Estimation of the Number of Metastatic Lymph Nodes in Dukes' C Colorectal Cancer

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Abstract. *Background: Colorectal cancer staging is decided by the depth of tumor invasion and the node (N) category. Evaluation of the metastatic lymph node number (MLN) varies. The purpose of this study was to investigate the N-category as a function of MLN. Patients and Methods: Patients with colorectal cancer (n=551) who underwent curative resection were grouped based on the MLN, and appropriate cut-off values were decided based on survival. The validity of the new cut-off values was analyzed as a prognostic factor. Results: The median number of lymph nodes retrieved per patient was 19, and the median MLN was 2. The survival and recurrence rates allowed MLN groupings of 1-4, 5-7, and ≥8. In particular, when grouping was performed using MLN ≤4 and ≥5, the 5-year survival rate for patients with MLN ≥5 (56.8%) was significantly worse than that of these with MLN ≤4 (78.6%) (p<0.0001). Receiver operating characteristic (ROC) curve analysis showed the highest accuracy to be with MLN=5. Multivariate analysis using a Cox proportional hazard model identified MLN ≥5 as an independent adverse prognostic factor (hazard ratio=1.84; 95% confidence interval=1.2801-2.6295; p=0.0012). Conclusion: MLN ≥5 is an independent predictor of 5-year survival for patients with Dukes' C colorectal cancer. It is possible that tumor staging in colorectal cancer differs between facilities, with particular ramifications for patients with stage III disease.*

The depth of invasion and lymph node metastasis are well-known important factors impacting on the prognosis of cancer (1-4). Information regarding these factors is easily obtained following surgery, but some issues remain. The stage grouping of colorectal cancer has been classified with a system that uses the metastatic lymph node number (MLN) (1, 2), or the site of metastasis (3, 5), or both (6) as the node category (N-category). Japanese stage grouping is defined in the Japanese Classification of Colorectal Carcinoma (JCCC) prepared by the Japanese Society for Cancer of the Colon and Rectum (JSCCR). The JSCCR, based on many years of clinical research data, considers that the site of lymph node metastasis is more important than the N-category, regardless of the MLN. According to the JSCCR classification, the pericolic/perirectal lymph nodes near the tumor are classified as N1, the lymph nodes around the main artery as N3, and the lymph nodes in between as N2 (5). However, to be consistent with the Tumor, Nodes, and Metastasis (TNM) staging system (6), the JCCC N-category was revised in 2009 to take both the metastatic site and the MLN into consideration, rather than only the site. Thus, N1 now indicates metastasis in 1-3 pericolic/perirectal or intermediate lymph nodes, N2 indicates metastasis in four or more pericolic/perirectal or intermediate lymph nodes, and N3 indicates metastasis in main or lateral lymph nodes (7). The TNM classification was again revised in 2010, and stage classification became more complicated due to detailed classification of the N-category (8). The validity of the revised classification was verified only for colon cancer (9). Verification was also carried out in Japan in accordance with the seventh edition of the TNM classification, and the results showed that the prognosis of stage IIIA was better than the prognoses of stages IIB and IIC (10).

We have investigated classification of the MLN in the N-category for colon cancer in our institution in the past. The N-category more closely reflects survival when classification is performed using MLN categories of 1, 2-6, and ≥7 (11). Those results suggested further analysis of the cut-off values for MLN as the standard for stage grouping. Accordingly, we investigated the N-category as a function of MLN based on the outcome of patients with Dukes' C colorectal cancer for whom data have been registered in the database system with a consistent method in our single institution since 1975.

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Key Words: TNM classification, node category (N-category), retrieved lymph node number (RLN), Dukes' C, colorectal cancer.

