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REVIEW

Impact of metastatic lymph node ratio in node-positive colorectal cancer

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Abstract

Colorectal cancer (CRC) is one of the most common malignant diseases in the world. Presently, the most widely used staging system for CRC is the tumor nodes metastasis classification system, which classifies patients into prognostic groups according to the depth of the primary tumor, presence of regional lymph node (LN) metastases, and evidence of distant metastatic spread. The number of LNs with confirmed metastasis is related to the severity of the disease, but this number depends on the number of LNs retrieved, which varies depending on patient age, tumor grade, surgical extent, and tumor site. Numerous studies and a recent structured review have demonstrated associated improvements in the survival of CRC patients with increasing numbers of LNs retrieved for examination. Hence, the impact of lymph node ratio (LNR), defined as the number of metastatic LNs divided by the number of LNs retrieved, has been investigated in various malignancies, including CRC. In this editorial, we review the literature demonstrating the clinicopathological significance of LNR in CRC patients. Some reports have indicated the advantage of considering the LNR compared to the number of LNs retrieved and/or LN status. When the LNR is taken into consideration for survival analysis, the number of LNs retrieved and/or the LN status is not always found to be a prognostic factor. The cut-off points for LNRs were proposed in numerous studies. However, optimal thresholds for LNRs have not yet received consensus. It is still unclear whether the LNR has more prognostic validity than N stage. For all these reasons, the potential advantages of LNRs in the staging system should be investigated in large prospective data sets.

Key words: Lymph node ratio; Lymph node; Colorectal cancer; Prognostic factor; Tumor nodes metastasis stage

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INTRODUCTION

Colorectal cancer (CRC) is among the most common malignant diseases in the Western world, whereas cancers of the upper gastrointestinal tract (esophagus and stomach) and liver are more predominant in the Eastern world. However, many Asian countries, including Japan, have experienced a

2-4-fold increase in the frequency of CRC during the past few decades[1,2].

The principal feature of a cancer staging system is its ability to provide an accurate prognosis and to guide appropriate clinical decisions regarding postoperative management and follow-up. In 1932, Dukes[3] developed a classification system for rectal cancer. This system classified cancers on the basis of tumor extension and lymph node (LN) status. This classification system is still being widely used for the prognostic evaluation of patients who undergo surgery for CRC. Subsequently, numerous modifications have been proposed to improve the prognostic predictive ability of the original Dukes classification[4-6]. Metastasis to regional LNs is an important prognostic factor and is used for clinical decision-making regarding the selection of the most appropriate cancer treatment[7-9]. Currently, the most widely used staging system is the tumor nodes metastasis (TNM) classification system[10]. The TNM staging system classifies patients into prognostic groups according to the depth of the primary tumor, presence of regional LN metastases, and evidence of distant metastatic spread. Regional LN status (N) is determined on the basis of the number of positive LNs retrieved and is classified as follows: no regional LN metastasis (N0), metastasis in 1-3 regional LNs (N1), and metastasis in 4 or more regional LNs (N2).

In Japan, the Japanese classification of colorectal carcinoma has been widely used[11]. This staging system classifies patients into different stages according to the depth of tumor invasion, LN metastasis, and hepatic, peritoneal, and extrahepatic distant metastasis, with extrahepatic distant metastasis not including hepatic and/or peritoneal metastasis. LN metastasis beyond the regional LNs is classified as distant metastasis. Treatment varies according to the progression of distant metastases. Aggressive resection for hepatic and/or peritoneal metastasis obtains a favorable survival rate.

LN status is determined on the basis of the number and location of positive LNs retrieved and is classified as follows: no evidence of LN metastasis (N0), metastasis in 1-3 pericolic/perirectal or intermediate LNs (N1), metastasis in 4 or more pericolic/perirectal or intermediate LNs (N2), and metastasis in the main LNs at the root of the artery or lateral LNs (N3). Some researchers, however, believe that the TNM staging system may not result in optimal staging and have proposed alternative LN parameters.

TOTAL NUMBER OF DISSECTED LYMPH NODES AND N STAGE

For correct nodal staging, it is necessary to thoroughly examine postoperative specimens and obtain an adequate number of nodes. At present, specimens are fixed for histologic study and LNs are usually obtained visually or by palpation by a pathologist. The fat-clearance technique has been shown to increase the accuracy of LNs harvested in surgical specimens compared with the manual dissection method[12-14]. The former method has enabled the upstaging of more than 50% of stage Ⅱ cases to stage Ⅲ, by allowing the identification and examination of previously undetected LNs[15]. Serial node dissection, *ex vivo* nodal mapping, and immunohistochemical staining have also been proposed as novel and viable techniques to improve LN evaluation[16]. However, these tests are time-consuming and expensive and are thus used infrequently. The American College of Pathologists has issued guidelines that advocate the use of additional techniques on resected colorectal specimens if fewer than 12 nodes are identifiable using conventional methods[17]. This may be a valid method for ensuring the judicious use of special techniques.

Ratto *et al*[18] investigated the different pathologic methods for LN identification in CRC patients. In Group 1, the specimens were fixed "*en bloc*" and a pathologist examined the specimens and identified the LNs visually and by palpation. In Group 2, the mesentery of the excised specimen was dissected away from the bowel. According to the site, the mesentery was divided into 3 specimen segments and fixed. After fixation, the pathologist identified the LNs. The mean number ± standard deviation of LNs found per patient was 29.6 ± 16.7 in Group 2, which was significantly higher than that detected in Group 1 (11.3 ± 5.8, $P < 0.01$). The mean number of involved LNs diagnosed in Group 2 (5.9 ± 11.5) was higher than that in Group 1 (2.9 ± 2.4, $P = 0.002$). In Group 2, the metastatic rate (37.5%) was significantly higher than that of Group 1 (30.2%, $P < 0.05$); similar characteristics were demonstrated while stratifying the patients according to the tumor site. However, the metastatic incidences were analogous in the 2 groups (Group 1, 7.7%; Group 2, 7.4%; $P = 0.3$).

