

Risk Factors for Metastasis to No.253 Lymph Node for Colorectal Cancer Patients

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Abstract

Background: No.253 lymph nodes metastasis is related to poor prognosis of colorectal cancer, while the role of No.253 lymph nodes dissection in colorectal cancer is still controversial.

Methods: A total of 157 patients who were received laparoscopic radical resection of colorectal cancer with preservation of the left colon artery + D3 lymph node dissection (low ligation + high dissection) in our hospital were enrolled. No.253 lymph nodes of each patients were dissected and sent for examination. Clinico-pathological factors correlated with No.253 lymph nodes metastasis, including gender, age, tumor location, tumor size, length of tumor from the anus, whether lymphovascular invasion, whether perineural invasion, tumor markers CEA, CA125 and CA199, tumor T stage, whether it is distant metastasis, the total number of lymph nodes harvested, tumor type, and histologic grade were respectively analyzed.

Results: A total of 2286 lymph nodes were sent for examination, of which 557 No.253 lymph nodes were sent for examination. Among them, 5 patients had a total of 27 No.253 lymph node metastases. Preoperative CA125 level ($X^2=4.736$, $p=0.030$), whether perineural invasion ($X^2=8.086$, $p<0.01$), whether lymphovascular invasion ($X^2=7.053$, $p<0.01$), tumor type ($X^2=21.019$, $p<0.01$), histologic grade ($X^2=15.315$, $p<0.01$) were significantly correlated with positive No.253 lymph nodes metastasis. A multivariate logistic regression analysis showed that none of risk factor from above are independent risk factors for No.253 lymph node metastasis ($P>0.05$).

Conclusion: Preoperative CA125 level, whether perineural invasion, whether lymphovascular invasion, tumor type, histologic grade were risk factors of the No.253 lymph nodes metastasis. Multivariate analysis showed that five risk factors from above were not the independent risk factor for No.253 lymph nodes metastasis. Colorectal cancer patients with the risk factors above were suggested to receive radical resection + D3 lymph node dissection.

Background

Colorectal cancer is one of the common malignant tumors, with the third highest incidence rate and the fourth highest mortality rate worldwide(1). According to data from the National Cancer Center of China, the incidence and mortality of colorectal cancer in our country are gradually increasing(2). Although in recent years, breakthroughs have been made in the treatment of colorectal cancer, radical surgery is still the first choice for improving survival and quality of life of patients with resectable and resectable colorectal cancer after neoadjuvant therapy. In 1982, Heald et al. proposed total mesorectal excision (TME) for rectal cancer(3). In 2009, Hohenberger et al. proposed complete mesocolic excision (CME) to remove the tumor and perform regional lymph node dissection without destroying the integrity of the colonic membrane(4). Advances in surgical concepts and equipment have improved the surgical treatment of colorectal cancer, but there are still controversies about the scope of regional lymph node dissection during surgical operations.

According to the Japanese Classification of Colorectal Carcinoma, the lymph nodes at the root of the inferior mesenteric artery (IMA) are named No. 253 lymph nodes. The JSCCR guidelines recommend routine D3 lymph node dissection (including 253 groups of lymph nodes), and D2 dissection is only used for patients with T1 and some T2 stage colorectal cancer(5).The NCCN guidelines recommend routine low-position ligation and D2 dissection, and at least 12 lymph nodes are obtained during the operation for pathological evaluation. Unless suspected metastatic lymph nodes are found in preoperative imaging, extended dissection is not allowed(6).

Metastasis of No.253 lymph nodes is suggested to be related to poor prognosis of colorectal cancer, but the value of dissection still needs further evaluation and discussion(7–9). Selective lymph node dissection in 253 groups may be beneficial to the prognosis of some patients. Therefore, further analysis of the risk factors of No.253 lymph node metastasis has important reference value for the selection of surgical methods and the scope of dissection. At present, there are few studies on the risk factors of lymph node metastasis in group 253. Related studies have found that age, tumor size, T stage, degree of differentiation, and preoperative tumor marker levels are important factors affecting lymph node metastasis at the root of mesenteric vessel(10–12). However, these studies have small samples and limited risk factors. Therefore, this study adopts a retrospective analysis method to assess the risk factors of 253 lymph node metastasis, to provide individualized basis for the scope of lymph node dissection during radical resection of colorectal cancer in different patients, and to improve the surgical benefit of patients.