Patients and Methods

The protocols described in this study were approved by an Institutional Ethics Committee (#2271). We investigated 551 patients who provided written informed consent with Dukes' C primary colorectal adenocarcinoma who underwent curative resection from the cecum to the rectum. The operations were performed at the Department of Surgery of Kurume University Hospital between January 1985 and December 2007. Patients with familial adenomatous polyposis, inflammatory bowel disease, and rectal cancer who underwent preoperative chemoradiation were excluded from the study. In cases of simultaneous colorectal cancer, the most advanced lesion was included in the data. Metachronous advanced colorectal cancer lesions were excluded. The average age of the patients was 64.3±12.2 years (median=65 years), and 344 patients were male (62.4%). The site of the tumor was the colon in 369 patients (66.9%) and the rectum in 182 patients.

Follow-up system. The patients were followed-up after surgery. Each patient was examined every three months for the first three years, and the carcinoembryonic antigen (CEA) level was measured. Computed tomography (CT) examinations were performed every 6-12 months. From the fourth year on, CEA was determined every six months, and a CT examination was performed annually. The median follow-up period was 68 months, and patients were followed-up for at least five years or until death. The outcome was confirmed at the time of the last consultation, but when that was not possible, a postcard was sent to ascertain the outcome. The survival end-point was death due to any cause.

Surgical treatment for colorectal cancer and handling of specimens. All operations for colorectal cancer were performed in accordance with the standard operative techniques in Japan by a surgeon specializing in colorectal surgery or by his or her assistant. The standard operative techniques consisted of complete mesocolic excision (CME) of colonic tumors (12) and total mesorectal excision (TME) of rectal tumors (13). Both techniques of CME and TME in colorectal cancer surgery are aimed at obtaining a specimen with intact layers and maximal lymph node harvest. Lymph node dissection was performed by en *bloc* excision of lymph nodes along the major artery at the site of the tumor. Resection of the intestinal tract was performed with a margin of approximately 10 cm from tumors in the colon, and 3 cm on the anal side in the case of rectal tumors. Figure 1 shows the method for lymph node retrieval following TME by the surgeon prior to formalin fixation. The opened fresh intestine was placed on a board with the mucosal side up, and the edge was stretched and pinned to reproduce its original appearance. After formalin fixation for several days, the tumor was sectioned at 5-mm intervals. All specimens and all lymph nodes were examined by an expert pathologist. The details of all clinicopathological data for each patient were entered into the department's computer database.

Determining MLN cut-off values. All patients were classified as a function of the MLN, and the numbers of cases, numbers of retrieved lymph nodes (RLN), lymph node ratio (LNR: the ratio of metastatic lymph nodes to examined lymph nodes), recurrence rates, and overall survival rates were calculated. The survival rates were estimated by the Kaplan–Meier method. Various cut-off values were set for the MLN (namely 2, 3, 4, 5, 6, and 7), and the hazard ratios between two classified groups (*e.g.* 1 *versus* ≥2) were estimated using a Cox proportional hazard model. In addition, receiver operating characteristic (ROC) curves were used to estimate the MLN cut-off value that had the greatest impact on the outcome. Based on those results, the MLN cut-off value with the greatest clinical importance was determined.

Adverse prognostic factors based on the new classification. The N-category was modified in accordance with the MLN cut-off value that was considered to be appropriate, and the clinicopathological characteristics of each group were examined. Various potential prognostic factors (namely the gross tumor type, preoperative CEA value, maximum tumor diameter, RLN, LNR, histological type, lymphatic invasion, and venous invasion) were investigated based on the cumulative survival rate. The median values for continuous variables (preoperative CEA value, maximum tumor diameter, RLN, LNR) were classified into two groups by cut-off values. The histological type was classified into the "well-differentiated type" and "other" based on the degree of differentiation. Lymphatic invasion (ly) and venous invasion (v) were classified into two groups, *i.e.* absent (0) to mild (1), and moderate (2) to severe (3), in accordance with the Department's standard classification (14, 15). In brief, "ly" was defined as occurring only when cancer cells were floating in an endothelial-lined space, and "v" was defined as tumor cells in a space lined by endothelial cells and smooth muscle or elastic fibers. Potential prognostic factors that showed a statistically significant difference in univariate analysis were subjected to multivariate analysis using a Cox proportional hazard model. $p<0.05$ was considered to be statistically significant. All statistical analyses were performed using JMP 9.0.2 software (SAS Institute, Inc., Cary, NC, USA).

