Prognostic Impact of Lymphatic Invasion of Colorectal Cancer: A Single-center Analysis of 1,616 Patients Over 24 Years

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Abstract. *Background: The degree of lymph node metastasis represents an important prognostic factor for cancer. Lymphovascular invasion is a traditional tool for estimating the aggressiveness of colorectal cancer. Aim: To determine correlations between lymphatic invasion and lymph node metastasis or disease stage, and clarify the prognostic impact of lymphatic invasion. Patients and Methods: Patients (N=1,616) who underwent curative resection of primary colorectal adenocarcinoma at the Kurume University Hospital were included. Lymphatic invasion was calculated as an average and the degree was also determined (Ly0-3). Clinicopathological factors including lymphatic invasion were assessed by uni- and multivariate analyses to determine factors affecting survival. Survival was compared between different degrees of lymphatic invasion and lymph node metastasis. Results: Lymphatic invasion was absent (Ly0) in 806 patients (50%), and lymph node metastasis was absent (N0) in 1,085 patients (67%). Ninety-one percent of N0 patients were Ly0-1, 72% of N1 were Ly0-1, and 54% of N2 were Ly2-3. All patients with stage 0 disease (100%) were Ly0, 95% of stage I were Ly0-1, 46% of stage II were Ly1-2, and 36% of stage III were Ly2-3. Five- and 10-year survival rates were 83% and 68% in Ly0, 73% and 56% in Ly1, 66% and 49% in Ly2, 63% and 48% in Ly3, 81% and 67% in N0, 69% and 57% in N1, and 60% and 52% in N2, respectively ($p<0.0001$ each). Conclusion: Lymphatic invasion in colorectal cancer correlates well with the status of lymph node metastasis and disease stage, representing an independent prognostic factor after curative resection. Lymphatic invasion can be used for evaluating tumor aggressiveness and estimating patient survival, irrespective of the actual number of positive lymph nodes found.*

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Key Words: Lymphatic invasion, prognosis, colorectal cancer.

Colorectal cancer remains one of the most common malignant tumors in the world (1, 2). It is well-known that not only the presence or absence of lymph node metastasis, but also the degree of presence, is an important prognostic factor, along with depth of tumor invasion, and is useful in determining the adjuvant chemotherapy and surveillance program (3, 4).

Although the prognostic import of lymph node metastasis is widely accepted in colorectal cancer, 12 nodes or more must be examined to adequately assess the degree of lymph node metastasis (5, 6). The number of lymph nodes able to be examined depends on the extent of resection, recovery from the specimen, and counts of slides, and can therefore vary widely among patients, hospitals, and countries (7, 8).

Lymphovascular invasion is a traditional factor used in estimating the aggressiveness of colorectal cancer (9-11). In 1995, we demonstrated the prognostic importance of lymphatic invasion in rectal cancer and advocated the subdivision of stage III (Dukes' C) tumors according to lymphatic invasion (12). The present study examined correlations between lymphatic invasion and lymph node metastasis or disease stage, and clarified the prognostic impact of lymphatic invasion, based on a large series and long-term follow-up of patients with colorectal cancer curatively treated.

Patients and Methods

Participants comprised of 1,616 patients who underwent curative resection of primary colorectal adenocarcinoma of stage I, II, or III at the Department of Surgery at Kurume University, Fukuoka, Japan, between 1982 and 2005. Patients who had been treated with local excision or preoperative chemoradiotherapy and those with concomitant inflammatory bowel diseases or adenomatous familial polyposis were excluded. This study was approved by our hospital Ethics Committee (#06043) and informed consent was obtained from patients prior to enrollment.

Age and sex of patients, site, gross type, size (maximum tumor diameter), preoperative serum level of carcinoembryonic antigen (CEA), depth of wall invasion, status of lymph node metastasis, histopathological differentiation, degree of lymphatic and venous invasion, and presence or absence of postoperative adjuvant chemotherapy were extracted from operation records and pathology reports. These findings were based on the Japanese Classification

Table I. *Clinicopathological factors and survival rates*.

