Distribution of Lymph Node Metastases Is an Independent Predictor of Survival for Sigmoid Colon and Rectal Cancer

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Objective: This study evaluated the prognostic significance of the distribution of lymph node metastases (LND) in patients with colorectal cancer.

Background: The impact of the LND on survival in colorectal cancer is unknown.

Methods: A total of 1205 consecutive patients who underwent potentially curative surgery for sigmoid colon or rectal cancer with high ligation of the inferior mesenteric artery (IMA) from January 1997 to February 2008 were assigned to 4 groups based on LND: LND0, no lymph node metastases—615 patients (51.0%); LND1, metastases in the pericolic nodes—324 patients (26.9%); LND2, metastases in the intermediate nodes—172 patients (14.3%); and LND3, node metastases at the origin of the IMA—94 patients (7.8%).

Results: The 5-year overall survival rates of patients with LND0, LND1, LND2, and LND3 were 83%, 63%, 52%, and 28%, respectively ($P < 0.001$). The 5-year disease-free survival rates of patients with LND0, LND1, LND2, and LND3 were 83%, 54%, 43%, and 21%, respectively ($P < 0.001$). On multivariate analysis, LND was an independent prognostic factor for both overall survival and disease-free survival. However, the 5-year local recurrence-free survival rate was not inversely related to the LND. On a subset analysis that compared stage III disease with stage IV disease, the 5-year overall survival and disease-free survival rates were 45% and 31% for the patients with stage IV disease compared with 40% and 32% for the patients with stage III, LND3 disease, respectively ($P = 0.761$ and 0.704). For the patients with pN1 tumors, the overall survival and disease-free survival did not differ significantly according to the LND ($P = 0.471$ and 0.347, respectively). However, for patients with pN2 tumors, the overall survival and disease-free survival curves among the LND groups significantly differed ($P < 0.001$ and <0.001, respectively).

Conclusion: LND is an independent predictor of survival for colorectal cancer patients, but it does not predict local recurrence. The N categorization including LND may enhance the prognostic value of the TNM staging system for patients with node-positive sigmoid colon or rectal cancer.

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The presence or absence of lymph node metastases in colorectal cancer is an important prognostic factor for survival and identifying the candidates for postoperative therapy. The guidelines from the American Joint Conference on Cancer (AJCC) and the TNM Committee of the International Union Against Cancer (UICC) recommend a minimal assessment of 12 lymph nodes for accurate staging; however, the distribution of lymph node metastases (LND) is not taken into consideration.[1] Although the TNM classification of malignant tumors is the standard staging system for colorectal carcinoma, the Japanese classification staging system is based on the distribution rather than the absolute number of metastatic lymph nodes,[2,3] and a debate exists as to whether the number or LND provides the more accurate prognosis.[4–10] Moreover, few studies have prospectively evaluated the impact of LND on survival for patients with sigmoid colon or rectal cancer. The aim of this study was to investigate the prognostic significance of LND in patients with sigmoid colon or rectal cancer.

METHODS

Patients Population

Between January 1997 and February 2008, 1333 consecutive patients who to undergo surgical resection with high ligation of the inferior mesenteric artery (IMA) for adenocarcinoma of the sigmoid colon or rectum were prospectively enrolled in this study. Of these, 128 patients who underwent preoperative chemoradiotherapy were excluded because chemoradiotherapy may alter the number of lymph nodes and their metastatic pattern.[11,12] Thus, a total of 1205 patients were included in this analysis. This study was reviewed and approved by the appropriate institutional review board.

Preoperative Staging

The preoperative clinical staging tools that were used included a physical examination, colonoscopy or double-contrast barium enema, abdomino-pelvic computed tomography (CT), chest x-ray or CT, positron emission tomography (PET) scanning, a complete blood cell count, liver function tests, and the serum carcinoembryonic antigen (CEA) level. The location of the tumor was defined as the distance between the caudal margin of the tumor and the anal verge, and this was measured by digital examination and rigid proctoscopy. The rectal cancers were grouped according to their distance from the anal verge: lower rectum (0–7 cm) and upper rectum (8–15 cm). In case of a rectal cancer, endorectal ultrasound (ERUS) and/or pelvic magnetic resonance imaging (MRI) were performed to assess the extent of local tumor invasion.

Surgery and Adjuvant Therapy

All the lymph nodes surrounding the root of the IMA were dissected in every patient, regardless of whether LND were detected. The completeness of resection was determined for each patients on the basis of the operative and pathology reports and this was classified as follows: R0 (negative gross and pathologic margins), R1 (negative gross margins with positive microscopic margins), and R2 (positive gross margins). Postoperative adjuvant treatment was dependent on the patient's general condition or compliance and the preference of the physician. Postoperative 5-fluorouracil-based chemotherapy was considered for all the patients with T3-4 or node-positive disease.[13] Postoperative radiotherapy consisted of 45 to 50.4 Gy in 25 to 28 fractions delivered to the pelvis using a 4-field box technique.[14,15] Of the 1205 patients, 853 (70.8%) received postoperative chemotherapy and 87 (7.2%) received postoperative chemoradiotherapy.

Pathologic Examination

After the tumor was removed, the surgeon immediately identified and isolated the lymph nodes and recorded both their number and distribution.[16] The lymph node status was confirmed by a pathologist after microscopic examination. Tumor stage was defined according

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to the seventh edition of the American Joint Commission on Cancer (AJCC) TNM staging system.[2] We classified LND according to the Japanese classification of colorectal carcinoma.[3] The patients were grouped into 4 categories as (1) LND0, no lymph node metastases; (2) LND1, metastases in the pericolic or perirectal nodes; (3) LND2, metastases in the sigmoid colic or inferior mesenteric trunk nodes (intermediate nodes); and (4) LND3, node metastases at the origin of the IMA (Fig. 1).

Follow-Up

The patients were followed at 3-month intervals for 2 years, at 6-month intervals for the next 3 years and then annually thereafter. Follow-up examinations were conducted on a semiannual basis or when a suspicion of recurrence existed, and these examinations included a clinical history, physical examination, serum CEA assay, chest x-ray or CT, abdomino-pelvic CT or MRI, colonoscopy, and PET scanning, if available. Recurrence was determined by clinical and radiological examinations or using histological confirmation. Local recurrence was defined as recurrent disease in the pelvis, including recurrence at the site of bowel anastomosis and on the pelvic sidewalls. Distant metastasis was defined as disease outside the pelvis. The main pattern of recurrence was recorded as the first site of detectable failure during the follow-up period.