Results

Table I shows each MLN, the data regarding the number of cases, primary lesion site, RLN, LNR, recurrence rate, and 5-year survival rate. The mean RLN per specimen was 29 (inter-quartile range=19-44), and the mean MLN was 2 (inter-quartile range=1-4). The group with MLN=1 was the largest (38%), and the largest MLN was 14. The number of cases in each group decreased as the MLN increased. The groups with a larger MLN also had a larger RLN, and the LNR was comparatively high. The recurrence rate increased in the groups with a larger MLN, whereas the survival rate decreased. The survival and recurrence rates were similar within each MLN grouping of 1-4, 5-7, and ≥8. Table II shows the results of analysis of the relationship between the MLN cut-off values and the survival rate. Statistically significant differences were found between each of the MLN groupings. In particular, using an MLN cut-off of 5, the differences in the recurrence rates and the significant differences in the 5-year survival rates became large. In addition, the ROC curves for the MLN and survival period showed that the greatest accuracy was achieved when MLN=5 (Figure 2). Overall, we surmised that an MLN cut-off value of 5 was appropriate.

On that basis, the cases were divided into two MLN groups, namely ≤4 and ≥5. Table III shows the data for the

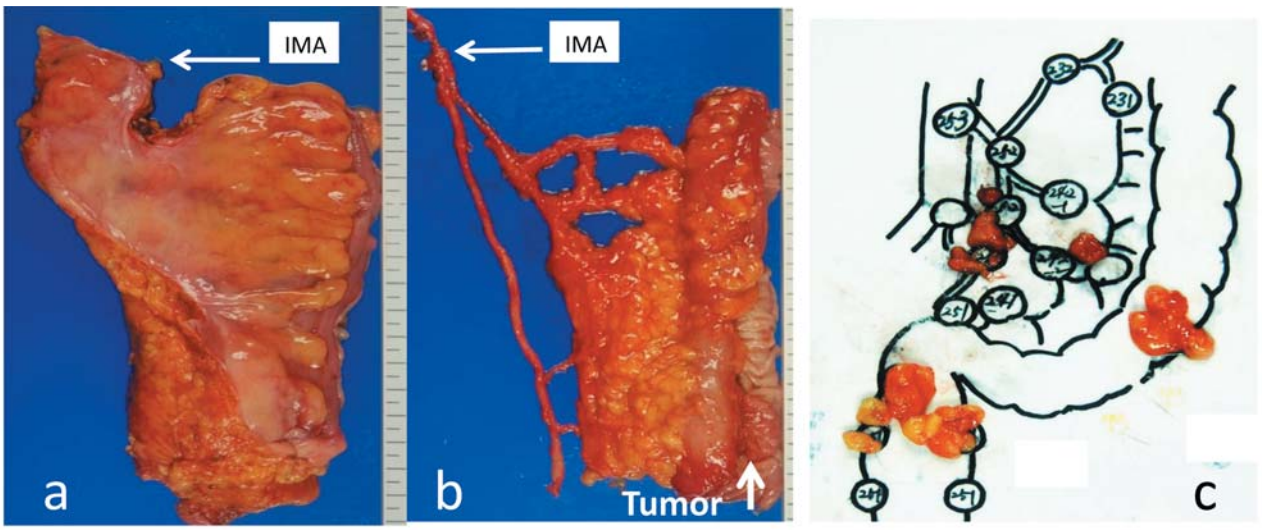

Figure 1. *The methods for lymph node retrieval after the fresh specimen is removed. a: Fresh specimen after anterior resection for advanced sigmoid colon cancer in which the pedicle of the inferior mesenteric artery (IMA) was ligated. b, c: The lymph nodes along the feeding vessels (IMA) were retrieved from the mesorectum and kept separately according to the lymph node stations, and then fixed in formalin. The pericolic nodes in the fat tissue beside the tumor were left intact for the correct judgment of depth of invasion.*

