

# Lymph Node Metastasis and Its Risk Factors in Rectal Cancer Running Head: Risk Factors of Lymph Node Metastasis

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**ABSTRACT Objective:** To identify risk factors of lymph node metastasis in rectal cancer. **Methods:** Data from 1250 patients with rectal cancer who underwent radical resection from 2004 to 2008. Univariate and multivariate analysis were performed to identify risk factors associated with lymph node metastasis. The relationship between pT stage and tumor size was analyzed by correlate analysis. **Results:** The incidence of lymph node metastasis was 41.0% for patients with rectal cancer. In the univariate analysis, age ( $P=0.008$ ), tumor size( $P=0.003$ ), pT stage( $P<0.001$ ) and differentiation( $P<0.001$ ) were correlated with LNM. In multivariate analysis, only age( $P=0.017$ ,  $OR=0.988$ , 95% confidence interval (CI): 0.978-0.998), pT stage ( $P<0.001$ ,  $OR=1.952$ , 95% CI: 1.656-2.302) and differentiation ( $P<0.001$ ,  $OR=3.697$ , 95% CI: 2.112-6.472) were independent factors for lymph node metastasis. A positive association was found between tumor size and pT stage by correlate analysis in rectal cancer. **Conclusion:** Age, pT stage and differentiation might be predictive factors for lymph node metastasis. Tumor size and pT stage had positive correlation in rectal cancer.

**Key words:** Lymph node metastasis; Rectal cancer; Risk factors

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## Introduction

Rectal cancer was one of the leading cause of cancer death in the United States<sup>[1]</sup>. In China, it was the fifth cause of cancer-related death and its incidence was increasing every year <sup>[2]</sup>. Lymph node metastasis (LNM) was the main metastatic mode of rectal cancer<sup>[3]</sup>. Total mesorectal excision(TME) had achieved excellent outcomes for patients with rectal cancer<sup>[4,5]</sup>. However, even the patients underwent radical resection with TME, about 5%-40% of them had local recurrence<sup>[6,7]</sup>.

It had already known that LNM might be the most important factors for local recurrence and poor prognosis for rectal cancer<sup>[8]</sup>. Many researchers studied the related factors about LNM. Many clinicopathological features had been found to be associated with LNM. In 1998, Bjelovic studied the LNM in 46 patients with carcinoma of the rectum and sigmoid colon and found histologic type, macroscopic growth pattern and depth of tumor invasion were potentially factors for LNM <sup>[9]</sup>. In a study of colorectal cancer, multivariate analysis revealed that an increasing T stage and tumor with high grade pathology were identified as the independent predictive factors for the presence of LNM <sup>[10]</sup>. Moreover, in Wu's study, tumor diameter, infiltration and differentiation were significant factors for LNM of rectal cancer <sup>[11]</sup>. In these studies, the relationship between LNM and clinicopathologic factors were still unclear. Currently, our group retrospectively analyzed clinicopathological factors of 1250 patients with rectal cancer who underwent radical

surgery with TME. Moreover our group studied the relationship between tumor size and pT stage in these patients. Therefore, this study was to investigate the risk factors for LNM in order to make effective selection of patients who could benefit from lymph adenectomy.

## 1 Methods

### 1.1 Patients selection

Patients who underwent a radical operation in the colorectal department of colorectal surgery, Liao Ning tumor hospital, Shen Yang, China, between February 2004 and October 2008 were included in this retrospective study. The patients with recurrent cancer were excluded, patients who had synchronous or metachronous tumors, patients who underwent transanal local excision or endoscopic mucosal resection, patients who had been treated with neoadjuvant therapy and patients with incompleted medical record. The study protocol was approved by the Ethics Committee of Research Center of Liao Ning Tumor hospital.

### 1.2 Pretreatment evaluation and treatments

Pretreatment evaluation included digital rectal examination, computed tomography (CT) scans included chest, abdomen and pelvis and flexible endoscopy. All patients received radical rectal resection according to the principle of TME. For all patients, removal of longer than 3 cm for rectum distal to the lower margin of tumor was required. Lymph node were meticulously dissected from the enbloc specimens. Then, the resected lymph nodes were stained with hematoxylin and eosin and examined by pathologists for metastasis at Liao Ning Tumor Hospital. The pT classification representing the depth of wall invasion was performed using stan-

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dard criteria of 7th TNM staging system.