Statistical Analysis

Statistical analyses were carried out using SPSS for Windows, version 14.0 (SPSS, Chicago, IL, USA). Differences between groups were tested using the χ^2-test and analysis of variance (ANOVA) as appropriate. The survival rates were calculated using the Kaplan–Meier method, and the prognostic factors and survival curves were compared using the log-rank test. Covariates with trend-significant effects ($P < 0.10$) on the univariate analysis were selected for multivariate analysis using a Cox regression model. A P value ≤ 0.05 was deemed statistically significant.

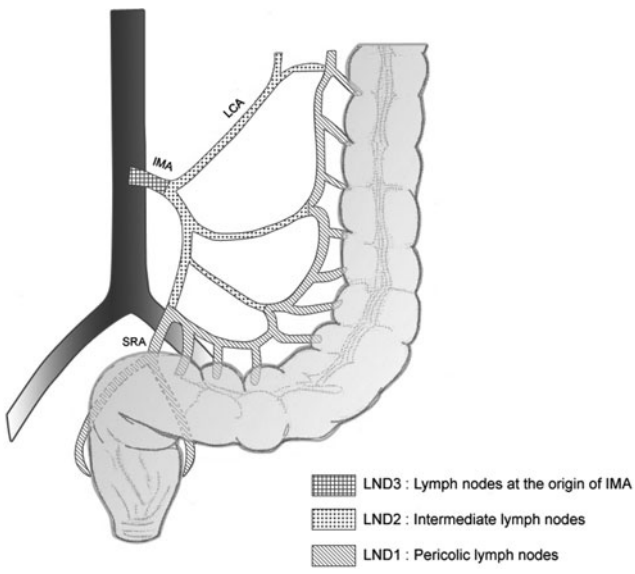

FIGURE 1. Definition of the distribution of lymph node metastases (LND).

RESULTS

The analysis included 712 (59.1%) men, and the median age was 62 years (range: 23–90). There were 347 patients (28.8%) with sigmoid colon cancers, 450 (37.3%) with upper rectal cancers, and 408 (33.9%) with lower rectal cancers. The median preoperative serum CEA level was 4.0 (range: 0.1–900.0) ng/mL. Of the 1205 patients, 1039 patients (86.2%) underwent anterior resection, 133 (11.1%) underwent abdominoperineal resection (APR), and 33 (2.7%) underwent Hartmann's procedure. Histologically, 560 tumors (46.5%) were well differentiated, 540 (44.8%) were moderately differentiated, 54 (4.5%) were poorly differentiated, and 51 (4.2%) were mucinous. The median number of resected lymph nodes was 12 (range: 1–158). Using the 7th AJCC TNM staging system, 197, 400, 442, and 166 patients had stage I, II, III, and IV cancers, respectively. The distribution of potential prognostic factors according to the LND subgroup is shown in Table 1. Age, differentiation, the primary tumor (pT) category, pN category, lymphovascular invasion, perineural invasion, the completeness of resection, and the preoperative serum CEA levels significantly differed among the 4 LND groups.

With a median follow-up period of 54.2 months (range: 0.2–161.5), the 5-year overall survival and disease-free survival rates of this cohort were 69% and 64%, respectively. The overall survival curves among the 4 LND groups significantly differed; the 5-year overall survival rates of the patients with LND0, LND1, LND2, and LND3 were 83%, 63%, 52%, and 28%, respectively ($P < 0.001$, Fig. 2A). Additionally, the disease-free survival curves among the 4 LND groups significantly differed; the 5-year disease-free survival rates of the patients with LND0, LND1, LND2, and LND3 were 83%, 54%, 43%, and 21%, respectively ($P < 0.001$, Fig. 2B). Among the patients who underwent R0 resection of their colorectal cancer (1032/1205 patients, 85.6%), LND remained a significant predictor of a poor outcome. The 5-year overall survival rates of the patients with LND0, LND1, LND2, and LND3 were 85%, 73%, 66%, and 39%, respectively ($P < 0.001$, Fig. 2C). Similar results were found for disease-free survival. The disease-free survival rates at 5 years for the patients with LND0, LND1, LND2, and LND3 were 85%, 63%, 57%, and 31%, respectively ($P < 0.001$, Fig. 2D).

The univariate analysis indicated that the factors associated with overall survival were age, tumor size, differentiation, the type of surgery, the pT category, the pN category, the cM category, lymphovascular invasion, perineural invasion, the number of lymph nodes harvested, lymph node ratio, the completeness of resection, the preoperative CEA level, and the LND (Table 2). The factors associated with disease-free survival were tumor size, differentiation, the pT category, the pN category, the cM category, lymphovascular invasion, perineural invasion, lymph node ratio, the completeness of resection, the preoperative CEA level, postoperative chemotherapy, and the LND (Table 2). The variables LND and the pN category as well as lymph node ratio were highly correlated because of the fact that the variable LND can be considered as a more precise classification of the pN category as well as lymph node ratio. Therefore, the pN category and lymph node ratio was excluded from the multivariate survival analysis. The multivariate analysis revealed that age, tumor size, the type of surgery, lymphovascular invasion, the number of lymph nodes harvested, the completeness of resection, the preoperative CEA level, and the LND were independent prognostic factors for overall survival (Table 3). Additionally, the pT category, the cM category, lymphovascular invasion, perineural invasion, the completeness of resection, the preoperative CEA level, postoperative chemotherapy, and the LND were independent prognostic factors for disease-free survival (Table 3). The multivariate analysis confirmed that the LND was significantly and independently associated with a worse prognosis for both overall survival and disease-free survival.

TABLE 1. Correlation Between the Distribution of Lymph Node Metastases (LND) and the Clinicopathologic Factors