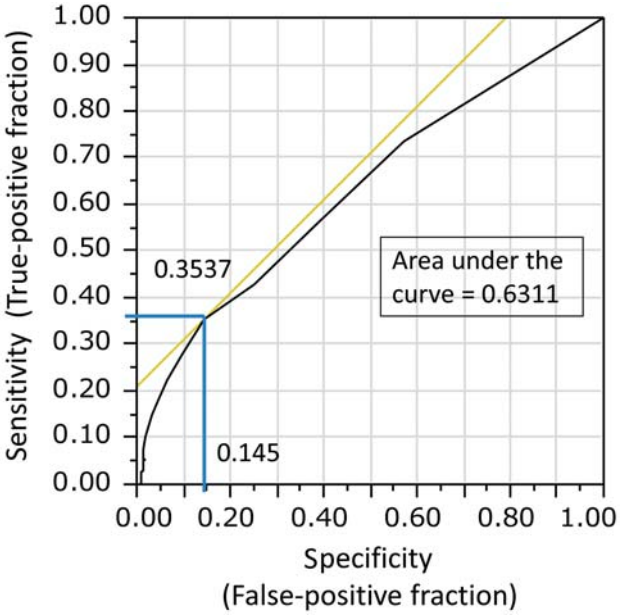

Figure 2. *Cut-off point of metastatic lymph node number (MLN) using receiver operating characteristic (ROC) curve analysis. The best point with highest true-positive and lowest false-positive survival rates was analyzed. The ROC curve analysis showed the sensitivity (0.3537), specificity (0.855), odds ratio (2.2097), and smaller chi-square, p-value (0.0012) at a cut-off point of MLN=5.*

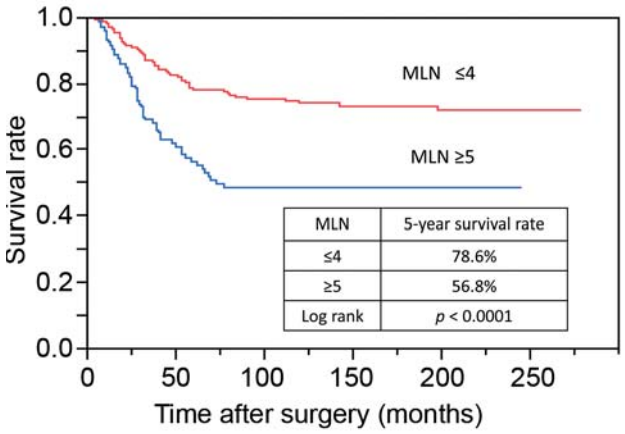

Figure 3. *Overall survival. The 5-year overall survival rate of patients according to metastatic lymph node number (MLN). The rate of patient with MLN ≤4 was 78.6%, which is significantly better than that of those with MLN ≥5 (p<0.0001).*

clinicopathological characteristics of the patients in those two groups. The group with MLN ≥5 had a larger tumor size and included more cases of an invasive type, with a large percentage of the tumor around the circumference of the bowel compared with the group with MLN ≤4. Histologically, the group with MLN ≥5 had a more poorly-differentiated tumor type, and this group included significantly more cases of severe lymphatic invasion and venous invasion ($p<0.0001$). The 5-year survival rate in the group with MLN ≥5 was 56.8%, which was significantly worse than the rate in the group with MLN ≤4 ($p<0.000$, Figure 3).

