



# The relation between oncologic outcomes and metastatic lymph node location following laparoscopic resection of stage III colon cancer

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Accepted: 11 January 2019 / Published online: 23 January 2019  
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## Abstract

**Purpose** Colon cancers are staged by assessing more than 12 lymph nodes, but there is still a controversy over the number of lymph nodes. Only a few studies of metastatic lymph node position in colon cancer have been published with its significance not completely understood. This study aimed to compare survival rates according to metastatic lymph node position following radical lymph node dissection for stage III colon cancers.

**Methods** This retrospective study evaluated data prospectively collected at a tertiary teaching hospital from 349 patients who underwent laparoscopic colectomy with radical node dissection between December 2009 and December 2014. Lymph nodes were numbered and classified into lymph node metastasis (LNM) groups LNM1, LNM2, and LNM3 and their short- and long-term outcomes were compared.

**Results** The LNM1, LNM2, and LNM3 groups included 229, 94, and 26 patients, respectively. Patient characteristics differed by locations ( $p < 0.001$ ). A mean 34.6 lymph nodes were harvested, and a mean 2.6, 5, and 9 metastatic nodes were identified, respectively ( $p < 0.001$ ), a finding that is proportional to the cancer stage ( $\tau\text{-}b = 0.284$ ,  $p < 0.001$ ;  $\rho = 0.3$ ,  $p < 0.001$ ). The 5-year disease-free survival rate did not differ among the three groups; however, the LNM3 group had the poorest overall and cancer-specific survival rates. Risk factors associated with cancer-specific survival rate were identified with neural invasion, poorly differentiated tumors, and the location of pathologic lymph nodes (LNM).

**Conclusion** Metastatic lymph node location affects oncologic outcomes of stage III colon cancer. The patients for LNM3 metastasis should receive a more aggressive adjuvant treatment.

**Keywords** Laparoscopy · Stage III colon cancer · Lymph node location · Radical lymphadenectomy

## Introduction

Lymph node metastasis in colon cancers is an important factor in determining adjuvant therapy and prognosis. The surgical

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Colon cancers are staged by assessing more than 12 lymph nodes, but there is still a controversy over the number of lymph nodes. The authors have classified metastatic lymph nodes into D1, D2, and D3 groups and compared the short- and long-term outcomes following laparoscopic colonic resection and radical lymphadenectomy. The number of metastatic nodes was proportional with the stage, and principal (D3) node metastasis showed the lowest overall and cancer-specific survival.

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extent of colorectal cancer has been continuously proposed for radical lymph node resection. In 1995, Heald introduced the concept of total mesorectal excision (TME) in rectal cancer [1]; in 2009, Hohenberger proposed radical resection in advanced right-side colon cancer consisting of complete mesocolic excision (CME) with central vascular ligation (CVL) [2]. The American Joint Conference on Cancer (AJCC) [3] and TNM committee of the International Union Against Cancer (UICC) [4] recommend the identification of at least 12 lymph nodes to determine exact cancer stage. However, studies have consistently reported that the greater the number of harvested lymph nodes, the better the oncologic outcome [5]. This is explained as a stage migration effect according to missed lymph node metastases, especially at the boundaries of stage II and III colon cancers [6]. Meanwhile, only a few studies of metastatic lymph node position in colon cancer have been published with its significance not completely understood. This study aimed to compare short- and long-term outcomes in patients with stage III

colon cancers according to metastatic lymph node position following laparoscopic colonic resection and radical lymph node dissection.

