

## Risk Factors for Lymph Node Metastasis in Pathological T1b Colorectal Cancer

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**Abstract.** *Background/Aim:* The rate of lymph node metastasis (LNM) of colorectal carcinoma (CRC) with a submucosal (SM) invasion depth of 1000  $\mu\text{m}$  or more can reach 12.5%, which is the most common reason for additional resection in daily practice. Other studies have reported that the rate of LNM is less than 2%, regardless of the depth of invasion, if the lesions show good histology, lymphovascular infiltration is negative, and tumor budding is limited. The purpose of this study was to investigate new risk factors for LNM in T1b colorectal cancer. *Patients and Methods:* The 239 patients who were diagnosed with pathological T1b CRC after colorectal surgical resection at the Osaka Police Hospital in Japan between January 2008 and December 2018 were retrospectively reviewed in this study. *Results:* The LNM rate was 11.3% (27/239). The variables identified as being significant factors using multivariate analysis were: i) lymphatic invasion (Ly)-positive [odds ratio (OR)=5.97; 95% confidence interval (CI)=2.27-15.74], ii) female gender (OR=3.49; 95%CI=1.38-8.85), and iii) left-sided colorectal involvement (OR=4.98; 95%CI=1.22-20.39). If none of these risk factors were present with T1b, the LNM rate was 0% (0/28). *Conclusions:* Ly-positive, female gender, and left-sided colorectal involvement could be risk factors for LNM in T1b CRC.

Colorectal cancer (CRC) is the third most common cancer in the world (1). With the increase in the implementation of CRC screening programs, the frequency of early cancer is expected to increase. (2). The recently reported favorable

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long-term results of endoscopic resection (ER) for T1 CRC suggest that superficial T1 CRC with a submucosal (SM) invasion depth of less than 1000  $\mu\text{m}$  may have a very low risk of metastasis (3, 4). ER is considered an attractive therapeutic option for T1 CRC because of its less invasive profile compared to surgical resection (5). Surgical resection is recommended when the vertical margin is positive. However, if the vertical margin is negative, surgical resection is recommended in cases of: i) T1b (depth of SM invasion  $\geq 1000 \mu\text{m}$ ), ii) lymphovascular invasion-positive, iii) undifferentiated histopathological types (poorly differentiated adenocarcinoma, signet-ring cell carcinoma, or mucinous carcinoma), or iv) budding grade of BD2/3 (6). According to the results of a study by the Japanese Society for Cancer of the Colon and Rectum (JSCCR), the lymph node metastasis (LNM) rate of CRC with an SM invasion depth of 1000  $\mu\text{m}$  or more was 12.5% (7). On the other hand, several studies have reported that the rate of LNM was less than 2%, regardless of the depth of invasion, if the lesions showed good histology, no lymphovascular infiltration, and limited tumor budding (8, 9). In a study of 548 cases of T1 cancer, deep invasion was found in 89.8% of the additional resections (10), which is the most common reason for additional resection in daily practice.

The purpose of this study was to investigate new risk factors for LNM in T1b CRC.

### Patients and Methods

**Patient selection, data extraction, and definitions.** Patients diagnosed with pathological T1b CRC after colorectal surgical resection at the Osaka Police Hospital in Japan between January 2008 and December 2018 were included in this study. The exclusion criteria were i) synchronous CRC, ii) concomitant surgical procedures for other cancers, iii) local recurrence after ER, iv) distant metastasis, or v) treatment other than surgery.

Information on various clinicopathological factors of the patients, including sex, age, tumor location, histological type, and LNM, was obtained from medical records and retrospectively analyzed. Histological types were classified as either differentiated

(differentiated papillary, well or moderately differentiated tubular adenocarcinoma) or undifferentiated (undifferentiated and poorly differentiated adenocarcinoma, signet-ring cell carcinoma, or mucinous carcinoma). Tumor budding was not included due to low reporting rate in the pathology reports.

Tumors arising from the cecum to the ascending and transverse colon were defined as tumors on the right side, and tumors arising from the descending colon to the rectum were defined as tumors on the left side.

This study was reviewed and approved by the institutional review boards of the participating institutions. Written consent was obtained from each patients.