Table IV presents the results of the univariate and multivariate analyses of the clinicopathological factors related

Table I. *Prognosis in Dukes C colorectal cancer.*

MLN	Cases	Colon (%)/rectum (%)	Retrieval LN Av. (med)	LNR Av. (med)	Recurrence rate	5-year survival rate
1	211	146 (69)/65 (31)	29.6 (25)	0.059 (0.040)	22.7%	81.2%
2	100	67 (67)/33 (33)	30.8 (28)	0.093 (0.071)	27.0%	76.8%
3	75	54 (72)/21 (28)	31.0 (27)	0.139 (0.111)	30.7%	70.1%
4	54	34 (63)/20 (37)	34.0 (32)	0.153 (0.125)	24.1%	80.4%
5	31	19 (61)/12 (39)	33.0 (30)	0.199 (0.167)	35.5%	67.1%
6	21	11 (52)/10 (48)	46.0 (46)	0.168 (0.130)	42.9%	64.2%
7	13	8 (62)/5 (38)	35.2 (31)	0.251 (0.226)	46.2%	76.9%
8	11	6 (54)/5 (46)	44.0 (37)	0.520 (0.500)	54.5%	51.9%
9	12	10 (83)/2 (17)	44.1 (42)	0.308 (0.263)	58.3%	28.5%
≥10	23	9 (39)/14 (61)	44.3 (48)	0.340 (0.300)	69.6%	33.3%
Total	551	369 (67)/182 (33)	32.6 (29)	0.121 (0.083)	30.1%	74.0%

Table II. *Analysis of cut-off value of metastatic lymph node number for overall survival.*

Cut-off number	MLN	No. of patients	Rate of recurrence	5-year survival rate	Chi-square	*p*-Value
2	1 *vs.* ≥2	211 *vs.* 340	23% *vs.* 35%	81.2% *vs.* 69.2%	10.59	0.0011
3	≤2 *vs.* ≥3	311 *vs.* 240	24% *vs.* 38%	80.3% *vs.* 65.9%	14.13	0.0002
4	≤3 *vs.* ≥4	386 *vs.* 165	25% *vs.* 41%	78.3% *vs.* 64.0%	12.46	0.0004
5	≤4 *vs.* ≥5	440 *vs.* 111	25% *vs.* 50%	78.6% *vs.* 56.8%	29.31	<0.0001
6	≤5 *vs.* ≥6	471 *vs.* 80	26% *vs.* 55%	77.7% *vs.* 52.8%	32.31	<0.0001
7	≤6 *vs.* ≥7	492 *vs.* 59	27% *vs.* 59%	77.2% *vs.* 48.6%	34.64	<0.0001
8	≤7 *vs.* ≥8	505 *vs.* 46	27% *vs.* 63%	77.2% *vs.* 40.2%	34.49	<0.0001

to the prognosis. Univariate analysis identified the following factors as being statistically significant, independent, adverse prognostic factors: tumor location (rectum), depth of invasion (T3/4), lymphatic invasion (ly2-3), venous invasion (v2-3), LNR (≥0.0909), and MLN ≥5. These five factors were then used in multivariate analysis using a Cox proportional hazard model, and MLN ≥5 was identified as being an independent adverse prognostic factor (hazard ratio=1.84; 95% confidence interval=1.2801-2.6295; p=0.0012).

Discussion

Stage grouping showing the degree of progression of cancer is useful for determining adjuvant chemotherapy and the surveillance program to be employed. Stage grouping using the TNM classification is widely performed around the world today. The prognostic impact of lymph node metastasis is widely accepted in colorectal cancer, and stage grouping is decided based on the MLN. The seventh edition of the TNM staging system for colorectal cancer revised the N-category so that N1a defines metastasis in only one regional lymph node, N1b is metastasis in 2-3 regional lymph nodes, N2a is metastasis in 4-6 regional lymph nodes, and N2b is metastasis in seven or more regional lymph nodes (8). However, the rationale for deciding the cut-off value for MLN in the N-category is unclear. Accordingly, in this study, we investigated the significance of the N-category by stratifying the outcome of Dukes' C colorectal cancer as a function of the MLN. Regardless of the MLN cut-off value that we set at our single institution, the survival of groups classified above and below those cut-off values was significantly different. We, thus, decided that it was appropriate to use an MLN cut-off value of 5 and classify the cases into two groups. This is different from the seventh edition of the TNM classification and from the Japanese classification based on the sixth edition of the TNM. Differences in the surgical technique may be one reason for that variation. Most institutions in Japan perform lymph node dissection by the standard method of *en bloc* excision of lymph nodes along the major artery at the site of the tumor (16, 17). West *et al.* (18) compared resected specimens from different hospitals and found that there were differences in the scope of mesenteric resection and in the distance between the tumor and vascular ligation.