Methods

Patients

In this study, 187 colorectal cancer patients were selected for radical resection of colorectal cancer at the Department of Gastrointestinal Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, from October 2018 to June 2020. Eligibility criteria of this study included: (1)pathologically proven colorectal carcinoma; (2)Laparoscopic radical resection of colorectal cancer with preservation of the left colon artery + D3 lymph node dissection (low ligation + high dissection); (3)No history of other malignant tumors; (4)No serious perioperative complications and no death during hospitalization; Excluding 30 patients with incomplete clinical and pathological data, a total of 157 patients were included in the study.

Clinicopathological statistics

The No.253 lymph node is located at the root of the inferior mesenteric artery. To study the risk factors of No.253 lymph node metastasis, the clinicopathological statistics in this study include: gender, age, tumor location, tumor size, length of tumor from the anus, whether lymphovascular invasion, whether perineural

invasion, tumor markers CEA, CA125 and CA199, tumor T stage, whether it is distant metastasis, the total number of lymph node harvested, tumor type, and histologic grade.

Statistical analysis

SPSS 23.0 software was used for data processing and analysis, and $p < 0.05$ was considered statistically significant. Taking No.253 lymph node metastasis as the dependent variable and the clinicopathological statistics from above as the independent variable, the relationship between the above factors and No.253 lymph node metastasis was explored through Chi-square test. The single factor of $p < 0.05$ was included into the multivariate logistic regression model for analysis to discuss the independent risk factors of lymph node metastasis in 253 groups.

Results

Patients characteristics

A total of 157 patients underwent laparoscopic radical resection of colorectal cancer with preservation of the left colon artery + D3 lymph node dissection (low ligation + high dissection) in the Department of Gastrointestinal Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, from October 2018 to June 2020, included 105 males(66.9%) and 52 females(33.1%). The age ranges from 32 to 85 years old (60.47 ± 10.35). There were 98 patients' tumor distance from the anus > 10 cm (62.4%), 59 patients' tumor distance from the anus ≤ 10 cm (37.6%). Preoperative tumor marker examination showed 40 patients' CEA > 5 U/mL(25.5%) and 117 patients' CEA ≤ 5 U/mL(74.5%) ; 5 patients' CA125 > 35 U/mL(3.2%), 152 patients' CA125 ≤ 35 U/mL(96.8%) ; 12 patients' CA199 > 37 U/mL(7.6%), 145 patients' CA125 ≤ 37 U/mL(92.4%). Pathological examination results showed tumor type: 150 patients with adenocarcinoma(95.5%), 7 patients with mucinous adenocarcinoma/signet ring cell carcinoma(4.5%) ; degree of differentiation: 20 patients with poorly differentiated and moderately differentiated (including special types)(12.7%), 137 patients with moderately differentiated and well differentiated(83.3%) ; whether perineural invasion: 40 patients with perineural invasion(25.5%), 117 patients without perineural invasion(74.5%) ; whether lymphovascular invasion: 26 patients with lymphovascular invasion(16.6%), 131 patients without lymphovascular invasion(83.4%) ; the maximum tumor diameter: 32 patients' maximum tumor diameter ≥ 5 cm(20.4%), 125 patients' maximum tumor diameter < 5 cm(79.6%) ;whether it is distant metastasis: 8 patients with distant metastasis(5.1%), 139 patients without distant metastasis(94.9%) ; number of lymph nodes harvested: 94 patients' number of lymph node harvested ≥ 12 (59.9%), 63 patients' number of lymph node harvested < 12 (40.1%) ; T stage: T1-2 60 patients with T1-2 (38.2%), 97 patients with T3-4 (61.8%) ; tumor location: 124 patients in rectal(79.0%) while 33 patients in sigmoid colon and others(21.0%). As shown in Table 1.

