Clinical Significance of Lymph Node Ratio and Location of Nodal Involvement in Patients with Right Colon Cancer

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Key Words

Colorectal carcinoma · Lymph node metastasis ·
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Abstract

Background/Aims: Increasing negative lymph node count has been reported to be associated with better outcomes in patients with colon cancer. The present study aimed to clarify the clinical significance of the lymph node ratio (LNR) and location of lymph node metastasis (LNM) in patients with stage III right colon cancer. **Methods:** We enrolled 820 patients who had undergone curative resection due to colon cancer at a single institution between 1991 and 2005. Among them, 197 underwent curative resection for T2–T4 right colon cancer. We evaluated the oncological outcomes according to LNR (quartiles) and distribution of LNM (n1 = LNM adjacent to the colon or along the vascular arcades of the marginal arteries; n2 = LNM along the major vessels; n3 = LNM near the roots of the major vessels). **Results:** The rates of LNM in T2, T3 and T4 right colon cancer were 11.1, 38.6 and 58.0%, respectively ($p < 0.0001$). Recurrence rates were 27.3, 37.5 and 57.1% in patients with n1, n2 and n3 LNM, respectively

($p < 0.0001$). LNR ($p < 0.0001$) and distribution of LNM ($p = 0.046$) were independent risk factors for recurrence in patients with stage III right colon cancer. **Conclusions:** Some patients with extensive LNM benefited from lymph node dissection with high ligation. Those with T3–T4 right colon cancer are suitable candidates for lymph node dissection with high ligation. Adding the concept of LNR and location of LNM to conventional TNM staging could improve the accuracy of evaluating nodal status.

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Introduction

Colorectal cancer is the second most common cause of cancer death in the USA and Japan, and the occurrence of this disease is rapidly increasing in Japan [1, 2]. Although there has been remarkable progress in chemotherapy for colorectal cancer, the standard therapy for resectable colorectal cancer is still curative resection with lymph node dissection. The introduction of total mesorectal excision led to a decrease in the local recurrence of rectal cancer and improved survival [3–5]. Complete me-

socolic excision (CME) for colon cancer has recently been proposed as well as total mesorectal excision for rectal cancer [6]. Mesocolic excision with high ligation of the main feeding artery has been a standard technique for advanced colon cancer in Japan [7, 8]. However, high ligation of the supplying arteries and the draining veins for right colon cancer is sometimes complicated because of variations in vascular branches [9, 10]. The precise indication for CME in patients with stage III right colon cancer has not been clarified.

Recent studies have reported that the concept of the lymph node ratio (LNR), which is the proportion of metastatic to examined lymph nodes, is a prognostic factor in patients with stage III colorectal cancer [11–16]. On the other hand, it has been reported that the distribution of lymph node metastasis (LNM) is a prognostic factor in patients with stage III colon cancer [7]. However, LNR and the location of LNM have not been investigated simultaneously as prognostic factors in patients with stage III colon cancer.

The present study aimed to clarify the value of lymph node dissection with high ligation of the primary feeding artery for right colon cancer. We also evaluated the clinical significance of the LNR and the distribution of LNM in patients with stage III right colon cancer.

Patients and Methods

Patients

We reviewed the medical charts of 820 patients who underwent curative surgery for colon carcinoma at a single institution (the Department of Surgical Oncology, Tokyo Medical and Dental University, Tokyo, Japan) between January 1991 and December 2005. Among them, 197 underwent curative resection with high ligation of the main feeding arteries and CME for T2–T4 right colon cancer. The standard practice of nodal dissection for advanced colon cancer at our institution involves ligating the major artery to the region of resection at its origin. Resection of the right colon involves resection of the ileocolic artery and right colonic artery at their origin from the superior mesenteric artery. We usually ligate only the right branch of the middle colic artery, although the lymph nodes around the root of the middle colic artery are dissected. The resected specimen with the mesentery was stretched and pinned to a cork board. The surgeon identified the lymph nodes, isolated them and recorded both their number and distribution. In this study, the surgeons harvested the lymph nodes from the specimen to evaluate the precise location of nodal metastases; we acknowledge that this technique is not the custom in the vast majority of centers in North America or Europe. After formalin fixation, the specimens and lymph nodes were examined by the pathologist. Patients with familial adenomatous polyposis, kindred with cancer family syndrome or ulcerative colitis were excluded from this study. We evaluated the oncological outcomes according to the distribution of LNM.