Differences in the RLN and operative results may be due to differences between the European and US methods for

Table III. *Characteristics of new classification by lymph node metastatic grade.*

Variable	Category	MLN ≤4 n=440 (%)	MLN ≥5 n=111 (%)	*p*-Value
Gender	Male	231 (63.9)	63 (56.8)	0.1698
	Female	159 (36.1)	48 (43.2)	
Age	Years (median)	66	60	0.0008
Location	Colon	301 (68.4)	68 (79.3)	0.3626
	Rectum	139 (31.6)	43 (38.7)	
Gross type	Expansive	397 (90.2)	90 (81.1)	0.0108
	Infiltrative	43 (9.8)	21 (18.9)	
CEA value*	Median (average)	3.5 (14.6)	3.6 (21.2)	0.4305
% of position†	Median	75%	85%	0.0291
Maximum size	Median (mm)	50	53	0.0027
Depth of invasion	T1	19 (4.3)	1 (0.9)	0.0822
	T2	35 (7.9)	5 (4.5)	
	T3	124 (28.2)	29 (26.1)	
	T4	262 (59.6)	76 (68.5)	
Histological type	Well	236 (53.6)	41 (36.9)	<0.0001
	Other	205 (46.4)	70 (63.1)	
ly	0, 1	314 (71.4)	42 (37.8)	<0.0001
	2, 3	126 (28.4)	69 (62.2)	
v	0, 1	365 (83.1)	68 (61.3)	<0.0001
	2, 3	74 (16.9)	43 (38.7)	
RLN	Median	27	37	<0.0001
LNR	Median	0.0625	0.2105	<0.0001
Recurrence	Absent	329 (74.8)	56 (50.4)	<0.0001
	Present	111 (25.2)	55 (49.6)	

*CEA value, pre-operation value; †% of position, percentage of the tumor around the circumference of the bowel; ly, lymphatic invasion; v, venous invasion; RLN, retrieved lymph node number; LNR, lymph node ratio; MLN, metastatic lymph node number.

resection of the mesentery along the intestinal tract and the Japanese method. The higher MLN differs as a function of the RLN, and reports have suggested that the MLN has prognostic significance. Kim *et al*. (19) and Prandi *et al*. (20) reported that examination of at least 10 lymph nodes is necessary to increase the yield of positive lymph nodes. Tapper *et al*. (21) and Nelson *et al*. (22) stated that 12-17 lymph nodes must be retrieved to decide the stage grouping. In the present study, we found that the MLN, rather than the RLN, is clearly linked to recurrence and survival. Our method in which the surgeon harvests the lymph nodes from the removed specimen and fixes them in formalin, differs from the Western method in which pathologists fix the tumors. Differences in the methods for handling resected specimen and the methods for retrieval of lymph nodes may lead to differences in the RLN. The accuracy of diagnosis of lymph node metastasis also involves subjective elements such as the extent of dissection, the dissection procedures, and the handling of specimens (23). In addition, the patient's age and the location of tumors have been suggested to impact the MLN (24). A Japanese group suggested that at least a 12-node threshold may be required to improve the predictive capacity for individual patients and as a quality control parameter for hospital performance (25).

