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The Impact of Metastatic Lymph Node Size on Long-term Outcomes for pStage III Colon Cancer

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Abstract. *Aim: To clarify the impact of metastatic lymph node size on long-term outcomes in patients undergoing curative colectomy for pathological stage III colon cancer. Patients and Methods: This study enrolled patients who underwent curative colectomy for pStage III colon cancer between January 2013 and December 2015. All patients were divided into four groups based on the short-axis diameter of the largest MLN: Group A, <5 mm; Group B, ≥5 mm and <10 mm; Group C, ≥10 mm and <15 mm; Group D, ≥15 mm. Results: A total of 209 patients were analyzed. The 5-year recurrence-free survival rates of Groups A, B, C, and D were 82.3%, 74.6%, 74.5% and 60.7%, respectively. In multivariate analysis, Group D (hazard ratio=3.95; 95% confidence interval, 1.34-11.65; p=0.01) was independently associated with worse RFS. Conclusion: Bulky MLNs might be a poor prognostic factor in node-positive colon cancer.*

Lymph node (LN) metastasis is one of the most important prognostic factors in patients undergoing curative resection for colon cancer (1). To assess the degree of LN metastasis, it is essential to determine the number of metastatic LNs (MLNs); this number was incorporated into the TNM staging system both in the Union for International Cancer Control and in the American Joint Committee on Cancer (2, 3). Furthermore, multiple studies demonstrated that the number of LNs examined was associated with long-term outcomes in colon cancer because stage migration was avoided by harvesting a large number of LNs (4-6). Meanwhile, there was also reported that combining the number of tumor deposit and the number of MLNs improved the prognostication accuracy of TNM staging in stage III colon cancer (7). Little is known about how LN size influences prognosis. In node-negative colon cancer, large non-MLNs were reported to be associated with better prognosis due to a strong immune response (8-11). In node-positive colon cancer, the impact of MLN size on prognosis is controversial because few studies have examined this question, and their results differed in terms of whether MLN size affected long-term outcomes (12, 13). This study was conducted to clarify the impact of MLN size on long-term outcomes in patients undergoing curative resection for pathological stage III colon cancer.

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Key Words: Colon cancer, lymph node metastasis, lymph node size, long-term outcome, stage III colon cancer.

Patients and Methods

Patient selection. Patients who underwent curative colectomy for primary pathological stage III colon cancer at Shizuoka Cancer Center in Japan between January 2013 and December 2015 were included. The exclusion criteria were synchronous or metachronous colorectal cancer and concomitant surgical procedures for other cancers. Patient characteristics and pathological and surgical findings were recorded in a prospective database. Data collection and analysis were approved by the institutional review board of Shizuoka Cancer Center Hospital (institutional code: J2019-135). The cecum, ascending colon, and transverse colon were classified as the right-sided colon, and the descending colon and sigmoid colon were classified as the left-sided colon. Pathological T or N stage was classified according to the tumor node metastasis (TNM) classification system (2).

Measurement of lymph node size. After removal of fresh specimens, colorectal surgeons manually identified all LNs. The short-axis diameter of each dissected LN was measured, and the LN was fixed in 10% buffered formalin for 24 hours; the pathological diagnosis was recorded for each dissected LN, as previously reported (14-16). All eligible patients were divided into four groups based on the short-axis diameter of the largest MLN: Group A, <5 mm; Group