Variable		Number of patients	Survival rate		*p*-Value
			5-Year	10-Year	
Age	<65 years	782 (48)	84%	72%	
	≥65 years	834 (52)	68%	49%	<0.01
Gender	Female	597 (37)	81%	68%	
	Male	1019 (63)	73%	56%	<0.01
CEA	≤5 ng/ml	960 (63)	82%	68%	
	>5 ng/ml	565 (37)	67%	53%	<0.01
Site	Colon	1005 (62)	77%	61%	
	Rectum	611 (38)	75%	59%	0.431
Size	<4 cm	795 (49)	79%	64%	
	≥4 cm	821 (51)	73%	57%	<0.05
Gross	Localized	1473 (65)	77%	63%	
	Infiltrative	143 (35)	66%	52%	<0.01
Histological type	Well-differentiated	1117 (69)	78%	63%	
	Other	499 (31)	71%	54%	<0.01
Depth	T0/T1/T2	535 (33)	84%	72%	
	T3/T4	1081 (67)	71%	57%	<0.01
Node category	N0	1076 (67)	81%	67%	
	N1	375 (23)	69%	57%	
	N2	156 (10)	60%	52%	<0.01
Lymphatic invasion	Ly0	806 (50)	83%	68%	
	Ly1	530 (33)	73%	56%	
	Ly2	186 (12)	66%	49%	
	Ly3	94 (6)	63%	48%	<0.01
Venous invasion	V0	491 (30)	83%	69%	
	V1	937 (58)	76%	60%	
	V2	122 (8)	67%	48%	
	V3	66 (4)	53%	37%	<0.01
Stage*	0	106 (7)	86%	74%	
	I	381 (24)	85%	70%	
	IIA	303 (19)	79%	63%	
	IIB	287 (18)	75%	59%	
	IIIA	41 (3)	82%	71%	
	IIIB	338 (21)	69%	52%	
	IIIC	160 (10)	61%	44%	<0.01
Adjuvant therapy	Administered	760 (47)	81%	65%	
	Not administered	847 (53)	72%	56%	<0.01

*TNM seventh edition (ref.#15), CEA: carcinoembryonic antigen.

of Colorectal Carcinoma, as outlined by the Japanese Society for Cancer of the Colon and Rectum guidelines (13, 14).

Surgical specimens were fixed in 10% formalin, and the entire tumor mass was cut into sections approximately 5-mm-thick. Perirectal fat tissue was not removed from specimens and was contained in the sections. These sections were embedded in paraffin, and 5-μm-thick sections were cut and mounted on large glass slides. All sections were stained with hematoxylin-eosin and elastica van Gieson.

Lymphatic invasion was examined based on the histological features of normal lymphatic vessels and evaluated as positive only when cancer cells were floating within an endothelial-lined lymphatic channel. We excluded pseudolymphatic invasion, in which cancer cells were present in a space without endothelial lining, due to tissue shrinkage artifacts during the process of making the tissue slides.

The average number of lymphatic invasions per section was calculated and the degree of lymphatic invasion was determined using the following criteria (10): Ly0, no lymphatic invasion; Ly1, slight lymphatic invasion (0<Ly≤1 per section); Ly2, moderate lymphatic invasion (1<Ly≤2 per section); and Ly3, marked lymphatic invasion (more than 2 per section).

Disease stage was defined according to the Seventh edition of the TNM staging system by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) (15), although stage III was divided based only on the number of lymph node metastases into IIIA (1-3 nodes) and IIIB (≥4 nodes).

Histopathological diagnoses were made by one of the authors (S.K.) throughout the study period. All data were entered into a computer (PC-9801 VN2; NEC, Tokyo, Japan) using the dBASE III PLUS software (Ashton-Tate, Torrance, CA, USA).