Location of LNM

The distribution of LNM was classified as n0 (no LNM), n1 (LNM adjacent to the colon or along the vascular arcades of the marginal arteries), n2 (LNM along the major vessels) or n3 (LNM near the roots of the major vessels).

Lymph Node Ratio

We calculated the LNR as the proportion of metastatic to examined lymph nodes and then classified the LNRs into subgroups according to the following quartiles: >0 to <0.07 , ≥ 0.07 to <0.15 , ≥ 0.15 to <0.30 and ≥ 0.30 .

Follow-Up Program

All patients were strictly followed up. During the first 3 years, patients were followed up every 3 months with clinical assessment and measurement of serum carcinoembryonic antigen, and every 6 months with chest X-rays and abdominal ultrasonography or computed tomography. For the next 2 years, all tests were performed every 6 months. Colonoscopy was performed 1 year after surgery and every 2 years for the next 4 years.

Statistical Analysis

Data were statistically analyzed using JMP 8 (SAS Institute Inc., Cary, N.C., USA). All data are expressed as means $\pm$ standard deviation. Data concerning age and number of lymph nodes were analyzed using the Mann-Whitney U test and Kruskal-Wallis test for 2 and 3 or more groups, respectively. Associations between each parameter and LNM or recurrence were analyzed using the χ^2 test. Independent risk factors for LNM and recurrence were determined using logistic regression analysis after forward stepwise selection. The actuarial survival of patients was calculated using the Kaplan-Meier method. Overall survival rates in all groups were compared using the log-rank test. Cox's proportional hazard regression analysis was applied to determine which factors independently affected postoperative survival. Forward selection was adopted in a stepwise regression procedure. Statistical significance was established at $p < 0.05$ for all results.

Results

Patient Characteristics

The characteristics of the patients, most of whom had lymphovascular invasion, are listed in table 1. The numbers of patients with stage I (T2), II and III cancers were 24, 91 and 82, respectively.

Lymph Node Metastasis

The mean number of lymph nodes harvested from 82 of the 197 patients was 20 ± 12 . The median number of positive nodes was 3 (range 1–23). The rates of LNM in patients with T2, T3 and T4 right colon cancer were 11.1, 38.6 and 58.0%, respectively. The numbers of patients with n1, n2 and n3 LNM were 44 (53.6%), 24 (29.3%) and 14 (17.1%), respectively. The numbers of patients with TNM N1 and N2 were 54 (65.9%) and 28 (34.1%), respec-

Table 1. Risk factors for LNM

		Univariate analysis			Multivariate analysis		
		LNM (–)	LNM (+)	p value	odds ratio	95% CI	p value
Gender	male	61 (61)	39 (39)	0.45			
	female	54 (56)	43 (44)				
Location of colon cancer	ascending colon	60 (62)	37 (38)	0.47			
	cecum	34 (52)	31 (48)				
	transverse colon	21 (60)	14 (40)				
Depth of tumor invasion	T2	24 (89)	3 (11)	0.0001	1	0.79–12.1	0.10
	T3	62 (61)	39 (39)		3.1		
	T4	29 (42)	40 (58)		5.4		
Histological type	well-differentiated adenocarcinoma	63 (68)	29 (32)	0.0049	1	0.91–3.40	0.093
	other	50 (49)	53 (51)		1.8		
	unknown	2	0				
Lymphatic invasion	absent	36 (97)	1 (3)	<0.0001	1	3.25–200	0.0020
	present	79 (49)	9 (51)		25.0		
Venous invasion	absent	17 (89)	2 (11)	0.0038	1	0.50–14.3	0.25
	present	98 (55)	80 (45)		2.7		

Values represent numbers of patients (percentage), unless indicated otherwise. CI = Confidence interval.