Table 1
Characteristics of patients (n = 157)

Characteristics	Cases	Constituent ratio(%)
Age:		
≤ 60	73	46.5
> 60	84	53.5
Gender:		
Male	105	66.9
Female	52	33.1
Distance from the anus:		
≤ 10 cm	59	37.6
> 10 cm	98	62.4
Tumor location:		
Rectum	124	79.0
Sigmoid colon and others	33	21.0
Pathologic types:		
adenocarcinoma	150	95.5
Signet-ring cell carcinoma and mucinous adenocarcinoma	7	4.5
Histologic grade:		
Well differentiate and moderately differentiate	137	87.3
Poorly differentiate and unknown	20	12.7
Distant metastatic:		
M0	149	94.9
M1	8	5.1
Lymphovascular invasion:		
Yes	26	16.6
No	131	83.4
Perineural invasion:		

Characteristics	Cases	Constituent ratio(%)
Yes	40	25.5
No	117	74.5
Tumor size:		
≤ 5 cm	32	20.4
> 5 cm	125	79.6
Number of lymph nodes harvested:		
≤ 12	63	40.1
> 12	94	59.9
T stage:		
T1-2	60	38.2
T3-4	97	61.8
CEA (ng/ml)		
> 5 ng/ml	40	25.5
≤ 5 ng/ml	117	74.5
CA125(U/ml)		
> 35 U/ml	5	3.2
≤ 35 U/ml	152	96.8
CA199(U/ml)		
> 37 U/ml	12	7.6
≤ 37 U/ml	145	92.4

Potential risk factors for No.253 lymph nodes metastasis

All 157 patients' No.253 lymph nodes were sent for examination. A total of 2286 lymph nodes were sent for examination, of which 557 No.253 lymph nodes were sent for examination. Among them, 5 patients had a total of 27 No.253 lymph node metastases. Through the Chi-square test, the clinicopathological statistics of the above patients were analyzed, and it was found that the preoperative CA125 level ($\chi^2 = 4.736$, $p = 0.030$), whether nerve invasion ($\chi^2 = 8.086$, $p < 0.01$), whether vascular invasion ($\chi^2 = 7.053$, $p < 0.01$), tumor type ($\chi^2 = 21.019$, $p < 0.01$), degree of differentiation ($\chi^2 = 15.315$, $p < 0.01$) were significantly

correlated with positive No.253 lymph nodes, while gender, age, tumor location, tumor size, length of tumor from the anus, tumor markers CEA, and CA199, tumor T stage, whether it is distant metastasis, the total number of lymph node harvested showed no significant correlated with positive No.253 lymph nodes. As shown in Table 2.

Table 2
Risk factors of No.253 lymph nodes (chi-square test)

Characteristics	Cases	No.253(+)	χ^2	P value
Age:			2.330	0.127
≤ 60	73	4		
> 60	84	1		
Gender:			2.558	0.110
Male	105	5		
Female	52	0		
Distance from the anus:			0.680	0.409
≤ 10 cm	59	1		
> 10 cm	98	4		
Tumor location:			0.003	0.955
Rectum	124	4		
Sigmoid colon and others	33	1		
Pathologic types:			15.315	< 0.01
adenocarcinoma	150	3		
Signet-ring cell carcinoma and mucinous adenocarcinoma	7	2		
Histologic grade:			21.019	< 0.01
Well differentiate and moderately differentiate	137	1		
Poorly differentiate and unknown	20	4		
Distant metastatic:			2.372	0.124
M0	149	4		
M1	8	1		
Lymphovascular invasion:			7.053	< 0.01
Yes	26	3		
No	131	2		