	LND0 (n = 615)	LND1 (n = 324)	LND2 (n = 172)	LND3 (n = 94)	*P*
Age, yr					0.028
<65	327 (53.2)	185 (57.1)	78 (63.9)	33 (70.2)	
≥65	288 (46.8)	139 (42.9)	44 (36.1)	14 (29.8)	
Gender					0.376
Male	358 (61.0)	182 (56.2)	97 (56.4)	55 (58.5)	
Female	229 (39.0)	142 (43.8)	75 (43.6)	39 (41.5)	
Tumor size, cm*	4.3 (0.3–22.0)	4.5 (1.4–15.0)	4.2 (1.5–10.0)	5.0 (2.0–11.5)	0.112
Location					0.870
Sigmoid colon	179 (29.1)	88 (27.2)	49 (28.5)	31 (33.0)	
Upper rectum	224 (36.4)	123 (38.0)	66 (38.4)	37 (39.4)	
Lower rectum	212 (34.5)	113 (34.8)	57 (33.1)	26 (27.6)	
Differentiation					<0.001
Well	330 (53.7)	134 (41.4)	65 (37.8)	31 (33.0)	
Moderate	257 (41.8)	161 (49.7)	81 (47.1)	41 (43.6)	
Poor	10 (1.6)	16 (4.9)	14 (8.1)	14 (14.9)	
Mucinous	18 (2.9)	13 (4.0)	12 (7.0)	8 (8.5)	
Type of surgery					0.077
Anterior resection	521 (84.7)	291 (89.8)	143 (83.1)	84 (89.4)	
APR + Hartmann's op	94 (15.3)	33 (10.2)	29 (16.9)	10 (10.6)	
pT category					<0.001
pT1	65 (10.6)	6 (1.9)	2 (1.2)	0	
pT2	132 (21.5)	24 (7.4)	12 (7.0)	4 (4.3)	
pT3	387 (62.9)	273 (84.3)	140 (81.4)	79 (84.0)	
pT4	31 (5.0)	21 (6.4)	18 (10.4)	11 (11.7)	
pN category					<0.001
pN0	615 (100)	0	0	0	
pN1	0	261 (80.6)	90 (52.3)	20 (21.3)	
pN2	0	63 (19.4)	82 (47.7)	74 (77.7)	
No. of lymph nodes harvested*	12 (1–95)	12 (1–158)	13 (2–67)	13 (3–37)	0.789
Lymphovascular invasion					<0.001
Negative	553 (89.9)	254 (78.4)	113 (65.7)	50 (53.2)	
Positive	62 (10.1)	70 (21.6)	59 (34.3)	44 (46.8)	
Perineural invasion					<0.001
Negative	546 (88.8)	242 (74.7)	116 (67.4)	47 (50.0)	
Positive	49 (11.2)	82 (25.3)	56 (32.6)	47 (50.0)	
Operative method					0.238
Open	465 (75.6)	248 (76.5)	130 (75.6)	80 (85.1)	
Laparoscopic	150 (24.4)	76 (23.5)	42 (24.4)	14 (14.9)	
Resection level completeness					
R0	580 (94.3)	269 (83.0)	126 (73.3)	57 (60.6)	<0.001
R1	23 (3.7)	22 (6.8)	12 (7.0)	6 (6.4)	
R2	12 (2.0)	33 (10.2)	34 (19.7)	31 (33.0)	
Preoperative CEA, ng/mL					<0.001
<5	351 (57.1)	140 (43.2)	70 (40.7)	37 (39.4)	
≥5	167 (27.2)	139 (42.9)	74 (43.0)	48 (51.1)	
Not available	97 (15.7)	45 (13.9)	28 (16.3)	9 (9.5)	

*Values are expressed as the median (range); values in parentheses are percentages unless otherwise indicated.

To determine whether LND predicted survival in patients with node-positive disease, we performed survival analyses on the basis of the LND in the 590 patients with node-positive tumors according to the location of tumors (Table 4). We found that the LND predicted the overall survival, the disease-free survival, and the distant metastasis-free survival in the patients with sigmoid colon and rectal cancer. However, the local recurrence-free survival rate was not inversely related to the LND. We also performed survival analyses in patients with node-positive tumors according to the LND and pN category (Table 5). We observed that the pN category predicted the overall survival, the disease-free survival, the local recurrence-free survival, and the distant metastasis-free survival in the patients with sigmoid colon and rectal cancer. To determine the independent predictors for local recurrence in patients with rectal cancer, we performed univariate and multivariate analyses for the 858 patients with rectal cancer (Table 6). The type of surgery, the pT category, the cM category, and the completeness of resection were the independent prognostic factors for local recurrence-free survival for patients with rectal cancer.

As shown in Table 3, the overall survival and disease-free survival rates were significantly affected by the LND status and this was independent of the tumor stage (the pT category and the cM category). We performed a subset analysis to compare the patients with stage III disease with the patients with stage IV disease, among the 1032 patients who underwent R0 resection for their colorectal cancer. The 5- and 10-year overall survival rates were 45% and 31% for the patients with stage IV disease (n = 45) compared with 40% and 33% for the patients with stage III, LND3 disease (n = 46), respectively ($P = 0.761$, Fig. 2E). Similar results were seen for disease-free