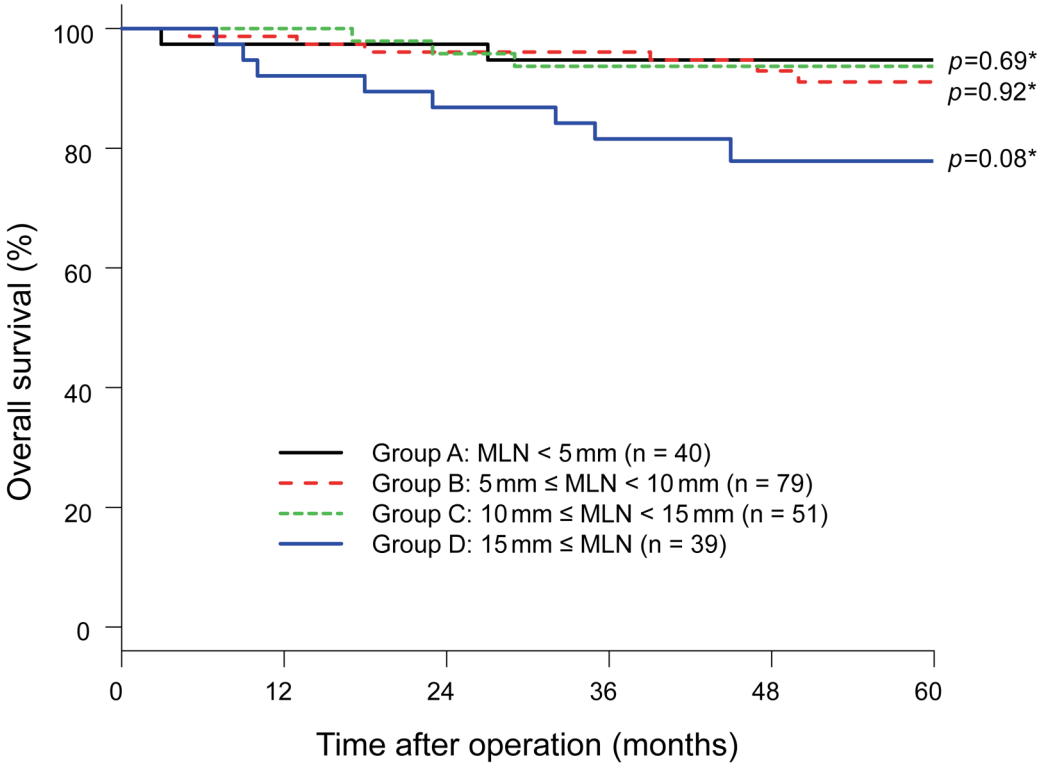

Figure 1. *Overall survival. Kaplan-Meier curves with log-rank tests by group of largest MLN size on overall survival. MLN, Metastatic lymph node. *Compared to Group A.*

B, ≥5 mm and <10 mm; Group C, ≥10 mm and <15 mm; and Group D, ≥15 mm. Clinicopathological characteristics and long-term outcomes were compared between groups.

Treatment. In accordance with the Japanese Society for Cancer of the Colon and Rectum Guideline for the Treatment of Colorectal Cancer (17), D2 LN dissection was performed for clinical T1 tumors, and D3 LN dissection was performed for tumors of clinical stage T2 or higher. In patients without LN metastasis who were older than 75 years or who had a high risk of preoperative complications from comorbidities, D2 LN dissection was performed for tumors of clinical stage T2 or higher. In D2 LN dissection, pericolic and intermediate LNs were removed. In D3 LN dissection, pericolic, intermediate and main LNs were removed and tumor-supplying arteries were divided at their origins. Laparoscopic surgery was the first choice; open surgery was performed only when laparoscopic surgery was judged unsuitable for ensuring oncological safety or when patients refused laparoscopic surgery. In principle, 5-fluorouracil–based adjuvant chemotherapy was administered to patients younger than 75 years who did not have any severe comorbidity.

Surveillance protocol. Surveillance was performed for 5 years after surgery. The surveillance protocol at our institution was as follows: an interview, physical examination and blood tests, including carcinoembryonic antigen and cancer antigen 19-9, were performed every 3 months for the first 3 years after surgery and then every 6 months thereafter. Chest, abdominal, and pelvic CTs were performed every 6 months. Colonoscopy was performed 1, 3, and 5 years after surgery. Recurrence was confirmed by pathological assessment or by progressively increasing tumor size in imaging studies.

Statistical analysis. Categorical variables are presented as numbers (percentages). Continuous variables are presented as medians (range). Categorical variables were compared using the chi-squared test and continuous variables were compared using the Mann-Whitney *U*-test. Overall survival (OS) and recurrence-free survival (RFS) were calculated using the Kaplan-Meier method and compared using the log-rank test. We performed univariate and multivariate analyses using the Cox proportional hazards regression model to identify clinicopathological factors affecting RFS. All statistical analyses were performed with the statistical program R version 1.40 (http://www.r-project.org/). A *p*-value less than 0.05 was considered statistically significant.