Characteristics	Cases	No.253(+)	χ^2	P value
Perineural invasion:			8.086	< 0.01
Yes	40	4		
No	117	1		
Tumor size:			1.322	0.25
≤ 5 cm	32	0		
> 5 cm	125	5		
Number of lymph nodes harvested:			0.871	0.351
≤ 12	63	1		
> 12	94	4		
T stage:			3.19	0.074
T1-2	60	0		
T3-4	97	5		
CEA (ng/ml)			0.574	0.449
> 5 ng/ml	40	2		
≤ 5 ng/ml	117	3		
CA125(U/ml)			4.736	0.030
> 35 U/ml	5	1		
≤ 35 U/ml	152	4		
CA199(U/ml)			1.117	0.291
> 37 U/ml	12	1		
≤ 37 U/ml	145	4		

A multivariate logistic regression analysis was performed on the above 5 statistically significant No.253 lymph node positive risk factors to assess whether the above 5 factors are independent risk factors for No.253 lymph node metastasis, the appeal parameter was set as an independent variable, and No.253 lymph node metastasis was set as the cause variables were included in the binary logistic regression model. The results showed that preoperative CA125 levels, whether nerve invasion, whether vascular invasion, tumor type, and degree of differentiation are not independent risk factors for No.253 lymph node metastasis(P > 0.05). As shown in Table 3.

Table 3
Independent risk factors of No.253 lymph nodes (Logistics test)

Characteristics	Regression coefficient	Standard error	Wald value	P value
Lymphovascular invasion	0.673	1.357	0.246	0.620
Perineural invasion	2.007	1.613	1.547	0.214
Histologic grade	2.304	1.423	2.621	0.105
CA125	2.226	1.701	1.712	0.191
Pathologic types	2.009	1.530	1.724	0.189

Discussion

Lymph node metastasis is the most important way of colorectal cancer metastasis, and it is also one of the important indicators for judging the prognosis of colorectal cancer(6). No.253 lymph node locates at the root of the inferior mesenteric artery. Lymph node metastasis of No.253 is a risk factor for poor prognosis of colorectal cancer(8). At present, in colorectal surgery, there is still controversy as to whether to clean No.253 lymph nodes. A large number of studies have reported that D3 lymph node dissection can reduce the risk of metastasis and improve the prognosis of some patients(8). On the other hand, some studies believe that the rate of No.253 lymph node metastasis is low, and patients with positive No.253 lymph node have a higher rate of recurrence and metastasis. D3 lymph node dissection increases the difficulty and risk of the operation(10, 13). This study tried to explore the risk factors of No.253 lymph node metastasis by retrospectively studying the clinical pathological data of patients, and provided individualized guidance on whether to clean No.253 lymph nodes in different patients with colorectal surgery.

The No.253 lymph node has low metastasis rate, reported in the literature at 3.1–13.9% (12, 14–16). Kim(14) et al. enrolled a total of 2040 patient case data, of which 76 cases were positive for sub mesenteric lymph nodes (including the No.252 lymph node and No.253 lymph node), accounting for 3.7% of the total number of cases. Among patients with stage III and IV, 7% were positive for sub mesenteric lymph nodes; Kanemitsu(17) et al. enrolled data on 1188 patients, of which 20 patients had positive No.253 lymph node, accounting for 1.7%; Chin(18) et al. collected data on 1389 patients, including 43 cases of patients had positive No.253 lymph node, accounting for 3.1%. In this study, a total of 157 patients were included, and 5 patients had positive No.253 lymph nodes, accounting for 3.5%; it was consistent with previous research reports.

No.253 lymph node metastasis is an independent risk factor for poor prognosis of colorectal cancer. Kang(8) et al. enrolled data from 625 patients, and the results showed that the 5-year disease-free survival rate (DFS) of the positive No.253 lymph node was 31.9%, which was significantly lower than the 69.4% of the negative No.253 lymph node. Cox survival analysis shows that positive No.253 lymph nodes

is an independent risk factor for 5-year DFS in patients with colorectal cancer, which is related to recurrence and metastasis.