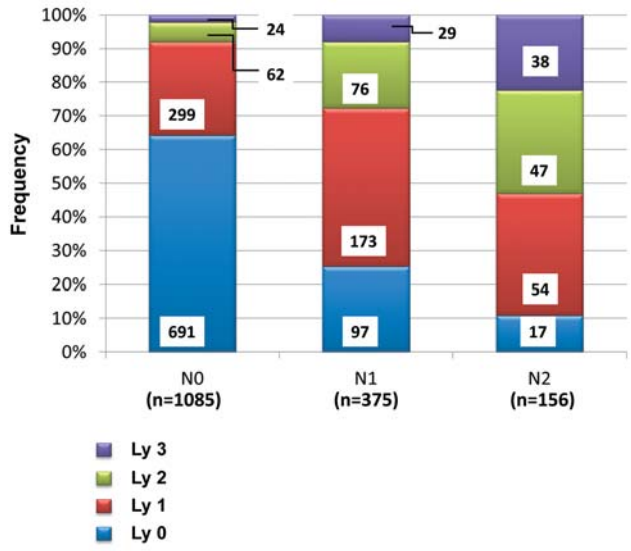

Figure 1. *Relationship between lymphatic invasion and lymph node status. Lymphatic invasion (Ly) was associated with the degree of lymph node metastasis (N) (p<0.0001).*

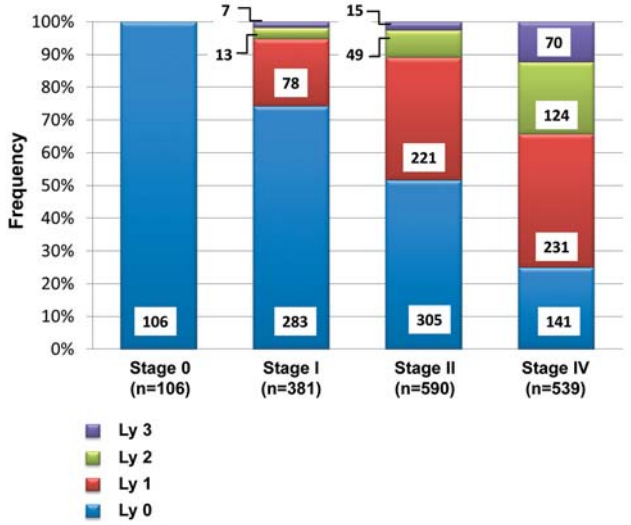

Figure 2. *Relationship between lymphatic invasion and stage. Lymphatic invasion was associated with disease stage (p<0.0001).*

Follow-up investigations were performed during outpatient visits, through letters, or over the telephone, and the last date of contact was regarded as the final date of confirmation. The final follow-up date was the December 31, 2010, and the median duration of follow-up was 100 months (range=60-326 months).

Differences were analyzed using the chi-square test and Student's t-test. Multivariate analysis was performed using Cox' proportional hazards model. Survival curves were analyzed by the Kaplan–Meier method and assessed using the Peto log-rank test.

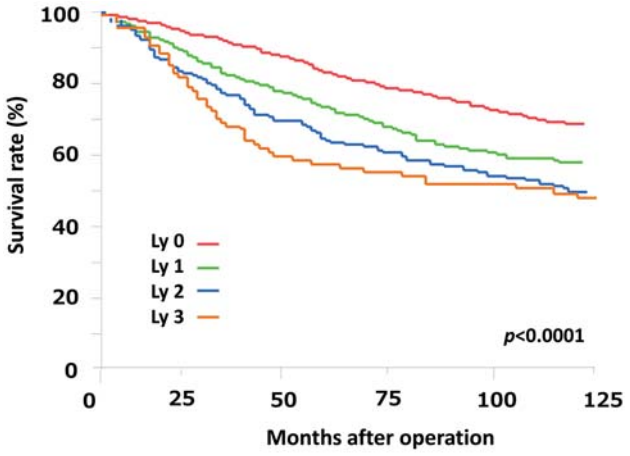

Figure 3. *Overall survival according to the degree of lymphatic invasion Overall survival was associated with the degree of lymphatic invasion. Five- and 10-year survival rates were 83% and 68% in Ly0, 73% and 56% in Ly1, 66% and 49% in Ly2, and 63% and 48% in Ly3, respectively.*