*Statistical analysis.* Clinicopathological factors were analyzed using Pearson's Chi-squared test and Fisher's exact test. Variables found to be significant in univariate analysis were analyzed by multivariate logistic regression analysis. If the 95% confidence interval (CI) for the odds ratio (OR) did not include 1.0, and if  $p$ -value<0.05, the difference was considered significant. All statistical analyses were performed using JMP version 14.0 (SAS Institute, Cary, NC).

## Results

The baseline characteristics of all patients (n=239) are presented in Table I. A total of 142 patients (59.4%) were treated with colorectal surgical resection alone as an initial treatment (surgery alone), and 97 patients (40.6%) underwent additional colorectal surgical resection after initial ER (surgery after ER). The number of patients positive for LNM was 27 (11.3%).

Risk factors for LNM in T1b CRC. Univariate analysis showed a significant difference in four risk factors (Table II), and the factors that were significantly different on multivariate analysis were: i) lymphatic invasion (Ly)-positive (OR=5.97; 95%CI=2.27-15.74), ii) female gender (OR=3.49; 95% CI=1.38-8.85), and iii) left-sided colorectal involvement (OR=4.98; 95%CI=1.22-20.39). Of these variables, Ly-positive had the highest OR (Table III).

The LNM rates for each combination of risk factors in this study (Ly-positive, female gender, left-sided colorectal involvement) are shown in Table IV. If no risk factors were present with T1b (depth of SM invasion  $\geq 1,000 \mu\text{m}$ ), the rate of LNM was 0%; if one risk factor was present, the rate was 2.7%; if two risk factors were present, the rate was 22.8%; and if all three risk factors were present, the rate was 31.6%. Thus, the rate of LNM increased with the number of positive risk factors, and when only T1b without the three risk factors was present, it was 0%.

## Discussion

It has been reported that the rate of LNM is 0% if the depth of invasion is  $<1,000 \mu\text{m}$  (7). In routine practice, T1b is the most commonly encountered reason for additional resection of T1 CRC (10). Colorectal surgery is still associated with

Table I. *Baseline characteristics.*

Number of cases	239
Age, years, median (range)	67 (27-87)
Gender	
Male, n (%)	152 (63.6)
Female, n (%)	87 (36.4)
Tumor location	
Right-sided colectomy, n (%)	171 (71.5)
Left-sided colectomy, n (%)	68 (28.5)
Procedure	
Laparoscopic surgery, n (%)	230 (96.2)
Open surgery, n (%)	9 (3.8)
Lymph node dissection	
D2, n (%)	175 (73.2)
D3, n (%)	64 (26.8)
Initial treatment	
Surgery alone, n (%)	142 (59.4)
Surgery after ER, n (%)	97 (40.6)
Lymphatic invasion	
Positive, n (%)	70 (29.3%)
Negative, n (%)	169 (70.7%)
Venous invasion	
Positive, n (%)	62 (25.9%)
Negative, n (%)	177 (74.1%)
Histological type	
Dif, n (%)	235 (98.3%)
Undif, n (%)	4 (1.7%)
Lymph node metastasis	
Positive, n (%)	27 (11.3%)
Negative, n (%)	212 (88.7%)

ER: Endoscopic resection; Dif: papillary, well or moderately differentiated tubular adenocarcinoma; Undif: poorly differentiated adenocarcinoma, signet-ring cell carcinoma, or mucinous carcinoma.

considerable morbidity and mortality (11, 12). Identification of factors that determine the indication for surgery is desperately needed. In the present study, three risk factors: i) Ly-positive, ii) female gender, and iii) left-sided colorectal involvement, were identified for LNM. In our study, when T1b was the only pathological risk factor in T1 CRC, the rate of LNM was extremely low, at 4.3%. In the absence of the three factors identified in the present study, the LNM rate was even less, at 0%. The three risk factors that were identified seemed to correlate better with LNM than those reported in the JSCCR guidelines (6).

Ly-positive had the highest odds ratio. The relationship between this factor and LNM has been widely reported and appears to be reliable (13). There was no significant variation in the extend of venous invasion with respect to histological type in the present study. This may be due to the small sample size. Tumor budding was not included, due to their low rates found in the pathology reports.