1.3 Statistical methods

All data were analyzed by spss 13.0 statistic software (Chicago, IL, USA). Chi-square test was used to compare the clinicopathological factors between patients with and those without LNM. Multivariate analysis was performed using logistic regression. Correlation between tumor size and pT stage was evaluated by spearman's correlation. P<0.05 was considered significant.

2 Results

2.1 Clinical characteristics of rectal cancer

1250 patients (686 men and 564 women) were included in the present study. The median age was 60 years old (range: 17-95 years old). 512 (41.0%) patients had LNM, whereas the remaining 738 (59.0%) patients were free of LNM. Clinicopathological features of 1250 patients included in this study were summarized in Table 1.

Table 1 Clinicopathological features of 1250 patients with rectal cancer

Clinicopathological features	Number (%)
Gender	
Male	686(54.9%)
Female	564(45.1%)
Age (year)	
≤ 60	655(52.4%)
> 60	595(47.6%)
Tumor size (cm)	
≤ 2.5	97(7.8%)
> 2.5	1153(92.2%)
pT stage	
T1	14(1.1%)
T2	231(18.5%)
T3	541(43.3%)
T4	464(37.1%)
Differentiation	
Well	1181(94.5%)
Poor	69(5.5%)
Circumference	
≤ 25%	141(11.3%)
> 25%, ≤ 50%	328(26.3%)
> 50%, ≤ 75%	303(24.2%)
> 75%, ≤ 100%	478(38.2%)

2.2 Predictive factors of LNM

The association between various clinicopathological characteristics and LNM was analyzed by Chi-square test (Table 2). Age younger than 60 years old (P=0.008), tumor size larger than 2.5 cm (P=0.003), tumor with deep invasion (P<0.001) and poor differentiation (P<0.001) were significantly associated with a high incidence of LNM. But sex and circumference of bowl were not. Moreover, the four characteristics that were associated with LNM by univariate analysis were analyzed by multivariate analysis. Age

(P=0.017, OR=0.988, 95% CI: 0.978-0.998), pT stage (P<0.001, OR=1.952, 95% CI: 1.656-2.302) and differentiation (P<0.001, OR=3.697, 95% CI: 2.112-6.472) were found to be significantly associated with LNM, whereas tumor size was not.

2.3 Association between pT stage and tumor size

A positive associationship was found between pT stage and tumor size (spearman r=0.317, P<0.001). Patients with increasing tumor size tended to have higher pT stage in rectal cancer (Table 3).

Table 2 Univariate and multivariate analysis of risk factors of lymph node metastasis of rectal cancer

	Local lymph node metastasis		Univariate analysis	Multivariate analysis		
	Positive	Negative		P value	OR	95%CI
Sex						
Male	266	420	P=0.083			
Female	246	318				
Age						
≤ 60 years	292	363	P=0.008	P=0.017	0.988	0.978-0.998
>60 years	221	374				
Tumor size						
≤ 2.5cm	26	71	P=0.003	P=0.126		
>2.5cm	487	666				
pT stage						
T1	1	13				
T2	51	180				
T3	212	329				
T4	249	215	P<0.001	P<0.001	1.952	1.656-2.302
Histologic grade						
Good	462	719				
Poor	51	18	P<0.001	P<0.001	3.697	2.112-6.472
Circumference of bowl						
≤ 25%	50	91				
≤ 50%	127	201				
≤ 75%	119	184				
≤ 100%	217	261	P=0.083			

Table 3 Correlation between tumor size and pT stage

Tumor size	pT stage		
	T1+T2	T3	T4
≤ 3cm	109	85	47
> 3cm, ≤ 4cm	75	138	110
> 4cm, ≤ 5cm	37	144	118
> 5cm, ≤ 6cm	17	97	98
> 6cm	7	77	91

3 Discussion

Despite the use of various modern diagnosis methods, such as ultrasonography, CT and MRI, LNM was still often incorrectly identified before surgery. As LNM was important factors for a patient and prognosis, many researchers had studied LNM and its related factors. They found many clinicopathological factors, such as differentiation , pT stage, tumor size and macroscopic growth pattern etc., were correlated with LNM [10-13]. In 1932, Dukes recog-

nized the importance of LNM and integrated this factor into staging system. Sufficient evaluation of LNM was necessary before and during surgical resection. In the current study, age, differentiation and pT stage were identified as three independent predictive factors for LNM, based on a large number of patients with rectal cancer who all underwent radical operation. It might be helpful for a doctor in the operation to do more meticulous lymph node examination.