No.253 lymph node metastasis suggests a higher risk of recurrence and metastasis, but the positive rate of No.253 lymph node is low. The clinical significance of No.253 lymph node dissection still needs to be discussed. Some studies believe that 253 lymph node dissection can improve the prognosis of patients. A systematic review of 3119 patients showed that No.253 lymph node dissection had no significant effect on the 5-year overall survival rate. However, a subgroup analysis showed that for patients with No.253 lymph node metastasis, dissection in No.253 groups can improve the prognosis(19). On the other hand, a systematic review by Zeng(7) et al. reported that lymph node dissection in the No.253 group did not improve the 5-year survival rate. In summary, selective dissection of 253 groups of lymph nodes for different patients may be beneficial to the prognosis of some patients.

The clinical and pathological data of patients enrolled in this study include gender, age, tumor location, tumor size, length of tumor from the anus, whether lymphovascular invasion, whether perineural invasion, tumor markers CEA, CA125 and CA199, tumor T stage, whether it is distant metastasis, the total number of lymph node harvested, tumor type, and histologic grade. Through chi-square analysis and multivariate Logistic test, the risk factors of No.253 lymph node metastasis and independent risk factors were explored.

In this study, 105 male patients and 52 female patients were enrolled, and all 5 patients with positive No.253 lymph node were male. The rate of No.253 lymph node metastasis in men was higher than that in women. There was no significant difference in lymph node metastasis ($\chi^2 = 2.558$, $p = 0.110$). It can be considered that gender has no related with No.253 lymph node metastasis. There is controversy about the correlation between age and lymph node metastasis. A study involving 1205 patients (10) showed that the rate of lymph node metastasis in the No.253 group of people less than 65 years old was higher, and the difference was statistically significant ($p = 0.028$), which may be related to the low degree of tumor differentiation in the low-age group. More studies have shown that lymph node metastasis in the No.253 group has no correlation with age(8, 12). In our study, the rate of lymph node metastasis in group No.253 in the age ≤ 60 years group was higher than that in the group over 60 years old (5.5% vs 1.2%), and the difference was not statistically significant, suggesting that age has no correlation with No.253 lymph node metastasis.

Preoperative tumor markers CEA, CA125, CA199 are the most commonly used clinical indicators for diagnosis, monitoring the progress of gastrointestinal tumors and treatment effects, and their application value in colorectal tumors has been widely recognized (20, 21). According to research reports, the level of preoperative tumor markers is related to lymph node metastasis. Sun(22) et al. showed that the preoperative increase in CEA level was positively correlated with No.253 lymph node metastasis and led to a poor prognosis. In this study, the lymph node metastasis rate in the No.253 group with elevated levels of tumor markers CEA, CA125, and CA199 was higher than that in the normal group. The preoperative CA125 level increased (20.0% vs 2.6%, $\chi^2 = 4.736$, $p = 0.030$) while compared with the normal

group, the difference is statistically significant. Through our study and previous study, we thought that higher level of preoperative tumor markers suggested higher risk of No.253 lymph node metastasis. Therefore, it is believed that the preoperative CA125 level is a risk factor for No.253 lymph node metastasis.

Studies have reported that tumor size is related to No.253 lymph node metastasis. Yi(12) et al. published a study involving 229 patients and showed that there was a difference in tumor size between the No.253 metastatic group and the No.253 non-metastatic group. In this study, the lymph node metastasis rate was higher in the tumor diameter > 5 cm group (4.0% vs 0%, $\chi^2 = 1.322$, $p = 0.250$), which was consistent with the report, but the difference was not statistically significant. In addition, tumor T staging is considered to be an important factor affecting lymph node metastasis of colorectal cancer. Studies have found that the deeper the tumor infiltrates the intestinal wall, the higher the No.253 lymph node metastasis rate (10, 23). Chin(18) et al. found that among 1389 patients, 43 patients with positive No.253 lymph node, including pT1 0%, pT2 1.0%, pT3 2.6%, and pT4 4.3%. In our study, T1 and T2 patients did not have lymph node metastasis, and 5 patients with T3 and T4 had lymph node metastasis (5.2% vs 0%, $\chi^2 = 3.190$, $p = 0.074$), which is consistent with the report, and the difference is not statistically significant. Our results are similar to previous studies.