Second, female patients were at a higher risk of LNM compared to male patients. This has been shown in another large study (14). However, there were no significant

Table II. *Univariate analysis of the risk factors for lymph node metastasis.*

	LNM (+) (n=27)	LNM (-) (n=212)	OR (95% CI)	p-Value
Age, years				
<65, n (%)	12 (13.6%)	76 (35.8)	1.43 (0.64-3.22)	0.3881
≥65, n (%)	15 (9.9%)	136 (64.2)		
Gender				
Female, n (%)	15 (17.2%)	72 (34.0)	2.43 (1.08-5.47)	0.0314
Male, n (%)	12 (7.9%)	140 (66.0)		
Tumor location				
Left-sided colorectum, n (%)	24 (14.0%)	147 (69.3)	3.54 (1.03-12.17)	0.0216
Right-sided colorectum, n (%)	3 (4.4%)	65 (30.7)		
Initial treatment				
Surgery after ER, n (%)	10 (10.3%)	87 (41.0)	0.85 (0.37-1.93)	0.6888
Surgery alone, n (%)	27 (11.3%)	125 (59.0)		
Lymphatic invasion				
Positive, n (%)	18 (25.7%)	52 (24.5)	6.15 (2.61-14.53)	<0.0001
Negative, n (%)	9 (5.3%)	160 (75.5)		
Venous invasion				
Positive, n (%)	13 (21.0%)	49 (23.1)	3.09 (1.36-7.01)	0.0081
Negative, n (%)	14 (7.9%)	163 (76.9)		
Histological type				
Undif, n (%)	1 (25.0%)	3 (1.4%)	2.68 (0.27-26.71)	0.4406
Dif, n (%)	26 (11.0%)	209 (98.6%)		

Dif: Papillary, well or moderately differentiated tubular adenocarcinoma; Undif: poorly differentiated adenocarcinoma, signet-ring cell carcinoma, or mucinous carcinoma; CI: confidence interval; OR: odds ratio; ER: endoscopic resection.

differences between males and females with location, age, morphology, or pathological factors in that paper. There have been several other reports on the association between patient sex and LNM (7, 15, 16), however, no significant relationship between patient sex and LNM risk in patients with T1 cancer was demonstrated, and further studies are required to clarify the lack or verification of this association.

Furthermore, left-sided colorectal tumor was a risk factor. Although the relationship between LNM and left-right body axis differences has not been reported, a high incidence of LNM has been reported in the rectum (17). The rectum has a well-developed anatomical collateral circulation, which may increase the likelihood of an invading tumor encountering a vessel. The left-sided colorectum contains the rectum, which may explain the difference in LNM.

This study has certain limitations, such as the small number of patients, and the fact that it was a retrospective, single-institute study. Thus, further large and multi-institutional studies are needed to confirm our findings.

In conclusion, we found that when T1b is the only pathological risk factor in T1 CRC, the rate of LNM is exceedingly low, however, Ly-positive, female, and left-sided colorectal involvement are potential risk factors for LNM.

Table III. *Multivariate analysis of the risk factors for lymph node metastasis.*

	OR	95% CI	p-Value
Lymphatic invasion-positive	5.97	2.27-15.74	0.0003
Female	3.49	1.38-8.85	0.0085
Left-sided colorectal	4.98	1.22-20.39	0.0255

CI: Confidence interval; OR: odds ratio.

### Conflicts of Interest

The Authors declare no conflicts of interest associated with this manuscript.

### Authors' Contributions

Study concept and design, data analysis and interpretation, statistical analysis and manuscript preparation were done by AN. Data acquisition was done by MO, quality control of data and algorithms were done by MI and AN. Manuscript editing was done by HA and manuscript review by KI, YN, MM, KF, JM, TA, and KK.

Table IV. Relationship between the number of risk factors in the present study and lymph node metastasis.

Risk factors	LNM (+)	LNM (-)	Total	Incidence of LNM (%)
No risk factors	0	28	28	0
One risk factor	3	110	113	2.7
a. Lymphatic invasion-positive	0	8	8	0
b. Female	0	25	25	0
c. Left-sided colorectal	3	77	80	3.8
Two risk factors	18	61	79	22.8
a + b	3	4	7	42.6
a + c	9	27	36	25.0
b + c	6	30	36	16.7
Three risk factors	6	13	19	31.6

LNM: Lymph node metastasis.

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