## Patients and methods

This retrospective study analyzed prospectively collected data of 349 patients who underwent laparoscopic colonic resection and radical lymph node dissection at a tertiary teaching hospital between December 2009 and December 2014. Radical D3 lymphadenectomy includes the principal nodes of the ileocolic artery; right colic artery, if present; middle colic artery; and inferior mesenteric artery. Lymph node harvest was performed in the operating room after specimen resection. The lymph node distributions were grouped according to the 2014 Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines for the treatment of colorectal cancer [7]. The area adjacent to the colon was classified as lymph node metastasis (LNM) 1, with the location of the principal node classified as LNM3 and the middle region as LNM2. LNM1 201, 211, 221, 231, and 241; LNM2 202, 212, 222, 232, and 242; and LNM3 203, 213, 223, and 253. Collected data included age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) classification, previous medical history, previous abdominal surgery, tumor location, preoperative carcinoembryonic antigen (CEA) level, operative duration excluding the initial anesthetic duration, and estimated blood loss (EBL). Pathological outcomes included tumor size; lymph node status; tumor, stage, invasion, and differentiation; and tumor margins. The following postoperative outcomes were also compared: postoperative complications, days to bowel movement and diet resumption, length of hospital stay, postoperative mortality, and number of patients treated with adjuvant chemotherapy. Oncological outcomes included 5-year local recurrence-free, overall, and cancer-specific survivals.

The preoperative evaluation included a CEA assay, chest and abdominopelvic computed tomography (CT), and total colonoscopy. Staging was based on the seventh edition of the TNM classification of colon cancer proposed by the UICC and the AJCC; cases included before 2010 were restaged. The patients visited the hospital every 3 months for the first 2 years and every 6 months from the third to fifth years. During follow-up, serum CEA analyses and chest and abdominopelvic CT were performed. Recurrence was defined as a pathologically identified or radiologically proven local or systemic metastasis. The study was approved by the Institutional Review Board of OOO Hospital (CNUH-2018-159).

## Statistical analysis

Intergroup differences were compared using one-way analysis of variance, the Kruskal–Wallis test for continuous data, and chi-square or test linear-by-linear association for categorical data. Correlation used nonparametric methods of Kendall and Spearman. The probabilities of recurrence and survival were estimated using Kaplan–Meier curve analyses. For multivariate analyses, we fit binary logistic regression models to identify significant risk factors from a set of significant main-effect variables ( $p < 0.10$ ). The statistical analyses were performed using SPSS (version 20; IBM, Armonk, NY, USA).  $p$  values  $< 0.05$  were considered statistically significant.

## Results

### Clinical characteristics

The patients' group allocations were as follows: LNM1, 229; LNM2, 94; and LNM3, 26. There were no differences with respect to the age, sex, BMI, ASA classification, comorbidities, previous abdominal surgery, or preoperative CEA in the three groups. Patient characteristics differed among cancer locations ( $p < 0.001$ ). Cecal, ascending, and transverse colon cancers were the most frequent in the LNM3 group, whereas descending and sigmoid colon cancers were most common in the LNM2 group (Table 1).

### Operative and pathologic outcomes

Surgical outcome variables of operating time and EBL did not differ among the three groups. There was one case of open conversion in LNM1 due to an intraabdominal adhesion caused by a previous abdominal surgery. There were no differences in tumor size, number of harvested nodes, or specimen margins from the proximal or distal colon; however, the closer the location to the principal area, the greater the number of metastasized nodes ( $p < 0.001$ ). This finding correlated with TNM stage ( $\tau\text{-}b = 0.284$ ,  $p < 0.001$ ;  $\rho = 0.3$ ,  $p < 0.001$ ). There was no intergroup difference in vascular and lymphatic invasion, but the LNM2 group had the highest proportion of cases of neural invasion ( $p = 0.014$ ), whereas the LNM3 group had the highest proportion of cases with poor differentiation ( $p = 0.003$ ) (Table 2).