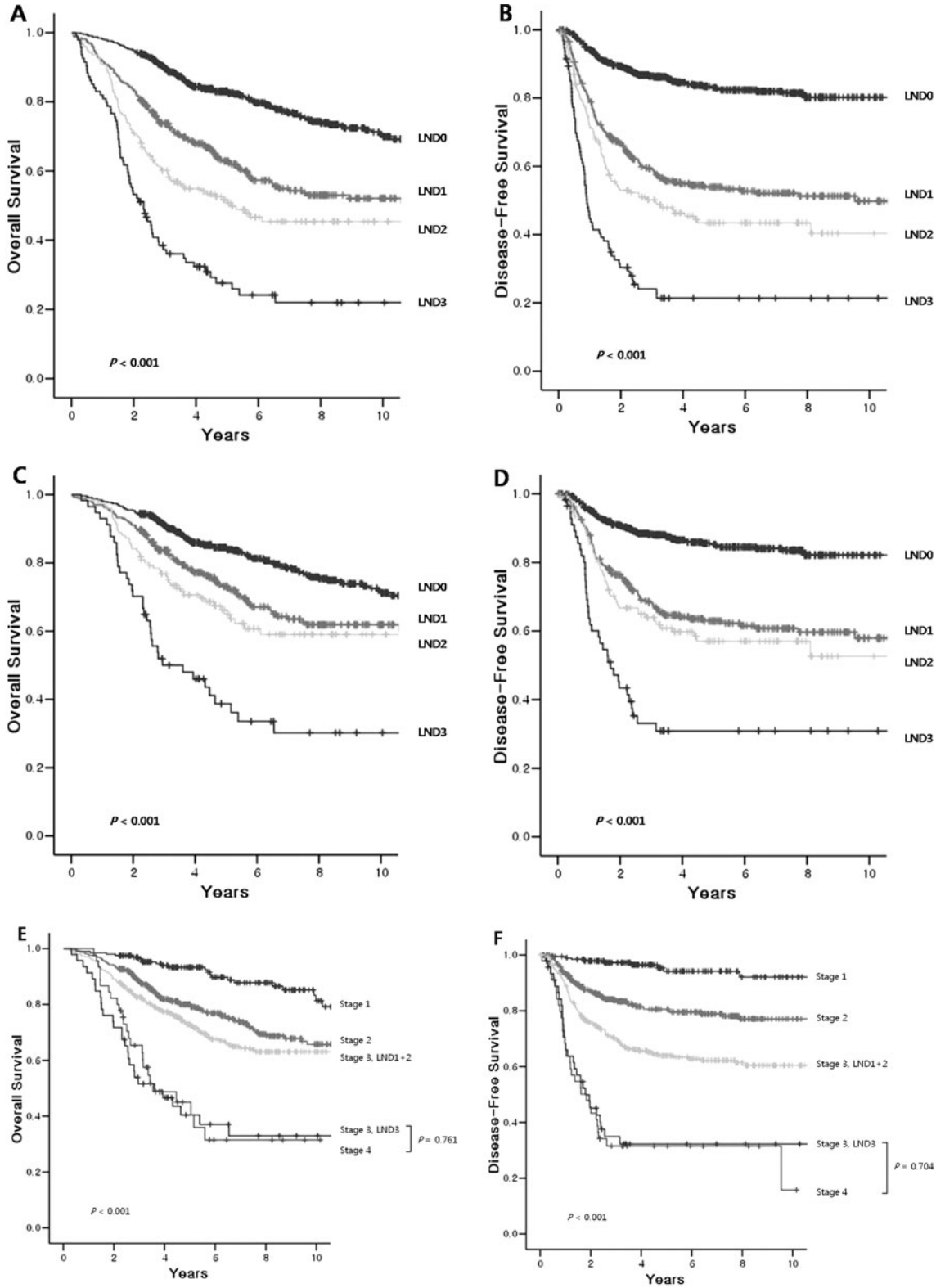

FIGURE 2. Kaplan–Meier curves depicting A, overall survival and B, disease-free survival among 1205 patients who underwent primary resection for their colorectal cancer, C, overall survival and D, disease-free survival among 1032 patients who underwent R0 resection for their colorectal cancer, and E, overall survival and F, disease-free survival of 1032 patients with R0 resection according to the TNM stage and the distribution of lymph node metastases (LND) status.

TABLE 2. Univariate Analyses of the Factors for 5-Year Overall Survival (OS) and Disease-Free Survival (DFS) in All the Patients (n = 1205)

		OS		DFS	
	N	%	*P*	%	*P*
All patients	1205	69		64	
Age, yr					
<65	685	71	0.009	63	0.389
≥65	520	66		67	
Gender					
Male	712	69	0.554	64	0.819
Female	493	68		64	
Tumor size, cm					
<4.5	583	74	<0.001	68	<0.001
≥4.5	622	64		61	
Location					
Sigmoid colon	347	67	0.413	70	0.146
Upper rectum	450	71		60	
Lower rectum	408	68		65	
Differentiation					
Well	560	73	<0.001	70	<0.001
Moderate	540	69		62	
Poor + mucinous	105	46		41	
Type of surgery					
Anterior resection	1039	70	0.009	65	0.214
APR + Hartmann's	166	61		61	
pT category					
pT1	73	93	<0.001	97	<0.001
pT2	172	91		89	
pT3	879	64		58	
pT4	81	51		46	
pN category					
Negative	615	83	<0.001	83	<0.001
Positive	590	54		46	
cM category			<0.001		<0.001
M0	1039	77		73	
M1	166	17		10	
Lymphovascular invasion					
Negative	970	73	<0.001	70	<0.001
Positive	235	50		40	
Perineural invasion					
Negative	951	73	<0.001	72	<0.001
Positive	254	51		38	
No. of lymph nodes harvested					
<12	543	65	0.002	65	0.707
≥12	662	72		64	
Lymph node ratio*					
<0.25	898	80	<0.001	76	<0.001
≥0.25	307	42		31	
Resection level completeness					
R0	1032	77	<0.001	73	<0.001
R1	63	48		39	
R2	110	2		0	
Preoperative CEA†, ng/mL					
<5	598	79	<0.001	74	<0.001
≥5	428	55		49	
Postoperative chemotherapy					
No	352	74	0.115	79	<0.001
Yes	853	67		58	
LND					
LND0	615	83	<0.001	83	<0.001
LND1	324	63		54	
LND2	172	52		43	
LND3	94	28		21	

LAR, low anterior resection.

*The cutoff value of 0.25 was the median value of the LNR in patients with positive lymph node metastases.

†Excluding 179 patients who did not have their CEA levels available.

survival, where the 5- and 10-year disease-free survival rates were 31% and 16% for the stage IV patients versus 32% and 32% for the patients with stage III, LND3 tumors, respectively ($P = 0.704$, Fig. 2F).

We performed survival analyses in patients with node-positive tumors according to the LND and the pN category (Fig. 3). For the patients with pN1 tumors, the overall survival and disease-free survival did not differ significantly according to the LND ($P = 0.471$ and 0.347, respectively, Fig. 3A and B). However, for patients with pN2 tumors, the overall survival and disease-free survival curves among the LND groups significantly differed ($P < 0.001$ and <0.001, respectively, Fig. 3C and D).

DISCUSSION

Lymph node metastasis is considered to be one of the most reliable prognostic factors for colorectal cancer. Lymph node

TABLE 3. Multivariate Analyses of the Factors for 5-Year Overall Survival (OS) and Disease-Free Survival (DFS) in All the Patients (n = 1205)

Factors	Hazards Ratio (CI)	*P*
OS		
Age	1.368 (1.123–1.668)	0.002
Tumor size	1.319 (1.073–1.625)	0.009
Differentiation (baseline, well differentiated)		
Moderate	0.937 (0.755–1.162)	0.554
Poor + mucinous	1.280 (0.941–1.741)	0.116
Type of surgery	1.504 (1.156–1.955)	0.002
pT category (baseline, pT1)		
pT2	1.009 (0.432–2.357)	0.983
pT3	2.258 (1.045–4.881)	0.038
pT4	2.033 (0.865–4.774)	0.103
cM category	1.403 (0.949–2.073)	0.090
Lymphovascular invasion	1.356 (1.075–1.711)	0.010
Perineural invasion	1.148 (0.911–1.447)	0.243
No. of lymph nodes harvested	0.696 (0.568–0.853)	<0.001
Resection level completeness (baseline, R0)		
R1	1.575 (1.018–2.436)	0.041
R2	5.912 (3.866–9.040)	<0.001
Preoperative CEA	1.386 (1.105–1.738)	0.005
LND (baseline, LND0)		
LND1	1.663 (1.296–2.133)	<0.001
LND2	1.978 (1.477–2.647)	<0.001
LND3	2.752 (1.960–3.862)	<0.001
DFS		
Tumor size	1.161 (0.943–1.431)	0.159
Differentiation (baseline, well differentiated)		
Moderate	1.041 (0.836–1.296)	0.721
Poor + mucinous	1.351 (0.984–1.854)	0.063
pT category (baseline, pT1)		
pT2	2.608 (0.597–11.389)	0.203
pT3	8.083 (1.970–33.170)	0.004
pT4	6.675 (1.556–28.641)	0.011
cM category	1.670 (1.188–2.348)	0.003
Lymphovascular invasion	1.439 (1.142–1.814)	0.002
Perineural invasion	1.408 (1.123–1.764)	0.003
Resection level completeness (baseline, R0)		
R1	1.783 (1.176–2.702)	0.006
R2	6.292 (4.318–9.168)	<0.001
Preoperative CEA	1.353 (1.079–1.696)	0.009
Postoperative chemotherapy	0.640 (0.476–0.842)	0.003
LND (baseline, LND0)		
LND1	2.496 (1.887–3.303)	<0.001
LND2	2.633 (1.918–3.615)	<0.001
LND3	3.599 (2.518–5.143)	<0.001