Results

Patient characteristics. A total of 216 patients underwent curative colectomy for primary pathological stage III colon cancer between January 2013 and December 2015. Patients who had synchronous or metachronous colorectal cancer (n=5) and who underwent concomitant surgical procedures for other cancers (n=2) were excluded. The remaining 209 patients were analyzed. We evaluated a total of 7305 LNs, of which 644 were

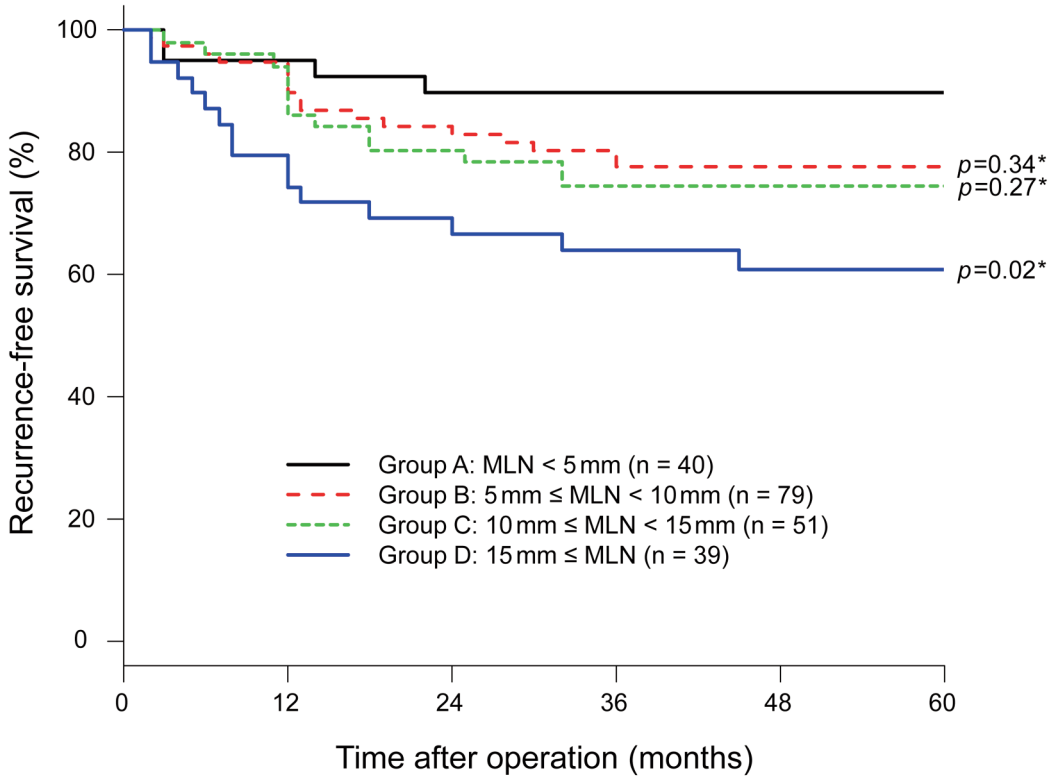

Figure 2. *Recurrence-free survival. Kaplan-Meier curves with log-rank tests by group of largest MLN size on recurrence-free survival. MLN, Metastatic lymph node. *Compared to Group A.*

metastatic. The median short-axis diameter of MLNs was 5 mm (range=1-40 mm) and the median short-axis diameter of the largest MLN in each patient was 8 mm (range=1-40 mm). Among the eligible patients, 40 (19%), 79 (38%), 51 (24%), and 39 (19%) were categorized into Groups A, B, C, and D, respectively. The patient characteristics are presented in Table I. There were no significant differences between Group A and the other Groups in terms of age, sex, operative approach, histology, or number of dissected LNs. The proportion of patients with right-sided colon cancer was higher in Group D than in Group A. The median tumor size was significantly larger in Groups C and D than in Group A. The proportion of patients undergoing D3 dissection was higher in Groups B, C, and D than in Group A. The proportion of patients with T3 cancers was higher in Group D than in Group A. The proportion of patients with N2 cancers and the number of MLNs were significantly higher in Groups B, C, and D than in Group A. The proportion of patients who underwent adjuvant chemotherapy was higher in Group C compared to Group A.