In recent years, the LNR has received great attention as a possible indicator for predicting prognosis (26, 27). Many reports have been published showing that the LNR is related to the prognosis of gastrointestinal cancer, but the cut-off values for the LNR have a wide range, *e.g*., 0.01-0.4 (28-31). If the LNR is around 1, the prognosis can be expected to be poor, but deciding on a universal cut-off value is thought to be difficult.

The location of metastatic lymph nodes has also been suggested to be important to the N-category (32). Newland *et al*. (33) performed a prospective study and concluded that rather than the MLN, the location of metastatic lymph nodes is the most important factor contributing to the prognosis. The distribution of lymph node metastasis improves the accuracy of evaluation of the involvement of the nodal status (34). In a comparative study, CME for colon cancer improved the oncological result (12). These findings indicate the importance of the extent of mesenteric resection, and that the definition of regional lymph nodes may be a problem that needs to be solved in the future.

For our present study, we excluded cases with rectal cancer that had been treated with chemoradiation and cases that had undergone neoadjuvant therapy. The objectives were to avoid assigning patients with diverse backgrounds to the

Table IV. *Univariate and multivariate analysis of independent prognostic factors.*

Variable	Category	Case number (%)	5-year survival rate (%)	Uni-* *p*-Value	Multivariate analysis		
					HR	95% CI	*p*-Value
Location	Colon	369 (67)	77.5	0.009	1		
	Rectum	182 (33)	66.9		1.39	0.9903-1.9378	0.0569
Gross type	Expansive	487 (88)	73.4	0.3609			
	Infiltrative	64 (12)	78.9				
% of position**	<90%	320 (58)	72.6	0.3421			
	≥90%	229 (42)	75.8				
Maximum size	<50 mm	260 (47)	69.9	0.0774			
	≥50 mm	289 (53)	77.6				
Depth of invasion	T1.2	60 (13)	87.4	0.0326	1		
	T3.4	491 (87)	72.5		1.75	0.9409-3.9238	0.1011
Histologic type	Well	277 (50)	77.7	0.0548			
	Other	274 (50)	70.1				
ly	0, 1	356 (65)	80.4	<0.0001	1		
	2, 3	195 (35)	62.6		1.54	1.0925-2.1789	0.0139
v	0, 1	453 (82)	79.0	<0.0001	1		
	2, 3	117 (18)	55.7		1.76	1.2164-2.5094	0.0029
RLN	≤11	51 (9)	70.3	0.9874			
	≥12	500 (91)	74.4				
LNR	<0.0909	285 (52)	81.3	0.0001	1	-	-
	≥0.0909	266 (48)	66.0		1.4392	0.9346-2.2388	0.096
MLN	≤4	440 (81)	78.6	<0.0001	1	-	-
	≥5	111 (19)	56.8		1.84	1.2801-2.6295	0.0012

*Uni-, Univariate analysis; **% of position, percentage of the tumor around the circumference of the bowel; ly, lymphatic invasion; v, venous invasion; RLN, retrieved lymph node number; LNR, lymph node ratio; MLN, metastatic lymph node number; HR, hazard ratio; CI, confidence interval.

same stage classification and to minimize variability of the results. For a pure study of cancer prognosis, the optimal approach would be to analyze a patient population that had undergone only curative surgery. Because of evolving treatment methods, it may be necessary to change the staging classifications, but there are limits to assigning patients with different backgrounds to the same category. Even today, use of a simple Dukes' classification that is based solely on the depth of invasion and whether or not there is lymph node metastasis continues. For research, comparison of different strata based on detailed stage classifications is necessary, but for use in daily practice, we believe that even a simple cancer staging classification is sufficient.

In conclusion, MLN ≥5 is an independent predictor of 5-year survival for patients with colorectal cancer. The cut-off value, however, differs according to surgical procedures or the method for handling the specimen. Use of a universal classification system is necessary to compare treatment results, but for research on prognostic risk factors, performing studies based on data from each institution and region will be useful.

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