Table 2. Association between clinicopathological features and LNR and distribution of LNM

		LNR				Distribution of LNM				
		>0 to <0.07	≥0.07 to <0.15	≥0.15 to <0.30	≥0.30	p value	n1	n2	n3	p value
Number of lymph nodes retrieved		30 ± 11	21 ± 9	18 ± 7	16 ± 8	<0.0001	23 ± 11	18 ± 6	23 ± 11	0.16
Number of positive nodes		1 ± 0.4	2 ± 1	4 ± 1	7 ± 5	<0.0001	3 ± 2	4 ± 3	6 ± 6	0.10
Gender	male	6 (15)	13 (33)	10 (26)	10 (26)	0.25	22 (56)	9 (23)	8 (21)	0.45
	female	14 (33)	9 (21)	12 (28)	8 (19)		22 (51)	15 (35)	6 (14)	
Location of colon cancer	ascending colon	8 (22)	11 (30)	12 (32)	6 (16)	0.23	21 (57)	10 (27)	6 (16)	0.29
	cecum	7 (23)	10 (32)	8 (26)	6 (19)		17 (55)	11 (35)	3 (10)	
	transverse colon	5 (36)	1 (7)	2 (14)	6 (43)		6 (43)	3 (21)	5 (36)	
Depth of tumor invasion	T2	1 (33)	0	2 (67)	0	0.0058	3 (100)	0	0	0.14
	T3	11 (28)	17 (44)	7 (18)	4 (10)		20 (51)	9 (23)	10 (26)	
	T4	8 (20)	5 (13)	13 (33)	14 (35)		21 (53)	15 (38)	4 (10)	
Histological type	well-differentiated adenocarcinoma	9 (31)	11 (38)	6 (21)	3 (10)	0.10	14 (48)	10 (34)	5 (17)	0.72
	other	11 (21)	11 (21)	16 (30)	15 (28)		30 (57)	14 (26)	9 (17)	
Lymphatic invasion	absent	0	1 (100)	0	0	0.43	0	0	1 (100)	0.086
	present	20 (25)	21 (26)	22 (27)	18 (22)		44 (54)	24 (30)	13 (16)	
Venous invasion	absent	0	0	2 (100)	0	0.13	1 (50)	1 (50)	0	0.72
	present	20 (25)	22 (28)	20 (25)	18 (23)		43 (54)	23 (29)	14 (18)	
Values represent numbers of patients (percentage), unless indicated otherwise.										

Table 3. Risk factors for recurrence

		Univariate analysis			Multivariate analysis after stepwise regression		
		recurrence (–)	recurrence (+)	p value	odds ratio	95% CI	p value
Gender	male	80 (80)	20 (20)	0.52			
	female	81 (84)	16 (16)				
Location of colon cancer	ascending colon	83 (86)	14 (14)	0.38			
	cecum	51 (78)	14 (22)				
	transverse colon	27 (77)	8 (23)				
Depth of tumor invasion	T2	26 (96)	1 (4)	0.0025	1	0.82–5.05	0.13
	T3	87 (86)	14 (14)				
	T4	48 (70)	21 (30)				
Histological type	well-differentiated adenocarcinoma	80 (87)	12 (13)	0.065			
	other	79 (77)	24 (23)				
	unknown	2	0				
Lymphatic invasion	absent	36 (97)	1 (3)	0.0065			
	present	125 (78)	35 (22)				
Venous invasion	absent	19 (100)	0	0.030	1	4.8 × 10 ⁹ –	0.022
	present	142 (80)	36 (20)				
Number of LNM	N0	108 (94)	7 (6)	<0.0001			
	N1	40 (74)	14 (26)				
	N2	13 (46)	15 (54)				
Location of LNM	n0	108 (94)	7 (6)	<0.0001	1	1.03–14.93	0.046
	n1	32 (74)	12 (26)				
	n2	15 (63)	9 (38)				
	n3	6 (43)	8 (57)				
LNR	0	108 (94)	7 (6)	0.0099	1	2.56–16.13	<0.0001
	<0.15	34 (81)	8 (19)				
	≥0.15 to <0.30	12 (55)	10 (45)				
	≥0.30	7 (39)	11 (61)				

Values represent numbers of patients (percentage), unless indicated otherwise. CI = Confidence interval.

tively. Among the various parameters studied, depth of tumor invasion ($p = 0.0001$), histological type ($p = 0.0049$), lymphatic invasion ($p < 0.0001$) and venous invasion ($p = 0.0038$) were risk factors for LNM in the univariate analysis (table 1). Multivariate analysis revealed that the depth of tumor invasion (T4; $p = 0.017$) and lymphatic invasion ($p = 0.0020$) were independent risk factors. None of the patients with T2 right colon cancer had n2 or n3 LNM (table 2). The distribution of LNM was not associated with any clinicopathological parameters (table 2).