Long-term outcomes. The median follow-up time was 54 months. Figure 1 and Figure 2 show the OS and RFS curves of each group, respectively. Table II shows the 5-year OS and RFS rates for each group. There were no significant differences in OS rates between groups. The RFS rate in Group D was significantly lower than that in Group A. The RFS rates in Groups B and C were also lower than that in Group A, although the differences were not significant. A larger maximum MLN diameter was associated with a lower RFS.

Prognostic factors. To identify clinicopathological factors affecting RFS, univariate and multivariate analyses were performed using Cox proportional hazards regression models, and the results are shown in Table III. Univariate analysis indicated that age above 70 years, Group D (largest MLN ≥15 mm), and the absence of adjuvant chemotherapy were all significantly associated with worse RFS. Multivariate analysis revealed that Group D [hazard ratio (HR)=3.95; 95% confidence interval (CI)=1.34-11.65; p=0.01] and the absence of adjuvant chemotherapy (HR=2.44; 95% CI=1.26-4.72; p<0.01) remained significantly associated with worse RFS.

Discussion

In this study, we evaluated the impact of MLN diameter on long-term outcomes following curative colectomy for

Table I. *Clinicopathological characteristics of the study patients.*

Characteristic	Group A MLN <5 mm n=40	Group B 5 mm ≤ MLN <10 mm n=79	*p*-Value*	Group C 10 mm ≤ MLN <15 mm n=51	*p*-Value**	Group D 15 mm ≤ MLN n=39	*p*-Value***
Age, years [median (range)]	69.5 (37-86)	69.0 (39-86)	0.61	65.0 (39-86)	0.12	70.0 (39-86)	0.74
Gender			0.24		0.14		0.50
Male	25 (62.5)	39 (49.4)		23 (45.1)		21 (53.8)	
Female	15 (37.5)	40 (50.6)		28 (54.9)		18 (46.2)	
Tumor location			0.25		0.20		0.02
Right-sided colon	19 (47.5)	47 (59.5)		32 (62.7)		29 (74.4)	
Left-sided colon	21 (52.5)	32 (40.5)		19 (37.3)		10 (25.6)	
Tumor size, cm [median (range)]	3.3 (0.5-8.0)	3.5 (1.0-10.0)	0.84	4.5 (1.5-11.0)	0.03	5.0 (1.0-11.0)	0.02
Operative approach			0.34		1.00		1.00
Laparoscopic surgery	39 (97.5)	79 (100)		49 (96.1)		38 (97.4)	
Open surgery	1 (2.5)	0 (0)		2 (3.9)		1 (2.6)	
LN dissection			0.03		<0.01		0.01
D3	17 (42.5)	50 (63.3)		41 (80.4)		28 (71.8)	
D2	23 (57.5)	29 (36.7)		10 (19.6)		11 (28.2)	
Histology			0.27		0.63		0.62
Well or mod	39 (97.5)	72 (91.1)		48 (94.1)		37 (94.9)	
Por or muc	1 (2.5)	7 (8.9)		3 (5.9)		2 (5.1)	
Pathological T stage			0.54		0.10		0.02
T1	8 (20.0)	9 (11.4)		3 (5.9)		1 (2.5)	
T2	6 (15.0)	15 (19.0)		5 (9.8)		6 (15.4)	
T3	10 (25.0)	26 (32.9)		22 (43.1)		20 (51.3)	
T4	16 (40.0)	29 (36.7)		21 (41.2)		12 (30.8)	
Pathological N stage			<0.01		<0.01		<0.01
N1	39 (97.5)	56 (70.9)		37 (72.5)		22 (56.4)	
N2	1 (2.5)	23 (29.1)		14 (27.5)		17 (43.6)	
Number of dissected LNs [median (range)]	31 (18-93)	33 (16-70)	0.65	34 (14-42)	0.32	34 (14-74)	0.39
Number of MLNs [median (range)]	1 (1-6)	2 (1-24)	<0.01	2 (1-19)	<0.01	3 (1-18)	<0.01
Adjuvant chemotherapy	19 (47.5)	52 (65.8)	0.07	38 (74.5)	<0.01	23 (59.0)	0.37