TABLE 4. Survival Rates by the Distribution of Lymph Node Metastasis (LND) in the Patients With Node-Positive Tumor According to the Location of Tumors (n = 590)

Factors	N	5-yr OS (%)	5-yr DFS (%)	5-yr LRFS (%)	5-yr DMFS (%)
Sigmoid colon					
LND1	88	64	64	96	68
LND2	49	61	59	96	60
LND3	31	35	28	85	33
P		0.008	<0.001	0.092	0.001
Upper rectum					
LND1	123	67	49	82	59
LND2	66	53	40	79	51
LND3	37	22	13	79	18
P		<0.001	<0.001	0.914	<0.001
Lower rectum					
LND1	113	58	52	78	65
LND2	57	43	35	75	46
LND3	26	28	27	84	28
P		0.006	0.004	0.969	<0.001

OS indicates overall survival; DFS, disease-free survival; LRFS, local recurrence-free survival; DMFS, distant metastasis-free survival.

TABLE 5. Survival Rates in the Patients With Node-Positive Tumor According to the Distribution of Lymph Node Metastasis (LND) and pN Category (n = 590)

Factors	N	5-yr OS (%)	5-yr DFS (%)	5-yr LRFS (%)	5-yr DMFS (%)
LND					
LND1	324	63	54	84	63
LND2	172	52	43	82	52
LND3	94	27	21	82	26
P		<0.001	<0.001	0.701	<0.001
pN category					
pN1a	180	70	66	89	75
pN1b	184	54	49	84	61
pN2a	118	51	32	83	37
pN2b	108	31	20	69	27
P		<0.001	<0.001	0.001	<0.001

OS, overall survival; DFS, disease-free survival; LRFS, local recurrence-free survival; DMFS, distant metastasis-free survival.

metastasis is currently classified by the number or distribution of positive lymph nodes.[2,3] The current seventh TNM N categorization has the advantage of simplicity based on the number of positive lymph nodes only; however, evidences exist to support the prognostic importance of LND.[4–9] Newland et al[9] showed that the location rather than the number of metastatic nodes was the most important prognostic variable associated with colorectal cancer. Hida et al[6] reported that the LND subcategories had a wider distribution range and 5-year survival rate than did the TNM staging system. Leibold et al[4] recently reported that the TNM staging classification based on the number of positive nodes alone may not provide an accurate assessment after preoperative chemoradiation. They argued that the treatment decreased the median number of involved lymph nodes. The authors suggested that rectal cancer staging after neoadjuvant chemoradiotherapy should incorporate the location of LND. Our study supports the concept that the LND is a valuable prognostic factor for patients with colorectal

TABLE 6. Predictive Factors for 5-Year Local Recurrence-Free Survival in the Patients With Rectal Cancer (n = 858)

	Univariate	Multivariate	
	P	*P*	Hazards Ratio (CI)
Age	0.728		
Gender	0.937		
No. of lymph nodes harvested	0.346		
Tumor size	0.058	0.364	1.221 (0.794–1.877)
Differentiation	0.034	0.671	1.158 (0.588–2.280)
Lymphovascular invasion	0.012	0.360	1.270 (0.762–2.117)
Perineural invasion	0.006	0.433	1.214 (0.747–1.973)
Preoperative CEA	0.020	0.325	1.260 (0.795–1.996)
Postoperative chemotherapy	0.001	0.493	1.255 (0.656–2.403)
LND	0.070	0.808	1.100 (0.512–2.364)
Type of surgery	0.017	0.028	1.714 (1.061–2.767)
pT category	<0.001	0.017	3.086 (1.222–7.793)
cM category	<0.001	0.001	2.640 (1.462–4.768)
Resection level completeness	<0.001	0.002	2.332 (1.374–3.957)

cancer. Our results indicate that LND is an independent prognostic factor for both overall survival and disease-free survival for patients with sigmoid colon and rectal cancer.

Despite evidence supporting the use of the LND staging/categorization system, the method has not been widely adopted because of its complexity and the previous controversial results.[5,7,8,10,17] The findings of Suzuki et al[10] suggested that the number of metastatic nodes was a better independent prognostic indicator for colorectal cancer than was the location of the positive nodes. In contrast, Tang et al[17] reported that both the number and the level of nodal involvement were independent prognostic factors for survival in 538 patients with stage III colorectal cancer. The results of a Cox regression analysis in our study revealed that LND is a significant independent predictor for both overall survival and disease-free survival, which is consistent with the results of Tang et al. Moreover, when the categories are broken down according to the location of tumor in the patients with node-positive tumors, the LND remained a significant predictor of a poor outcome.

The value of LND as a prognostic factor in rectal cancer is not clear.[5,18] Kobayashi et al[5] suggested that LND could not independently predict the outcome of treatment for patients with rectal cancer. In contrast, after reviewing 1188 patients who underwent curative resection for sigmoid colon or rectal cancer, Kanemitsu et al[18] showed that the 5- and 10-year survival rates of the patients with metastases in nodes at the origin of the IMA (LND3) were 40% and 21%, respectively, and the survival rates for patients with metastases to the inferior mesenteric trunk nodes were 50% and 35%, respectively. When we limited our analysis to the rectal cancer patients with node-positive disease, we observed that LND was a significant prognostic factor for the overall survival, disease-free survival, and distant metastasis-free survival, but not for local recurrence-free survival. Several possible explanations exist for this observation. First, numerous clinicopathological features have been associated with local recurrence in different series including the T category,[19] the N category,[20,21] APR,[22] lymphovascular invasion, and the circumferential resection margin.[23,24] A comparison of these studies is not feasible because the patient groupings, the staging systems, and the study designs often differed. Additionally, we found that the type of surgery, the pT category, the cM category, and the completeness of resection are independent factors that had an influence on local recurrence in patients with rectal cancer in this analysis. Second, metastasis in LND3 may be regarded as systemic disease, despite the insufficient anatomical and clinical evidence.[25] Kim et al[26] suggested that