In this study, poor differentiation was considered as a risk

factor for LNM. This result was consistent with some previous reports in which rectal cancer patients with poor differentiation tended to have LNM<sup>[9-10, 12]</sup> and poor prognosis<sup>[14, 15]</sup>. Patients with advanced pT stage, in this study, were also more likely to have LNM. This biological character of rectal cancer had already been proven<sup>[10, 13, 16]</sup> and other reports had indicated that patients with advanced pT stage had a poor prognosis<sup>[17, 18]</sup>. It was also found that age younger than 60 years old was a predictive factor for LNM. To our knowledge, this was the first report showing that the risk factor of LNM in rectal cancer was associated with the age of patients. Although it was difficult to explain precisely why rectal cancer patients with younger age carried higher risk of LNM, It was might inferred through by the Alici's study, the proportion of lymphatic invasion was present high in younger patients compared with elder patients of colorectal cancer was founded<sup>[19]</sup>. So, maybe it was the cause of younger patients with rectal cancer tending to have LNM.

In univariate analysis, it was found pT stage and tumor size were significantly correlated with LNM, but in multivariate analysis, only pT stage was associated with LNM. So, there might be some relationship between pT stage and tumor size. Therefore, we made correlate analysis between these two features. It was found significant correlation between them. In Wolmark's study, they found depth of tumor penetration was correlated with tumor size in Dukes C colorectal cancer<sup>[20]</sup>. This study found this relationship in rectal cancer, no matter what Dukes stage they were. This might suggest that, through tumor size, pT stage before operation could be inferred preliminarily.

Since this was a retrospective study, it was subjected to several limitations. Firstly, any prognostic analysis weren't made. Some studies had reported that patients with LNM had a poor prognosis<sup>[21, 22]</sup>. Therefore, our clinicopathological features regarding to LNM might be related to the risk of poor prognosis. To confirm it need further investigation. Secondly, sufficient parameters for us weren't had to identify the possible risk factors for LNM, such as dietary and Family history etc. Some bias might occur in this study.

In conclusion, besides the previous noted variables (pT stage, differentiation), age was also an important independent risk factor for predicting LNM in rectal cancer. This study found significant correlation between pT stage and tumor size by using correlate analysis. In summary, this study might help surgeons and pathologists to conduce a preliminary ascertainment for LNM, according to clinicopathological characteristics of patients.

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直肠癌的淋巴结转移的危险因素

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摘要 目的 本研究主要目的为确定直肠癌的淋巴结转移的危险因素。方法 通过对 1250 例于 2004 年 -2008 年行直肠癌根治性切除的患者进行单因素和多因素分析,以确定淋巴结转移相关的危险因素,同时对 PT 分期和肿瘤大小之间的关系进行了相关性分析。结果 直肠癌患者淋巴结转移发生率为 41%。在单因素分析中,患者年龄(P=0.008)、肿瘤大小(P=0.003)、PT 分期(P<0.0019)以及分化程度(P<0.001)和淋巴结转移相关。在多因素分析中,年龄(P=0.017,OR=0.988,95%可信区间 0.978-0.998)、PT 分期(P<0.001,OR=1.952,95%可信区间 1.656-2.302)和分化程度(P<0.001,OR=3.697,95%可信区间 2.112-6.472)是淋巴结转移的独立因素。结论 在直肠癌相关分析中,肿瘤的大小和 PT 分期呈正相关。年龄、PT 分期和肿瘤分化程度是淋巴结转移的独立因素。在直肠癌中,肿瘤的大小和 PT 分期呈正相关。

关键词 淋巴结转移;直肠癌;危险因素

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