Values in parentheses represent percentages unless otherwise stated. LN, Lymph node; MLN, metastatic lymph node; well, well differentiated adenocarcinoma; mod, moderately differentiated adenocarcinoma; por, poorly differentiated adenocarcinoma; muc, mucinous adenocarcinoma. *Comparing Group A to Group B. **Comparing Group A to Group C. ***Comparing Group A to Group D.

Table II. *Comparison of long-term outcomes by size of the largest metastatic lymph node.*

	Group A MLN <5 mm n=40	Group B 5 mm ≤ MLN < 10 mm n=79	*p*-Value*	Group C 10 mm ≤ MLN <15 mm n=51	*p*-Value**	Group D 15 mm ≤ MLN n=39	*p*-Value***
5-year overall survival rate (%)	94.9	91.2	0.92	93.9	0.69	77.9	0.08
5-year recurrence-free survival rate (%)	82.3	74.6	0.34	74.5	0.27	60.7	0.02

MLN, Metastatic lymph node. *Comparing Group A to Group B. **Comparing Group A to Group C. ***Comparing Group A to Group D.

pathological stage III colon cancer by classifying 209 patients into four groups according to the largest MLN diameter. Compared to the RFS in Group A (MLN <5 mm), that in Group D (MLN ≥15 mm) was significantly lower, and it was also lower in Groups B and C, but the differences were not significant. The multivariate analysis of RFS demonstrated that a maximum MLN diameter ≥15 mm was significantly associated with worse RFS, and the HR increased with MLN diameter. These results suggest that MLN diameter affected recurrence, and the presence of bulky MLNs was a poor

Table III. *Univariate and multivariate analyses by the Cox proportional-hazard regression model.*

	Overall	5-year RFS rate (%)	Univariate analysis			Multivariate analysis		
Variables			HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age								
<70 years	110 (52.6)	79.7	1			1		
≥70 years	99 (47.4)	66.8	1.89	1.89-3.28	0.03	1.36	0.72-2.56	0.34
Gender								
Male	108 (51.7)	75.4	1			1		
Female	101 (48.3)	72.1	1.06	0.62-1.83	0.82	1.01	0.56-1.82	0.98
Tumor location								
Right-sided colon	127 (60.8)	72.0	1			1		
Left-sided colon	82 (39.2)	76.7	0.78	0.44-1.38	0.40	1.25	0.67-2.36	0.48
Tumor size								
<5.0 cm	130 (62.2)	79.1	1			1		
≥5.0 cm	79 (37.8)	63.0	1.55	0.90-2.68	0.11	0.82	0.45-1.53	0.55
Lymph node dissection								
D3	136 (65.1)	73.2	1			1		
D2	73 (34.9)	74.6	0.93	0.52-1.68	0.81	0.96	0.46-2.00	0.94
pT								
T1	21 (10.1)	80.4	1			1		
T2	32 (15.3)	87.5	0.86	0.19-3.84	0.84	0.68	0.1-3.25	0.63
T3	78 (37.3)	80.5	1.41	0.41-4.86	0.59	1.03	0.27-3.90	0.97
T4	78 (37.3)	59.6	3.20	0.98-10.50	0.05	2.77	0.75-10.27	0.13
pN								
N1	154(73.7)	76.3	1			1		
N2	55 (26.3)	67.1	1.53	0.87-2.72	0.14	1.15	0.57-2.33	0.70
Histology								
Well or mod	196 (93.8)	74.6	1			1		
Por or muc	13 (6.2)	61.5	1.88	0.74-4.73	0.18	1.31	0.46-3.72	0.61
Group based on size of the largest MLN								
A: MLN <5 mm	40 (19.1)	82.3	1			1		
B: 5 mm ≤ MLN <10 mm	79 (37.8)	74.6	1.56	0.62-3.94	0.34	1.83	0.70-4.78	0.22
C: 10 mm ≤ MLN <15 mm	51 (24.4)	74.5	1.71	0.65-4.51	0.28	2.26	0.79-6.46	0.13
D: 15 mm ≤ MLN	39 (18.7)	60.7	3.00	1.16-7.73	0.02	3.95	1.34-11.65	0.01
Adjuvant chemotherapy								
Present	132 (63.2)	79.3	1			1		
Absent	77 (36.8)	63.3	2.10	1.22-3.62	<0.01	2.44	1.26-4.72	<0.01