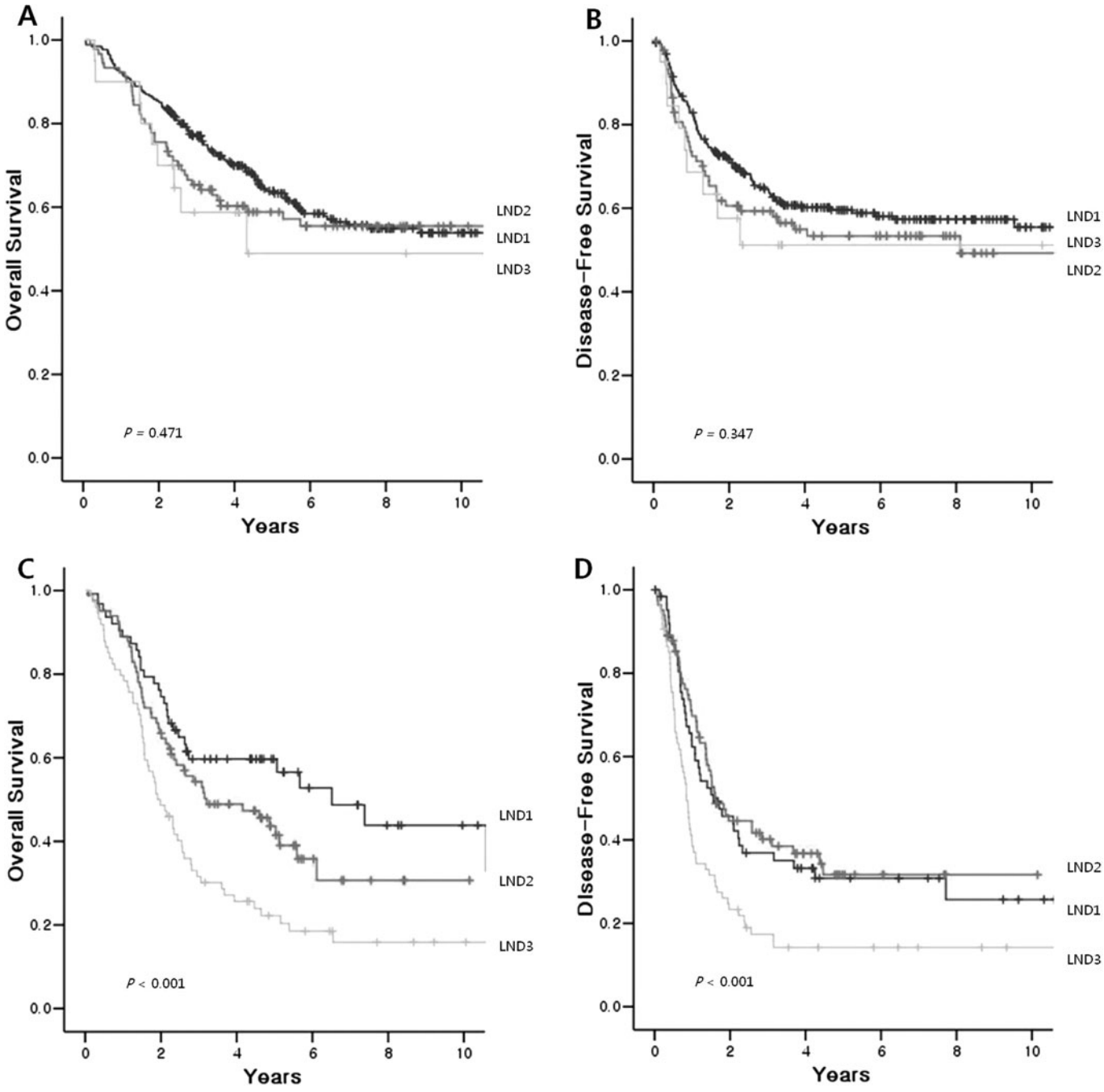

FIGURE 3. Kaplan–Meier curves by the distribution of lymph node metastases (LND) status depicting A, overall survival and B, disease-free survival among 371 patients with pN1 category and C, overall survival and D, disease-free survival among 219 patients with pN2 category.

IMA lymph node metastasis should be classified as systemic disease rather than regional disease with considering these prognostic and anatomical backgrounds. Those authors demonstrated that IMA node metastasis was an independent prognostic factor for survival and the predictive value of the category increased when it was included in stage IV disease. One of our most relevant finding was that both the overall survival and disease-free survival rates for the stage IV patients were not significantly different from the rates for the patients with stage III, LND3 disease. When we compared the administration of postoperative treatment between the stage III and stage IV groups for excluding the confounding effect of it among the groups, the overall incidence of administrating postoperative treatment, including chemotherapy and chemoradiotherapy did not significantly different between the stage III and stage IV groups (92.7% vs. 88.0%,

respectively, $P = 0.118$). This clear observation strongly suggests that IMA lymph node metastasis could be regarded as systemic disease. Finally, lateral spread, and particularly in lower rectal cancer, is a potential route for lymphatic metastasis,[27,28] and distal rectal tumors have a tendency toward lateral spread.[29] Thus, the LND alone may not accurately predict local recurrence in patients with rectal cancer. To the best of our knowledge, this is the first report on the association between the location of lymph node metastasis and local recurrence after surgery in rectal cancer patients.

The appropriate level of arterial ligation in the distally located colon or rectal cancer has not been definitely established because no randomized data exists on this topic. First, from the oncology perspective, cumulative results have shown no definite survival advantage between high ligation and low ligation of the IMA.[30–32] In contrast, a recent analysis that evaluated 2409 patients showed that high ligation reduced the recurrence rate and increased the survival rate after curative resections for certain stages of colorectal cancer.[33] Kanemitsu et al[18] suggested that high ligation of the IMA was beneficial in patients with node-positive disease. We concur with this and we confirmed that high ligation had a benefit in 7.8% of the 1205 patients in our study; otherwise, they would receive a R1 or R2 resection rather than the desired R0 resection. LND3 was detected in 7.8% of our patients, and this proportion is similar to that of previous studies; the reported incidence of metastatic lymph nodes at the origin of IMA is between 0.3% and 8.7% in patients with sigmoid colon or rectal cancer.[32] According to the distribution of potential prognostic variables with reference to the LND subgroups, the median number of retrieved lymph nodes was not different among the 4 LND groups in our series. The LND3 subgroup was highly associated with poor differentiation, an advanced pT category, positive lymphovascular or perineural invasion, and elevated preoperative CEA level. Interestingly, our study also revealed that LND3 disease was significantly correlated with younger patients. The mean number of positive lymph nodes was significantly different between the patients below and the patients over 65 years of age (2.2 vs. 1.6, $P = 0.002$). Although it is hard to unveil the reason, this may possibly be one of the reasons. Meanwhile, only 4 patients with pT2 cancers were classified as LND3, and LND3 was not observed in the patients with pT1 disease. Low ligation may be sufficient for pT1 sigmoid colon or rectal cancers. However, no preoperative or intraoperative method that can accurately assess this information exists, and in this study only 42 (44.7%) of the 94 patients with LND3 disease could be accurately detected using a preoperative clinical evaluation. Second, the effect of high ligation on the anastomotic integrity is controversial from an anatomical perspective. Some authors believe that high ligation significantly reduces perfusion of the proximal limb and it may consequently jeopardize the anastomotic safety.[34] However, high ligation allows better mobilization of the colon and therefore a tension-free anastomosis. Nano et al[35] concluded that the origin of IMA is the only safe point of ligation that avoids damage to the nervous system. Moreover, several investigations of patients who underwent high versus low tie techniques showed no significant difference of the anastomotic leak rates.[30,31,36] The incidence of anastomotic leakage in this series was 4.1% (n = 49; data not shown), which is comparable to the previous data.[37–39] Thus, our results indicate that high ligation of the IMA may not deteriorate the anastomotic integrity. We acknowledge that it is difficult to affirm that high ligation provides any benefit for the patients, because the survival of this LND3 group was the same as that for the patients with metastatic disease in our study. Further randomized studies are necessary to support high ligation as the technique of choice.