### Postoperative outcomes

Postoperative complications including superficial SSI, abdominal and anastomotic bleeding, anastomotic leakage, postoperative ileus, voiding difficulty, and pulmonary

**Table 1** Patient demographics and characteristics

	LNM1	LNM2	LNM3	<i>p</i> value
Age, years, mean ± SD	66.5 ± 10.1	63.3 ± 9.9	68.6 ± 9.8	0.140
Sex, <i>n</i> (%)				0.149
Male	112 (48.9)	57 (60.6)	14 (53.8)	
Female	117 (51.1)	37 (39.4)	12 (46.2)	
BMI, mean ± SD (kg/m <sup>2</sup> )	23.8 ± 6.2	23.3 ± 4.3	25.2 ± 13.8	0.407
ASA class, <i>n</i> (%)				0.311
1	49 (21.4)	29 (30.9)	4 (15.4)	
2	164 (71.6)	62 (66)	21 (80.8)	
3	16 (7)	3 (3.2)	1 (3.8)	
Comorbidities, <i>n</i> (%)				
DM	45 (19.7)	21 (22.3)	8 (30.8)	0.207
HTN	114 (49.8)	37 (39.4)	15 (57.7)	0.676
Previous abdominal surgery, <i>n</i> (%)	38 (16.6)	18 (19.1)	4 (15.4)	0.839
Cancer location, <i>n</i> (%)				< 0.001
Cecum/ascending	84 (36.7)	19 (20.2)	13 (50)	
Transverse	17 (7.4)	5 (5.3)	6 (23.1)	
Descending/sigmoid	128 (55.9)	70 (74.5)	7 (26.9)	
Preop. CEA, mean ± SD	11.9 ± 2.4	9.9 ± 1.7	11.3 ± 3.4	0.878

LNM, lymph node metastasis; SD, standard deviation; BMI, body mass index; ASA, American Society of Anesthesiologists; DM, diabetes mellitus; HTN, hypertension; Preop., Preoperative; CEA, carcinoembryonic antigen

dysfunction were identified but did not differ among groups. The first gas passage was at 2.1 days, first defecation was at 3.9 days, and diet resumption was at 2.2 days after surgery, and average total hospitalization was 8.4 days. Bleeding, pneumonia, and ultimately post-operative mortality were confirmed as one case in the LNM1 group. No difference in the use of adjuvant chemotherapy was noted among groups (Table 3).

### Oncological outcomes

The median follow-up was 35 months, and locoregional and distant metastasis did not differ among the three groups. Local recurrence occurred most frequent in the LNM3 group, but the difference was not statistically significant ( $p = 0.172$ ). There were no differences among the three groups, but the overall ( $p = 0.001$ ) and cancer-specific ( $p = 0.012$ ) survival rates were the lowest in the LNM3 group (Table 4; Fig. 1).

### Risk factors for cancer-specific survival rate

Cancer-specific survival rate was found to be lower when it had neural invasion (hazard ratio (HR) = 4.592; 95% confidence interval (CI) 1.919–10.989;  $p = 0.001$ ), poorly differentiated state (HR = 3.277; 95% CI 1.378–7.790;  $p = 0.007$ ), and the higher the number of LNM (HR = 2.078; 95% CI 1.264–3.418;  $p = 0.004$ ) (Table 5).

### Discussion

This study was designed to compare the short- and long-term outcomes according to metastatic lymph node in stage III colon cancer following laparoscopic colonic resection and radical lymph node dissection. Compared with tumor position, cecal, ascending, and transverse colon cancer more often invaded at the principal lymph node level than did descending and sigmoid colon cancer. The deeper the node invasion, the greater the number of metastatic lymph nodes, similar to the progression of TNM staging, and more frequently the tumor was poorly differentiated. Metastasis of the principal node indicated lower 5-year overall and cancer-specific survival rates. LNM was also identified as a risk factor affecting survival rates.