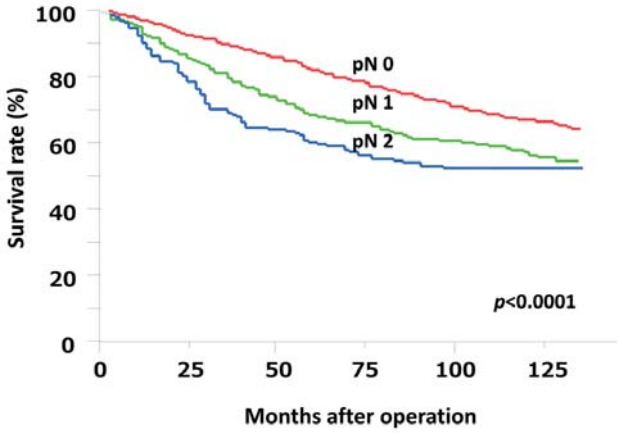

Figure 4. *Overall survival according to the degree of lymph node metastasis. Overall survival was associated with the degree of lymph node metastasis. Five- and 10-year-survival rates were 81% and 67% for N0, 69% and 57% for N1, and 60% and 52% for N2, respectively.*

Results

Data regarding lymphatic invasion, lymph node metastasis, disease stage and other clinicopatholigical results are shown in Table I.

Lymphatic invasion was significantly associated with the degree of lymph node metastasis and disease stage (p<0.0001 each; Figures 1 and 2).

Overall survival was significantly associated with the degree of lymphatic invasion (Figure 3) and lymph node metastasis (Figure 4). Five- and 10-year survival rates were

Table II. *Multivariate analyses of overall survival.*

Variable		Hazard ratio	95% Confidence interval		*p*-Value
Age	(<65 *vs.* ≥65 years)	2.2650	1.8657	2.6631	<0.01
Gender	(Female *vs.* male)	1.5337	1.2992	1.8169	<0.01
CEA	(≤5 *vs.* >5 ng/ml)	1.4181	1.2071	1.6650	<0.01
Size	(<4 *vs.* ≥4 cm)	1.1361	0.9533	1.3513	0.153
Gross type	(Localized *vs.* infiltrative)	1.3481	1.0393	1.7241	<0.05
Histological type	(Well *vs.* other)	1.0105	0.8449	1.2057	0.908
Tumor depth	(T0/T1/T2 *vs.* T3/T4)	1.4647	1.1600	1.8549	<0.01
Node status	(N0 *vs.* N1/N2)	1.1674	1.0329	1.3167	<0.05
Lymphatic invasion	(Ly0 *vs.* Ly1/Ly2/Ly3)	1.3276	1.1122	1.5867	<0.01
Venous invasion	(V0 *vs.* V1/V2/V3)	1.0272	0.8339	1.2701	0.802
Adjuvant therapy	(Yes *vs.* no)	1.5437	1.3029	1.8294	<0.01

CEA: Carcinoembryonic antigen.

Table III. *Multivariate analyses of recurrence-free survival.*

Variable		Hazard ratio	95% Confidence interval		*p*-Value
CEA	(≤5 vs. >5 ng/ml)	1.8466	1.4400	2.3872	<0.01
Site	(Colon vs. rectum)	1.3814	1.0758	1.7693	<0.05
Size	(<4 vs. ≥4 cm)	1.1206	0.8520	1.4637	0.412
Gross type	(Localized vs. infiltrative)	1.3797	0.9491	1.9526	0.090
Histological type	(Well vs. other)	1.2071	0.9288	1.5677	0.159
Tumor depth	(T0/T1/T2 vs. T3/T4)	2.0313	1.2917	3.2882	<0.01
Node status	(N0 vs. N1/N2)	1.3889	1.1691	1.6468	<0.01
Lymphatic invasion	(Ly0 vs. Ly1/Ly2/Ly3)	2.0449	1.4932	2.8365	<0.01
Venous invasion	(V0 vs. V1/V2/V3)	1.5473	1.0174	2.4366	<0.05
Adjuvant therapy	(Yes vs. No)	1.0812	0.8315	1.3990	0.558

CEA: Carcinoembryonic antigen.