Values in parentheses represent percentages unless otherwise noted. well, Well differentiated adenocarcinoma; mod, moderately differentiated adenocarcinoma; por, poorly differentiated adenocarcinoma; muc, mucinous adenocarcinoma; MLN, metastatic lymph node; RFS, recurrence-free survival; HR, hazard ratio; CI, confidence interval.

prognostic factor in pathological stage III colon cancer. Two previous studies evaluated the impact of MLN size on prognosis in stage III colorectal cancer (12, 13). One, which used a cutoff value of 5 mm to define a large MLN, reported that there were no significant differences in OS or disease-free survival (DFS) between patients with large and small MLNs (12). The other, which used a cutoff value of 10 mm, demonstrated that patients with large MLNs had worse OS and DFS than those with small MLNs, and large MLN diameter was identified as an independent poor prognostic factor in a multivariate analysis of DFS (13). Based on these results, patients in our study were classified into four groups to evaluate the relationship more precisely between MLN diameter and prognosis. Schrembs et al. analyzed the association between OS and the LN metastasis to LN size ratio (MSR) and demonstrated that smaller MSR values correlated with longer OS (18); that is, a high proportion of tumor components in MLNs was associated with worse prognosis. In our study, a maximum MLN diameter ≥15 mm was significantly associated with worse prognosis; therefore, most of the normal lymphatic tissue might be replaced by tumor cells in bulky MLNs. Furthermore, in gastric cancer and esophageal cancer, MLN size was also reported to be a poor prognostic factor (19-21). MLN size might reflect malignant potential in gastrointestinal cancers.

The absence of adjuvant chemotherapy was also associated with worse RFS in the multivariate analysis in this study. In pathological stage III colon cancer, adjuvant chemotherapy for 6 months is recommended by the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines (17). Recent large studies reported that adjuvant chemotherapy for 3 months was noninferior to 6 months in terms of disease-free survival in low-risk stage III colon cancer, including T1, T2, T3, and N1 disease (22, 23). However, even for this type of cancer, adjuvant chemotherapy for 6 months might be optimal if MLNs are bulky.

There are several limitations to this study. First, this was a retrospective study that was conducted at a single institution and that enrolled a relatively small number of patients. That might be why there were no significant differences in RFS between Group A (MLN <5 mm) and Group B (MLN ≥5 mm and <10 mm) or Group C (MLN ≥5 mm and <10 mm). Second, in both univariate and multivariate analyses of RFS, there were no significant differences in N stage, which has been considered to be the most powerful independent prognostic factor in stage III colon cancer (24-26). The reason for this discrepancy is unclear. The proportion of N2 cancers was significantly higher in Group D (MLN ≥15 mm) than in Group A (MLN <5 mm), which might have resulted in the difference in RFS between the two groups. Therefore, multivariate analysis that included both the N stage and MLN size was performed to minimize this bias.

In conclusion, our findings indicate that a maximum MLN ≥15 mm was significantly associated with worse RFS in stage III colon cancer. Bulky MLNs might be a poor prognostic factor in node-positive colon cancer.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

Chikara Maeda and Yamaoka Yusuke drafted the paper. Yamaoka Yusuke designed this study. Chikara Maeda, Yamaoka Yusuke, Akio Shiomi, Hiroyasu Kagawa, Hino Hitoshi, Shoichi Manabe, Shunichiro Kato, Marie Hanaoka and Akifumi Notsu obtained and analyzed data.

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