We observed that the number of lymph nodes harvested is an independent prognostic factor for overall survival for patients in multivariate analysis. The AJCC has recommended that 12 or more lymph nodes should be harvested in patients with colon cancer operated on with curative intent-to-treat surgery.[1] However, about 50% of these patients still have 12 or fewer lymph nodes removed, even though the standard practice is supposedly followed.[40–42] When we used a threshold of >12 resected lymph nodes as a measure of adequate lymphadenectomy for colorectal cancer, an inadequate lymph node yield was found in 45% of 1205 patients. This is comparable to previous studies. In addition, it is possible that special techniques may increase the number of metastatic lymph nodes.[43] We have not used these techniques at our institution because they are laborious and expensive, and are not used routinely.[44,45] Further studies are needed to resolve these issues on the relationship between the number of lymph nodes retrieved and the oncologic outcome of colorectal cancer.

In this study, the patients with both sigmoid colon and rectal cancer were enrolled in the analysis. This may be a possible limitation of our study because it is generally known that sigmoid colon and rectal cancer have different biological behaviors. However, we focused on the prognostic significance of the LND in this study and we found the same pattern for the prognostic stratification according to the LND, irrespective of the location of tumors. LND predicted the overall survival, the disease-free survival, and the distant metastasis-free survival, but not the local recurrence-free survival, in patients with sigmoid colon cancer, the same as for rectal cancer.

We acknowledge whether the LND is a better predictor than current pN category remains negative. In our study, pN category is a better predictor for local recurrence-free survival than the LND in patients with node-positive colorectal tumors. Moreover, the LND could not predict accurately the outcome of treatment in patients with pN1 category. However, we observed that the addition of the concept of LND to the current TNM classification would improve the accuracy in the prediction of survival in patients with pN2 category. These findings may be useful in the treatment of patients with node-positive sigmoid colon and rectal cancer and in the improvement of categorization based on nodal status.

This observation has several implications for clinical practice. First, the addition of the LND classification to future staging systems may be useful for prognostic stratification of the patients with sigmoid colon and rectal cancer. Second, the consideration of LND may provide a more appropriate criterion than the N category for deciding whether to administer postoperative chemotherapy in selected patients with node-positive colorectal cancer. Finally, our study primarily defined the prognostic role of LND in colorectal cancer, and so further trials using stratification by LND need to be performed. In conclusion, our study suggests that the LND is an independent predictor of survival for patients with sigmoid colon and rectal cancer, but it has no prognostic impact on local recurrence. The overall survival and disease-free survival rates for the stage III patients with IMA node metastasis were not significantly different from the rates for the stage IV patients. The N categorization including LND may enhance the prognostic value of the TNM staging system in patients with node-positive sigmoid colon or rectal cancer.

REFERENCES

1. Nelson H, Petrelli N, Carlin A, et al. Guidelines 2000 for colon and rectal cancer surgery. *J Natl Cancer Inst*. 2001;93:583–596.
2. Edge SB, Byrd DR, Compton CC, et al., eds. *AJCC Cancer Staging Manual,* 7th ed. Chicago, IL: Springer; 2010.
3. Japanese Society for cancer of the Colon and Rectum. *Japanese Classification of Colorectal Carcinoma*, 2nd ed. Tokyo, Japan: Kanehara & Co.; 2009.
4. Leibold T, Shia J, Ruo L, et al. Prognostic implications of the distribution of lymph node metastases in rectal cancer after neoadjuvant chemoradiotherapy. *J Clin Oncol*. 2008;26:2106–2111.
5. Kobayashi H, Ueno H, Hashiguchi Y, Mochizuki H. Distribution of lymph node metastasis is a prognostic index in patients with stage III colon cancer. *Surgery*. 2006;139:516–522.