This study included cases of transverse colon cancer, which was excluded from previous studies such as TME in the rectosigmoid colon and CME with CVL in right-sided colon cancer. The authors announced acceptable results of oncologic outcomes of laparoscopic and open surgery in cases of stage II and III transverse colon cancer when radical lymphadenectomy was performed [8]. Studies of lymph node location or level published to date were primarily of left-side colorectal cancers. In cases of principal lymph node metastasis, which affects the inferior mesenteric node, the survival rate was 31% in contrast to 50% for node-negative disease, indicating systemic nodes [9]. This was supported by a study of principal node metastasis in sigmoid and rectal cancers, which were

**Table 2** Operative and pathological outcomes

	LNM1	LNM2	LNM3	<i>p</i> value
Op. time, min, mean ± SD	139.8 ± 42.4	135.7 ± 42.9	134 ± 30.1	0.629
EBL, mL, mean ± SD	102 ± 13.7	78 ± 9.8	149 ± 27	0.184
Conversion to open, <i>n</i> (%)	1 (0.4)	0	0	0.504
Tumor size, cm, mean ± SD	4.5 ± 2.0	4.7 ± 2.1	5.5 ± 2.0	0.089
Harvested LN, mean (range)	35 (12–122)	32 (13–116)	40 (12–94)	0.072
Pathological LN, mean (range)	2.6 (1–19)	5 (1–22)	9 (1–42)	<0.001
TNM stage, <i>n</i> (%)				<0.001
IIIa	31 (13.5)	2 (2.1)	2 (7.7)	
IIIb	143 (62.4)	47 (50)	7 (26.9)	
IIIc	55 (24)	45 (47.9)	17 (65.4)	
Invasion, <i>n</i> (%)				
Vascular	74 (32.3)	37 (39.4)	12 (46.2)	0.088
Lymphatic	77 (33.6)	39 (41.5)	12 (46.2)	0.094
Neural	107 (46.7)	61 (64.9)	15 (57.7)	0.014
Differentiated, <i>n</i> (%)				
Well	56 (24.5)	18 (19.1)	5 (19.2)	0.303
Moderately	144 (62.9)	63 (67)	12 (46.2)	0.415
Poorly	20 (8.7)	12 (12.8)	8 (30.8)	0.003
Margin, cm (range)				
Proximal	11.1 (2–58)	10.5 (2.5–73)	13.6 (2–28)	0.195
Distal	8.0 (1–33)	8.3 (1.5–25)	9.8 (2–28)	0.347

LNM, lymph node metastasis; Op, operative; EBL, estimated blood loss; LN, lymph node; TNM, tumor node metastasis

similar in overall survival ( $p = 0.761$ ) and disease-free survival ( $p = 0.704$ ) rates to stage IV disease [10]. This study's findings implied that lymph node metastasis of whole-colon cancers includes right-sided and transverse colon cancers but

excludes rectal cancers, which are known to be biologically different from colon cancers.

The AJCC and TNM committees recommend that at least 12 lymph nodes be identified in a resected specimen

**Table 3** Postoperative outcomes

	LNM1	LNM2	LNM3	<i>p</i> value
Postop. complications, <i>n</i> (%)	19 (8.3)	7 (7.4)	4 (15.3)	0.750
Superficial SSI	6 (2.6)	3 (3.2)	1 (3.8)	
Abdominal bleeding	1 (0.4)	0	0	
Anastomosis bleeding	2 (0.9)	0	1 (3.8)	
Anastomosis leakage	4 (1.7)	1 (1.1)	2 (7.7)	
Ileus	2 (0.9)	1	0	
Voiding	4 (1.7)	2 (2.1)	0	
Pulmonary	2 (0.9)	0	0	
Gas passage, days (range)	2.1 (1–6)	2.3 (1–12)	2.1 (1–6)	0.623
Defecation, days (range)	3.9 (1–10)	3.9 (1–10)	3.5 (2–8)	0.618
Diet resumption, days (range)	2.2 (1–4)	2.1 (1–4)	2.1 (1–4)	0.608
Postop. hospital stay, days (range)	8.3 (3–72)	8.3 (6–51)	9.9 (6–46)	0.422
Postop. mortality, <i>n</i> (%)	1 (0.4)	0	0	0.504
Adjuvant chemotherapy, <i>n</i> (%)	131 (57.2)	49 (52.1)	14 (53.8)	0.475
FOLFOX	97 (42.4)	45 (47.9)	12 (46.2)	
5-FU	32 (14)	4 (4.3)	2 (7.7)	

