in dietary history, CRC has shown a steadily increasing incidence and is now the fifth leading cause of cancer-related death in China\[2,3\]. 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\[4\]. 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\%\[5,6\]. 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\[7\] reported that the incidence of lymph node metastasis was 5.6\% in T1-stage CRC, whereas Gao et al\[8\] demonstrated that the occurrence of lymph node metastasis was 5.5% in T1-stage CRC. Zheng et al\[9\] reported that elevated serum levels of tumor markers indicated 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. 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 10132 patients with CRC who received surgical therapy in six large-scale hospitals in China and were retrospectively analyzed. A statistical analysis was performed to analyze the features of lymph node metastasis and to evaluate its risk factors and prognostic value in patients with T1-stage CRC. These data will provide a theoretical basis for more effective treatment of patients with T1-stage CRC.

MATERIALS AND METHODS

Research subjects
In all, 321 cases of T1-stage CRC were screened from 10132 patients with CRC who received surgical therapy in six 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 who were inappropriate for statistical analysis, cases who had other malignant tumors, and cases who were treated by endoscopic resection.

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

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, two 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, CRC with lymph node metastasis is defined as stage III disease, but postoperative chemotherapy should be performed in CRC patients 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 GraphPad Prism software. Univariate analysis was performed using the $\chi^2$ test to analyze the association between 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% CI. Statistical significance was defined as $P < 0.05$.

RESULTS

Univariate analysis of correlation between lymph node metastasis and clinicopathological parameters of patients with T1-stage CRC
In all, 321 patients with T1-stage CRC were divided into a lymph node metastasis group (27 cases) and a 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, D-dimer value, preoperative hemoglobin level, tumor location, tumor size, general tumor type, or tumor tissue type ($P > 0.05$ for all).

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

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, D-dimer value, preoperative hemoglobin level, tumor location, tumor size, general tumor type, or tumor tissue type ($P > 0.05$ for all).

**Univariate analysis of correlation between clinicopathological parameters and 5-year 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 ($\chi^2 = 24.180, P < 0.001$) were associated with 5-year OS ($P < 0.05$ for all). Gender, smoking status, preoperative CA724, absolute granulocyte count, D-dimer value, preoperative hemoglobin level, tumor location, tumor size, general tumor type, and tissue type were not associated with 5-year OS ($P > 0.05$ for all). The Kaplan-Meier curve showed that the 5-year OS of patients in the lymph node metastasis yes group was significantly lower than that in the lymph node metastasis no group ($P < 0.001$).