Lymph Node Ratio

The LNR was associated with the depth of tumor invasion ($p = 0.0058$) and the number of positive lymph nodes

($p < 0.0001$; table 2). There was a negative correlation between the number of retrieved lymph nodes and the LNR ($p < 0.0001$).

Recurrence

Among 197 patients, 36 (18.3%) developed recurrence over a median follow-up period of 4.1 years. Recurrence rates were 6.1, 27.3, 37.5 and 57.1% in patients with n0, n1, n2 and n3 LNM, respectively ($p < 0.0001$). We found 3 locoregional recurrences in the present study (3/197, 1.5%). The locoregional recurrence rates in T2, T3 and T4 tumors were 0% (0/27), 0.99% (1/101) and 2.9% (2/69), respectively. Two of the 3 patients with locoregional recurrence also had distant metastasis. The depth of tumor invasion ($p =$

Fig. 1. a Overall survival curves according to the TNM stage. **b** Overall survival curves for patients with stage II cancer and stage III cancer (LNR < 0.15).

0.0025), lymphatic invasion ($p = 0.0065$), venous invasion ($p = 0.030$), number of LNM ($p < 0.0001$), location of LNM ($p < 0.0001$) and LNR ($p = 0.0099$) were risk factors for recurrence in the univariate analysis. Among these, stepwise regression analysis selected depth of tumor invasion, venous invasion, location of LNM and LNR as risk factors for recurrence. Logistic regression analysis revealed that venous invasion ($p = 0.022$), the location of LNM (n0–n2 vs. n3, $p = 0.046$) and LNR (0–0.14 vs. 0.15–1.0, $p < 0.0001$) were independent risk factors for recurrence (table 3).

Survival

The 5-year overall survival rates in patients with stages I ($n = 24$), II ($n = 91$) and III ($n = 82$) right colon cancer were 95.2, 86.3 and 65.0%, respectively ($p = 0.0055$; fig 1a). In terms of LNM distribution, the 5-year overall survival rates in patients with n1, n2 and n3 LNM were 76.4, 60.0 and 37.5%, respectively ($p = 0.0002$). There was no difference in overall survival between patients with LNR < 0.15 and those with stage II cancer ($p = 0.45$; fig. 1b). Depth of tumor invasion ($p = 0.017$) and lymphatic invasion ($p = 0.025$), number ($p = 0.0006$) and distribution ($p = 0.0002$) of LNM, and LNR ($p < 0.0001$) were prognostic factors according to the log-rank test (table 4). Among these, stepwise regression analysis selected depth of tumor invasion and location of LNM as variables for further analysis. Depth of tumor invasion (T2 vs. T3–T4, $p = 0.030$) and location of LNM (n0–n1 vs. n2–n3, $p = 0.0050$) were independent risk factors in the Cox proportional hazards model.

Discussion

Lymph flow in colorectal cancer was described a century ago [17]. Today, the standard treatment for resectable colorectal cancer is radical resection accompanied by systematic lymph node dissection. However, the optimal extent of lymph node dissection remains controversial. Some studies have shown an advantage of high ligation in patients with colorectal cancer [18–20], whereas others could not demonstrate such an advantage [21–24]. High ligation of major vessels is a standard procedure for advanced colorectal cancer in Japan, although few reports have addressed indications for this technique.

Vessels of the right colon vary anatomically. Garcia-Ruiz et al. [9] reported that it was unusual for the right colic artery to arise directly from the superior mesenteric artery (10.7%). Yamaguchi et al. [10] demonstrated variations in the anatomy of the veins of the right colon. Therefore, high ligation for right colon cancer is sometimes complicated, and thus indications for high ligation for right colon cancer should be clarified.

The present study demonstrated that among patients with LNM, 48.7% with T3 and 47.5% with T4 right colon cancer had more distant LNM than those with pericolic cancer. On the other hand, none of the patients with T2 right colon cancer had n2 or n3 LNM. This study also showed that the depth of tumor invasion was an independent risk factor for LNM. The extent of lymph node dissection should be determined according to the depth of tumor invasion. A suitable candidate for CME with high