LNM, lymph node metastasis; Postop., postoperative; SSI, surgical site infection

**Table 4** Long-term outcomes

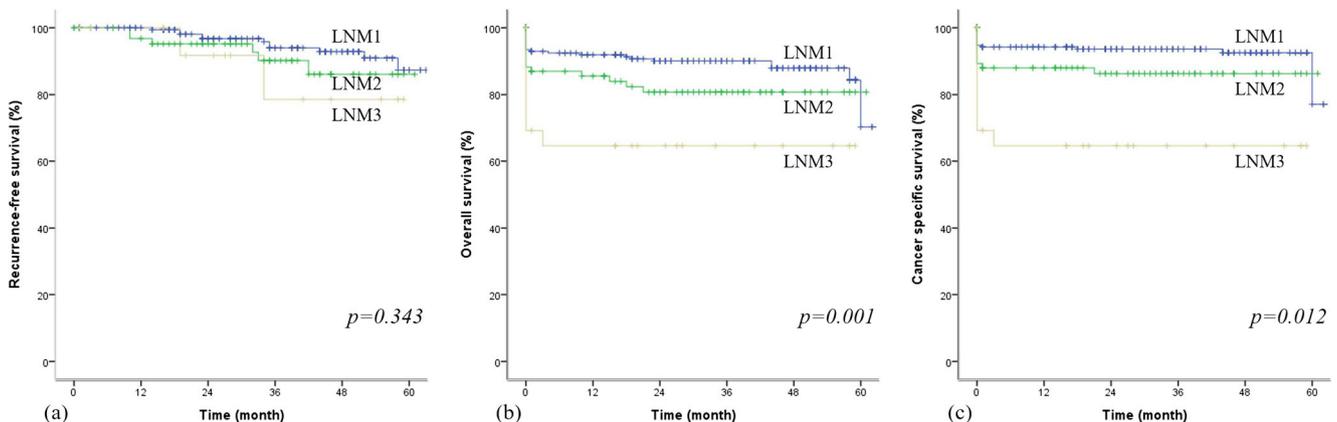
	LNM1	LNM2	LNM3	<i>p</i> value
Median follow-up, months (range)	36.5 (1–65)	31.5 (1–61)	31.6 (1–59)	0.454
Recurrence, <i>n</i> (%)				
Locoregional	8 (3.5)	3 (3.2)	3 (11.5)	0.172
Distant metastasis				0.257
Liver	8 (3.5)	3 (3.2)	2 (7.7)	
Lung	4 (1.7)	6 (6.4)	0	
Liver and lung	2 (0.9)	0	0	
Ovary, peritoneum	2 (0.9)	1 (1.1)	1 (3.8)	
5-year DFS (%)	87.3	86	78.6	0.343
5-year OS (%)	70.3	80.8	64.6	0.001
5-year CSS (%)	94.1	93.9	71.4	0.012

LNM, lymph node metastasis; DFS, disease-free survival; OS, overall survival; CSS, cancer-specific survival

to determine exact staging. However, controversy persists in studies published to date over the number of lymph nodes that require harvesting. A study of 345 patients from 1995 to 1999 reported a better disease-free survival rate in node-negative patients when the number of nodes analyzed was higher than that of a national cancer registry (OncoPool) [11]. A secondary analysis of the Intergroup Trial INT-00899, a trial of adjuvant chemotherapy provided for patients with high-risk stage II and III colon cancers, showed that the more the nodes were analyzed, the longer the survival ( $p = 0.0001$ ) [12]. Using this, those authors created a mathematical model by analyzing 1585 cases of stage II and III colon cancers. T1/T2 tumors showed a 25% reduction in true node negativity with the analysis of 18 nodes in contrast to the previous analysis [12]. The result using the Surveillance, Epidemiology, and End Results (SEER) database identified a median of nine lymph nodes but suggested the analysis of at least 15 to improve survival [13]. The following study published later that year announced that predictable outcomes should be based on the number of non-metastatic lymph nodes. When more than 13 negative nodes were harvested in