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

| Clinicopathological characteristic          | $n$ | Lymph node metastasis | $\chi^2$ | $P$ value |
|----------------------------------------------|-----|-----------------------|----------|-----------|
|                                              |     | Yes       | No       |           |
| Gender                                       |     |           |          |           |
| Male                                         | 172 | 11        | 161      | 1.955     | 0.162     |
| Female                                       | 149 | 16        | 133      | 0.436     | 0.509     |
| Age (yr)                                     |     | 174       | 161      |           |           |
| $\geq 60$                                    | 174 | 13        |          | 0.014     | 0.916     |
| $< 60$                                       | 147 | 14        | 133      | 0.424     | 0.514     |
| Smoking                                      |     |           |          |           |           |
| No                                           | 279 | 22        | 257      | 0.766     | 0.382     |
| Yes                                          | 42  | 5         | 37       |           |           |
| Preoperative CEA (ng/mL)                     |     |           |          |           |           |
| $< 5$                                        | 284 | 20        | 264      | 5.994     | 0.014     |
| $\geq 5$                                     | 37  | 7         | 30       |           |           |
| Preoperative CA199 (ng/mL)                   |     |           |          |           |           |
| $< 9$                                        | 173 | 9         | 164      | 5.015     | 0.025     |
| $\geq 9$                                     | 148 | 18        | 130      |           |           |
| Preoperative CA724 (ng/mL)                   |     |           |          |           |           |
| $< 2$                                        | 163 | 5         | 158      | 12.275    | 0.000     |
| $\geq 2$                                     | 158 | 22        | 136      |           |           |
| Granulocyte absolute value                   |     |           |          |           |           |
| $< 2.2$                                      | 32  | 4         | 28       | 0.771     | 0.380     |
| $\geq 2.2$                                   | 289 | 23        | 266      |           |           |
| D-dimer                                      |     |           |          |           |           |
| $< 0.21$                                     | 158 | 17        | 141      | 2.227     | 0.136     |
| $\geq 0.21$                                  | 163 | 10        | 153      |           |           |
| Preoperative hemoglobin                      |     |           |          |           |           |
| $< 132$                                      | 154 | 16        | 138      | 1.504     | 0.220     |
| $\geq 132$                                   | 167 | 11        | 156      |           |           |
| Vascular invasion                            |     |           |          |           |           |
| No                                           | 313 | 23        | 290      | 18.421    | 0.000     |
| Yes                                          | 8   | 4         | 4        |           |           |
| Tumor location                               |     |           |          |           |           |
| Rectum                                       | 170 | 17        | 153      | 1.184     | 0.277     |
| Colon                                        | 151 | 10        | 141      |           |           |
| Tumor size (cm)                              |     |           |          |           |           |
| $< 3$                                        | 190 | 19        | 171      | 1.526     | 0.217     |
| $\geq 3$                                     | 131 | 8         | 123      |           |           |
| Differentiation degree                       |     |           |          |           |           |
| High/moderate                                | 307 | 23        | 284      | 7.723     | 0.005     |
| Low                                          | 14  | 4         | 10       | 0.219     | 0.640     |
| Tumor general type                           |     |           |          |           |           |
| Ulcer                                        | 238 | 19        | 219      |           |           |
| Non-ulcer                                    | 83  | 8         | 75       | 2.293     | 0.130     |
| Tumor tissue type                            |     |           |          |           |           |
| Non-adenocarcinoma                           | 9   | 2         | 7        |           |           |
| Adenocarcinoma                               | 312 | 25        | 287      |           |           |
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closely related to lymph node metastasis\textsuperscript{[19,20]}. 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 \textit{et al}\textsuperscript{[21]} showed that the degree of differentiation of CRC was significantly associated with lymph node metastasis. In our study, the rates of lymph node metastasis in patients with highly/moderately and poorly differentiated T1-stage CRC were 7.5\% and 28.6\%, respectively. In addition, 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\textsuperscript{[22,23]}. Similarly, our study verified that vascular invasion was a positive independent risk factor for lymph node metastasis in T1-stage CRC\textsuperscript{[23]}. 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 in patients with rectal cancer. 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. 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. In this study, the survival analysis of T1-stage CRC patients 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 is also consistent with previous reports. 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. 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. 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%. 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 lymph node metastasis status is essential for decision-making regarding effective intraoperative therapeutic strategies for T1-stage CRC.

### Table 4 COX regression analysis of correlation between clinicopathological parameters and 5-year overall survival

| Parameter                                | RR   | P value | 95%CI Lower Bound | 95%CI Upper Bound |
|------------------------------------------|------|---------|-------------------|-------------------|
| Gender, Male vs Female                   | 1.784| 0.182   | 0.695             | 6.816             |
| Age (yr), < 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, (ng/mL), < 5 vs ≥ 5   | 1.121| 0.290   | 0.580             | 2.606             |
| Preoperative CA199, (ng/mL), < 9 vs ≥ 9 | 6.452| 0.011   | 1.411             | 14.481            |
| Preoperative CA724, (ng/mL), < 2 vs ≥ 2 | 0.935| 0.333   | 0.201             | 1.725             |
| Granulocyte absolute value, < 2.2 vs ≥ 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 (cm), < 3 vs ≥ 3             | 0.581| 0.446   | 0.261             | 21.193            |
| Vascular invasion, No vs Yes             | 0.343| 0.558   | 0.468             | 4.076             |
| Tumor location, Rectum vs Colon         | 0.210| 0.647   | 0.510             | 2.068             |
| Differentiation degree, High/moderate vs Low | 1.031| 0.310   | 0.435             | 13.792            |
| Tumor general type, Ulcer vs Non-ulcer  | 2.338| 0.126   | 0.811             | 5.471             |
| Tumor tissue type, Non-adenocarcinoma vs Adenocarcinoma | 0.783| 0.376   | 0.068             | 2.755             |
| Lymph node metastasis, No vs Yes        | 5.328| 0.021   | 1.264             | 17.592            |

### Research background

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%. 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 treatment of 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 CRC is valuable for patient survival in multiple centers 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 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 of this study was to explore the features and prognostic value of lymph node metastasis in patients with T1-stage CRC.

### ARTICLE HIGHLIGHTS

**Research background**

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%. 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 treatment of patients with T1-stage CRC.

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