The degree of differentiation is considered to be an important factor affecting the prognosis of colorectal cancer. Poorly differentiated and undifferentiated tumors are one of the basis for the diagnosis of stage II high colorectal cancer in the NCCN guidelines(6). Some studies believe that poor differentiation is a risk factor in No.253 lymph node metastasis(10, 22). In our study, the No.253 lymph node metastasis rate in the poorly differentiated group was significantly higher than that in the moderately/well differentiated group (20.0% vs 0.7%, $\chi^2 = 21.019$, $p < 0.01$), and the difference was statistically significant. The pathological types of tumors in this study include adenocarcinoma, mucinous adenocarcinoma and signet ring cell carcinoma. Studies have shown that mucinous adenocarcinoma and signet ring cell carcinoma are less common in colorectal cancer and have a poor prognosis(24). In our study, the metastasis rate of the mucinous adenocarcinoma/signet ring cell carcinoma group was significantly higher than that of the adenocarcinoma group (28.6% vs 2.0%, $\chi^2 = 15.315$, $p < 0.01$). The difference was statistically significant and consistent with the report.

Studies have reported that lymphovascular invasion and perineural invasion are related to poor colorectal prognosis. Patients with lymphovascular invasion and perineural invasion have a higher rate of No.253 lymph node metastasis (10, 25, 26). In our study, the No.253 lymph node metastasis rate in the lymphovascular invasion group was significantly higher than non-lymphovascular invasion group (11.5% vs 1.5%, $\chi^2 = 7.035$, $p < 0.01$), and the No.253 lymph node metastasis rate in the perineural invasion group was significantly higher than that in the non-perineural invasion group(10.0% vs 0.9%, $\chi^2 = 8.086$, $p < 0.01$), the difference between the two groups was statistically significant. The results are consistent with previous studies, and indicate that lymphovascular invasion and perineural invasion are risk factors for lymph node metastasis in the No.253 group.

Because of the limit of the technical level, it is difficult to evaluate the metastasis status of No.253 lymph node before operation. It is necessary to combine preoperative tumor markers, colonoscopy, endoscopic ultrasonography, preoperative pathological biopsy, CT, MRI, etc. to comprehensively evaluate the clinical pathology factors of each patient to predict the status of No.253 lymph node metastasis, and to provide a basis for the scope of lymph node dissection during surgery. The pathological examination was performed after the operation, and No.253 lymph nodes were sent to examination of the patients with rectal cancer and sigmoid colon cancer to provide guidance for postoperative adjuvant treatment.

There are some shortcomings in this study. As it is a single-center retrospective study, which has limitations and small sample size, leading to potential risk factors such as T staging, CEA, CA199, tumor size, etc. with no statistical significant difference. The follow-up study will continue to expand the sample size, and further confirm the risk factors related to No.253 lymph node metastasis. And we also look forward to conducting multi-center, large sample, prospective research to provide more evidence for the scope of 253 lymph node.

Conclusion

The scope of lymph node dissection during colorectal surgery is still controversial. Although the rate of No.253 lymph nodes metastasis is low, the prognosis of patients with No.253 lymph node metastasis is poorer. Through our retrospective study, we found that preoperative CA125 level, whether perineural invasion, whether lymphovascular invasion, tumor type, histologic grade were risk factors of the No.253 lymph nodes metastasis. Therefore, we believe that patients with colorectal cancer who have the above risk factors require routine No.253 lymph nodes dissection.

Abbreviations

CEA—carcinoembryonic antigen

CA125—carbohydrate antigen 125

CA199—carbohydrate antigen 199

Declarations

Ethics approval and consent to participate

The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology. Informed consent was obtained from all patients. Informed consent was obtained from all patients by written document.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Design of the work: CW, KT ; Literature research: ZD, YL; Data acquisition: ZD, DW, PH; Data analysis: ZD; Manuscript editing:ZD.

All authors read and approved the final manuscript.

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