6. Hida J, Okuno K, Yasutomi M, et al. Number versus distribution in classifying regional lymph node metastases from colon cancer. *J Am Coll Surg*. 2005;201:217–222.
7. Wong JH, Bowles BJ, Bueno R, Shimizu D. Impact of the number of negative nodes on disease-free survival in colorectal cancer patients. *Dis Colon Rectum*. 2002;45:1341–1348.
8. Ratto C, Sofo L, Ippoliti M, et al. Accurate lymph-node detection in colorectal specimens resected for cancer is of prognostic significance. *Dis Colon Rectum*. 1999;42:143–154.
9. Newland RC, Dent OF, Lyttle MN, Chapuis PH, Bokey EL. Pathologic determinants of survival associated with colorectal cancer with lymph node metastases. A multivariate analysis of 579 patients. *Cancer*. 1994;73:2076–2082.
10. Suzuki O, Sekishita Y, Shiono T, Ono K, Fujimori M, Kondo S. Number of lymph node metastases is better predictor of prognosis than level of lymph node metastasis in patients with node-positive colon cancer. *J Am Coll Surg*. 2006;202:732–736.
11. Rullier A, Laurent C, Capdepont M, et al. Lymph nodes after preoperative chemoradiotherapy for rectal carcinoma: number, status, and impact on survival. *Am J Surg Pathol*. 2008;32:45–50.
12. Baxter NN, Morris AM, Rothenberger DA, Tepper JE. Impact of preoperative radiation for rectal cancer on subsequent lymph node evaluation: a population-based analysis. *Int J Radiat Oncol Biol Phys*. 2005;61:426–431.
13. Huh JW, Kim HR, Kim YJ. Prognostic value of perineural invasion in patients with stage II colorectal cancer. *Ann Surg Oncol*. 2010;17:2066–2072.
14. Huh JW, Kim HR, Kim YJ. Proliferating cell nuclear antigen as a prognostic factor after total mesorectal excision of stage II-III rectal cancer. *Ann Surg Oncol*. 2009;16:1494–1500.
15. Huh JW, Kim HR. Postoperative chemotherapy after neoadjuvant chemoradiation and surgery for rectal cancer: is it essential for patients with ypT0-2N0? *J Surg Oncol*. 2009;100:387–391.
16. Huh JW, Kim YJ, Kim HR. Ratio of metastatic to resected lymph nodes as a prognostic factor in node-positive colorectal cancer. *Ann Surg Oncol*. 2010;17:2640–2646.
17. Tang R, Wang JY, Chen JS, et al. Survival impact of lymph node metastasis in TNM stage III carcinoma of the colon and rectum. *J Am Coll Surg*. 1995;180:705–712.
18. Kanemitsu Y, Hirai T, Komori K, Kato T. Survival benefit of high ligation of the inferior mesenteric artery in sigmoid colon or rectal cancer surgery. *Br J Surg*. 2006;93:609–615.
19. Das P, Skibber JM, Rodriguez-Bigas MA, et al. Clinical and pathologic predictors of locoregional recurrence, distant metastasis, and overall survival in patients treated with chemoradiation and mesorectal excision for rectal cancer. *Am J Clin Oncol*. 2006;29:219–224.
20. Huh JW, Jung EJ, Park YA, Lee KY, Sohn SK. Sphincter-preserving operations following preoperative chemoradiation: an alternative to abdominoperineal resection for lower rectal cancer? *World J Surg*. 2008;32:1116–1123.
21. Sugihara K, Kobayashi H, Kato T, et al. Indication and benefit of pelvic sidewall dissection for rectal cancer. *Dis Colon Rectum*. 2006;49:1663–1672.
22. Nagtegaal ID, van de Velde CJ, Marijnen CA, van Krieken JH, Quirke P. Low rectal cancer: a call for a change of approach in abdominoperineal resection. *J Clin Oncol*. 2005;23:9257–9264.
23. Bernstein TE, Endreseth BH, Romundstad P, Wibe A. Circumferential resection margin as a prognostic factor in rectal cancer. *Br J Surg*. 2009;96:1348–1357.
24. Nagtegaal ID, Marijnen CA, Kranenbarg EK, van de Velde CJ, van Krieken JH. Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit. *Am J Surg Pathol*. 2002;26:350–357.
25. Judo ES. The jejunum, ileum, and colon. In: Hollinshead WH, eds. *Anatomy for Surgeons*. New York, NY: Harper and Row; 1971.
26. Kim JC, Lee KH, Yu CS, et al. The clinicopathological significance of inferior mesenteric lymph node metastasis in colorectal cancer. *Eur J Surg Oncol*. 2004;30:271–279.
27. Sauer I, Bacon HE. Influence of lateral spread of cancer of the rectum on radicability of operation and prognosis. *Am J Surg*. 1951;81:111–120.
28. Deddish MR. Abdominopelvic lymphnode dissection in cancer of the rectum and distal colon. *Cancer*. 1951;4:1364–1366.
29. Steup WH, Moriya Y, van de Velde CJ. Patterns of lymphatic spread in rectal cancer. A topographical analysis on lymph node metastases. *Eur J Cancer*. 2002;38:911–918.
30. Surtees P, Ritchie JK, Phillips RK. High versus low ligation of the inferior mesenteric artery in rectal cancer. *Br J Surg*. 1990;77:618–621.
31. Pezim ME, Nicholls RJ. Survival after high or low ligation of the inferior mesenteric artery during curative surgery for rectal cancer. *Ann Surg*. 1984;200:729–733.
32. Lange MM, Buunen M, van de Velde CJ, Lange JF. Level of arterial ligation in rectal cancer surgery: low tie preferred over high tie. A review. *Dis Colon Rectum*. 2008;51:1139–1145.
33. Slanetz CA Jr, Grimson R. Effect of high and intermediate ligation on survival and recurrence rates following curative resection of colorectal cancer. *Dis Colon Rectum*. 1997;40:1205–1218.
34. Seike K, Koda K, Saito N, et al. Laser Doppler assessment of the influence of division at the root of the inferior mesenteric artery on anastomotic blood flow in rectosigmoid cancer surgery. *Int J Colorectal Dis*. 2007;22:689–697.
35. Nano M, Dal Corso H, Ferronato M, Solej M, Hornung JP, Dei Poli M. Ligation of the inferior mesenteric artery in the surgery of rectal cancer: anatomical considerations. *Dig Surg*. 2004;21:123–126.
36. Corder AP, Karanjia ND, Williams JD, Heald RJ. Flush aortic tie versus selective preservation of the ascending left colic artery in low anterior resection for rectal carcinoma. *Br J Surg*. 1992;79:680–682.
37. Huh JW, Park YA, Sohn SK. A diverting stoma is not necessary when performing a handsewn coloanal anastomosis for lower rectal cancer. *Dis Colon Rectum*. 2007;50:1040–1046.
38. Enker WE, Merchant N, Cohen AM, et al. Safety and efficacy of low anterior resection for rectal cancer: 681 consecutive cases from a specialty service. *Ann Surg*. 1999;230:544–552.
39. Park HW, Kim CN, Park JS, et al. Analysis of anastomotic leakage after an anterior resection for rectal cancer. *J Korean Soc Coloproctol*. 2009;25:340–346.
40. Le Voyer TE, Sigurdson ER, Hanlon AL, et al. Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of intergroup trial INT-0089. *J Clin Oncol*. 2003;21:2912–2919.
41. Baxter NN, Virnig DJ, Rothenberger DA, Morris AM, Jessurun J, Virnig BA. Lymph node evaluation in colorectal cancer patients: a population-based study. *J Natl Cancer Inst*. 2005;97:219–225.
42. Wang J, Kulaylat M, Rockette H, et al. Should total number of lymph nodes be used as a quality of care measure for stage III colon cancer? *Ann Surg*. 2009;249:559–563.
43. Haboubi NY, Clark P, Kaftan SM, Schofield PF. The importance of combining xylene clearance and immunohistochemistry in the accurate staging of colorectal carcinoma. *J R Soc Med*. 1992;85:386–388.
44. Wood TF, Saha S, Morton DL, et al. Validation of lymphatic mapping in colorectal cancer: in vivo, ex vivo, and laparoscopic techniques. *Ann Surg Oncol*. 2001;8:150–157.
45. Monig SP, Baldus SE, Zirbes TK, et al. Lymph node size and metastatic infiltration in colon cancer. *Ann Surg Oncol*. 1999;6:579–581.