cases of stage IIIB and IIIC cancer, 5-year cancer mortality was significantly lower [14]. This study reported a mean 34.6 harvested nodes (30.9 of which were negative), a higher number than published previously.

In addition to the study of the number of lymph nodes to increase outcome accuracy, it has been reported that oncologic outcome could be predicted through lymph node ratio (LNR; number of positive nodes divided by total number of harvested nodes). In 2007, Schumacher et al. reported a breakpoint for predicting disease-free survival based on an LNR of 0.18 in stage III colon cancer [15]. Studies revealed that LNR had better prognostic value than the N stage afterward. Using optimal cut-off values for prognostic differentiation of LNR, the prognostic value was better than the pN category ( $p < 0.05$ ) [16]. In a prospective nationwide Danish cohort, lymph node count and LNR were independent prognostic factors on multivariate analysis. LNR was superior to nodal stage in differentiating overall survival in cases of stage III colon cancer [17]. Nevertheless, LNR has the limitation of usually being used when the number of harvested lymph nodes was inadequate to meet the criteria.



**Fig. 1** Kaplan-Meier curves of recurrence-free survival (a), overall survival (b), and cancer-specific survival (c) in stage III

**Table 5** Multivariate analysis of risk factors affecting survival rate (logistic regression with backward elimination method)

	Odds ratio	95% CI		<i>p</i> value
		Lower	Upper	
Neural invasion	4.592	1.919	10.989	0.001
Poorly differentiated	3.277	1.378	7.790	0.007
LNM	2.078	1.264	3.418	0.004

CI, confidence interval; LNM, lymph node metastasis

Preventing under-staging, making decisions about adjuvant treatments, and predicting oncological outcomes based on the number of lymph nodes has been controversial. Surgeons' decisions about the extent of resection, pathologists' exact lymph nodal assessment, and biological features of the tumor as well as nodal status such as the number of lymph nodes, LNR, sentinel lymph node must be considered in outcome predictions [18, 19]. In addition, metastatic lymph node location, which this study found to be significant, might also help predict outcomes.

This study had limitations. It may be questioned whether the range of surgery (right-sided versus left-sided colorectal cancers) is comparable. This study included patients who underwent standard radical lymph node dissection known to date including principal nodes indicated in the JSCCR Guidelines. Of course, the Japanese D3 has already been proven to not differ in the number of lymph nodes in comparison to the CME used in Europe [20]. This may have led to selection bias due to its retrospective design despite the use of prospectively collected data. Nevertheless, we believe that metastatic lymph node location or distribution could predict prognosis as well as TNM staging.

## Conclusion

Metastatic lymph node location affects oncologic outcomes in stage III colon cancer. For patients with stage III colorectal cancer, aggressive surgery is required to include principal lymph nodes and postoperative chemotherapy should also be recommended when possible.

**Author contributions** Study conception and design: H D K and H R K. Acquisition of data: H D K, J K J, S Y L, C H K, Y J K, and H R K. Analysis and interpretation of data: H D K, J K J, S Y L, C H K, Y J K, and H R K. Drafting the article or revising it critically for important intellectual content: H D K, J K J, S Y L, C H K, Y J K, and H R K. Final approval of the version to be published: H D K and H R K.

## Compliance with ethical standards

The study was approved by the Institutional Review Board of Chonnam National University Hospital (CNUH-2018-159).

**Conflict of interest** The authors declare that they have no conflict of interest.

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