83% and 68% in Ly0, 73% and 56% in Ly1, 66% and 49% in Ly2, and 63% and 48% in Ly3; and 81% and 67% in N0, 69% and 57% in N1, and 60% and 52% in N2, respectively ($p<0.0001$ each, log-rank test).

Overall survival was affected by several patient factors, histopathological features of tumor, and treatment factors. Significant items according to univariate analysis were entered into multivariate analysis. The age and sex of patients, gross type, serum CEA levels, depth of invasion, degree of lymph node metastasis and lymphatic invasion, and presence or absence of adjuvant chemotherapy independently affected overall survival (Table II). Likewise, recurrence-free survival was affected by several patient factors, histopathological features of tumor, and treatment factors according to univariate analysis. Subsequent multivariate analysis showed that tumor site, serum CEA levels, depth of invasion, and degree of lymph node metastasis and lymphatic invasion independently affected recurrence-free survival (Table III). In particularly, depth of invasion and lymphatic invasion were independently associated with both overall and recurrence-free survival ($p<0.01$ each).

Discussion

This study revealed that lymphatic invasion was a powerful and independent prognostic indicator for colorectal cancer, and survival after curative resection was clearly associated with the degree of lymphatic invasion.

This study was prospective and included 1,616 patients with a median follow-up period of 100 months. We obtained complete tumor sections from all participants and lymphatic invasion was assessed by the same surgical pathologist based on objective criteria throughout the study period. To the best of our knowledge, this represents the only study in which tumors have been completely examined and more than 1,500 patients have been followed-up for over 20 years at a single university-based surgical center.

Lymph node staging of colorectal cancer is important, but is associated with some problems. The TNM staging system by the AJCC/UICC bases lymph node staging on the number of metastases (N0, 0 nodes; N1, 1-3 nodes; N2, ≥4

nodes), and 12 lymph nodes or more must be surgically-resected and histologically examined to achieve accurate staging (5, 6).

In the United States, however, only 37% of patients received adequate lymph node examination in 2001(7), with a median of nine lymph nodes being examined. In 2005, 60% of 1,300 hospitals failed to achieve the benchmark of measuring 12 nodes (16). The probability of missing a positive node that was in fact truly present has been calculated as 14% if 12 nodes are examined, rising to 20% for eight nodes examined, and 30% for only five nodes examined (17).

The number of lymph nodes examined depends on the extent of surgical resection, recovery from the resected specimen, and counts of microscopic slides, and thus varies widely among patients, hospitals, and countries (7, 8). This heterogeneity results in stage migration and Will Rogers' phenomenon when treatment outcomes are compared among hospitals and institutes (18-20).

Lymph node harvest is lower for rectal resection than for colonic resection (21), and is negatively influenced by preoperative chemoradiotherapy (22, 23). One study showed that after chemoradiation, only 28% of resections included 12 nodes or more, with 32% including fewer than six nodes, and there was no correlation between the number of lymph nodes harvested and the number of nodes found to be positive for cancer (24).

Twelve-node harvest is thus hazardous and sometimes difficult to achieve in daily surgical practice, and the ratio of metastatic to examined lymph nodes has sometimes been used for estimating lymph node staging because this ratio is an important prognostic factor (25). This lymph node ratio has been suggested for use in stratifying patients for treatment options and clinical trials of postoperative adjuvant therapy (25-27), particularly when fewer than 12 nodes are identified in the resected specimen (28).

Although both the number and ratio of lymph node metastases are significantly influenced by treatment modalities and patient characteristics, tumor findings, including depth of invasion and lymphatic invasion, are not and remain independent of surgical procedures. Lymphatic invasion is useful in identifying tumors with occult lymph node metastasis (29, 30), for high-risk patients with node-negative (Dukes' B) tumors warranting adjuvant chemotherapy (31, 32) and for candidates for aggressive surgical treatment after local therapy (33, 34).

In conclusion, lymphatic invasion of colorectal cancer correlates well with the status of lymph node metastasis and disease stage, and was an independent prognostic factor after curative resection. We emphasize the utility of lymphatic invasion for evaluating the aggressiveness of tumors and estimating patient survival, irrespective of the number of examined and positive lymph nodes found.

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