Table 4. Prognostic factors in patients with T2–T4 right colon cancer

		Univariate analysis			Cox hazard model after stepwise regression		
		number	%	p value	HR	95% CI	p value
Gender	male	100	51	0.48			
	female	97	49				
Location of colon cancer	ascending colon	97	49	0.31			
	cecum	65	33				
	transverse colon	35	18				
Depth of tumor invasion	T2	27	14	0.017	1	1.07–9.87	0.030
	T3	101	51		2.33		
	T4	69	35				
Histological type	well-differentiated adenocarcinoma	92	47	0.093			
	other	103	52				
	unknown	2	1				
Lymphatic invasion	absent	37	19	0.025			
	present	160	81				
Venous invasion	absent	19	10	0.13			
	present	178	90				
Number of LNM	N0	115	58	0.0006			
	N1	54	27				
	N2	28	14				
Location of LNM	n0	115	58	0.0002	1	1.17–2.28	0.0050
	n1	44	22		1.64		
	n2	24	12				
	n3	14	7				
LNR	0	115	58	<0.0001			
	<0.15	42	21				
	≥0.15 to <0.30	22	11				
	≥0.30	18	9				

HR = Hazard ratio; CI = confidence interval.

ligation is a patient with T3–T4 right colon cancer, whereas high ligation might be unnecessary for T2 cancer.

Hohenberger et al. [6] recently described improved oncological outcomes after adopting CME for colon cancer. They reduced 5-year local recurrence rates from 6.5 to 3.6% and increased cancer-related 5-year survival rates from 82.1 to 89.1%. All of our patients underwent CME with high ligation for right colon cancer. In the present study, the locoregional recurrence rates in T2, T3 and T4 tumors were 0, 0.99 and 2.9%, respectively. The recurrence rates in patients with n2 and n3 LNM were 37.5 and 57.1%, respectively. This means that >40% of patients with LNM around the roots of major vessels did not de-

velop recurrence after curative resection for right colon cancer, unless they had distant metastasis. Thus, CME with high ligation should be a standard treatment for advanced colon cancer, although the population of patients with n3 LNM who do not have distant metastasis may be small.

CME is not new [25], and surgical techniques have been applied in embryological tissue planes for colon cancer resection. However, this technique differs according to the surgeon. In fact, West et al. [26] reported that specimens resected at two different hospitals differed in terms of the area of the mesentery and the distance between the tumor and the high vascular tie.

The present study investigated the usefulness of the number and distribution of LNM, and LNR as prognostic markers for colon cancer. The location of LNM was an independent risk factor for both recurrence and survival. We used stepwise regression analysis due to the limited sample size. The number of LNM was excluded from further analysis of recurrence and survival partly because of colinearity. However, the number of LNM was an independent risk factor for recurrence and survival, unless LNR or LNM location was used (data not shown).

Some investigators have recently reported the usefulness of LNR for predicting the prognosis of patients after curative resection for colorectal cancer [11–16]. The present study demonstrated that LNR is a good predictor of recurrence after curative resection for right colon cancer. Adding the concept of LNR and location of LNM to conventional TNM staging could improve the accuracy of evaluating nodal status. Patients at high risk for recurrence with $n3$ LNM or $LNR \geq 0.15$ might be suitable candidates for cytotoxic adjuvant chemotherapy such as folinic acid, fluorouracil and oxaliplatin.

In the present study, high LNR led to both a high number of positive nodes and low number of lymph nodes retrieved. Kim et al. [13] reported the same tendency as in our study. In their study, the numbers of lymph nodes examined were as follows: 21 ($LNR < 0.1$),

18 ($LNR 0.1-0.2$), 16 ($LNR 0.2-0.4$) and 16 ($LNR > 0.4$). The reason why the patients with many positive nodes had fewer lymph nodes retrieved is unclear. A recent study showed that increasing the number of examined lymph nodes to more than 6 did not detect more positive nodes in patients with T3 colon cancer [27]. Our hypothesis is that the number of lymph nodes differs from one person to another and that individuals who naturally have fewer lymph nodes have a tendency to easily metastasize to lymph nodes. This issue should be clarified in further studies.

This retrospective study has potential limitations. The usefulness of CME with high ligation for advanced right colon cancer should be validated by a randomized controlled study. None of our patients received powerful adjuvant chemotherapy such as folinic acid, fluorouracil and oxaliplatin, or folinic acid, fluorouracil and irinotecan. The effectiveness of such adjuvant chemotherapy after CME with high ligation should also be clarified in further studies.

In conclusion, CME with high ligation of major vessels should be a standard therapy for patients with T3–T4 right colon cancer. Not only the number of LNM but also the distribution of LNM and the LNR should be considered with regard to prognosis after curative resection for right colon cancer.

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