Numerous studies and a recent structured review have demonstrated an improvement in the overall survival (OS) and/or disease-free survival (DFS) of CRC patients with increasing numbers of LNs retrieved for examination; such improvement has also been observed in patients with known LN-positive disease[19-28]. However, a population-based analysis revealed that the median number of LNs examined was 9 and that only 37% of patients with CRC received adequate LN evaluation (i.e. at least 12 LNs examined)[29]. This could be attributed to various patient-, tumor-, surgeon-, and/or pathologist-related variables. The two potentially modifiable variables are the completeness of LN evaluation by the pathologists conducting the examinations and the adequacy of the surgical resection method[30]. It is very important to establish the minimum number of LNs required for an acceptable accuracy in classifying a tumor as LN negative. The Working Party Report to the World Congress of Gastroenterology recommended that a minimum number of 12 LNs should be examined, although it was not stated how this figure was obtained[31]. Nonetheless, the agenda for adequate LN evaluation is still debatable. Recently, published studies assessing the number of LNs resected in CRC have reported wide variation in the extent of resection. Although these studies demonstrate a prognostic association between the number of LNs examined and survival, the cut-off values vary widely; i.e. from 6 to 40[19-21,24,32,33]. Current

guidelines established by the American Joint Committee on Cancer recommend the assessment of 12 or more nodes for accurate staging[9].

The number of resected LNs is important for staging and can be accomplished by adequate surgical resection and diligent pathologic examination. Despite the efforts of surgeons and pathologists, there are several other factors that could influence LN retrieval. It is generally considered that the right side of the colon is associated with a higher number of LNs examined than the left side of the colon and rectum[25,29,32,34]. This difference can be attributed to the fact that larger pieces of mesenteric lymphatic stations can be excised during right colectomy than during left colectomy[32]. Many rectal cancer patients receive preoperative radiotherapy, with or without chemotherapy. This neoadjuvant therapy has been shown to result in a significant decrease in both the size and number of LNs available for examination after resection[29,35]. In addition, older age and obesity may reduce the number of LNs retrieved[29,32,36]. Also, the number of LNs that can be retrieved may also depend on the immune response of a patient as the size and morphology of LNs are modified by immune responses[37,38].

LYMPH NODE RATIO

Recent studies on malignancies emphasize the importance of the number of LNs examined to establish a prognosis. There are two opposing views on the importance of lymphadenectomy in determining survival; some investigators believe that a complete lymphadenectomy has a therapeutic benefit, whereas others believe that it simply provides more accurate staging[39]. The number of LNs with confirmed metastasis is not only related to the severity of the disease, but also depends on the number of LNs retrieved, which varies depending on patient age, tumor grade, surgical extent, and tumor site. The impact of the lymph node ratio (LNR), which is the number of metastatic LNs divided by the number of retrieved LNs for each patient, was first investigated in gastric cancers, with reference to its application as a novel prognostic factor for identifying prognostic subgroups among gastric cancer patients with LN metastasis[40]. In this study, they evaluated the prognostic value of ratio groupings of LNR = 0.01-0.15, LNR = 0.16-0.30, and LNR > 0.31 in 401 patients with stage Ⅲ and Ⅳ gastric cancer. Multivariate survival analysis using Cox's proportional hazard model was applied to 3 forms of N status (LNR, N stage, and number of metastatic LNs). Among these 3 variables, LNR and N stage were independent prognostic factors [relative risk (RR), 2.4294 and 2.1150, $P = 0.0001$ and 0.0048, respectively]. However, the number of metastatic LNs was not an independent prognostic factor (RR, 0.6722, $P = 0.1092$). Subsequently, many studies have evaluated LNR in various malignancies, including gastric[41,42], esophageal[43], pancreas[44], breast[45,46], and bladder cancers[47]. However, to date, there have been no formal guidelines indicating that LNR should be used as an alternative to N stage.

LNR IN CRC

Surgical clearance and pathologic examination of the resected LNs has long been a standard component of operable CRC management. Complete LN dissection is still thought to provide the most accurate information regarding the disease when positive nodes are identified. LNR, which takes into account the degree of LN dissection, is an alternative to determining the absolute number of positive LNs. Indeed, experienced teams often perform meticulous and extensive LN dissection, which increases the probability of finding nodes. Therefore, patients with inadequate LN resection could receive less efficient adjuvant treatment[48]. There is a potential for stage migration when an inadequate number of LNs is harvested[22]. With respect to emerging diagnostic techniques, the concept of stage migration was first described by Feinstein *et al*[49] in 1985 and was termed as the Will Rogers Phenomenon.

Several studies have investigated the LNR in CRC [22,26-28,34,48,50-61] (Table 1). Berger *et al*[22] were the first to investigate the relationship between LNR and survival in patients with colon cancer. Of the 3411 assessable patients, 648 (19%) were N0, 1857 (54%) were N1, and 906 (27%) were N2. The mean number of retrieved LNs was 13. In a multivariate analysis, LNR was found to be a significant factor for OS, DFS, and cancer-specific survival (CSS) in patients in whom 10-15 LNs and more than 15 LNs were removed, but not for patients in whom less than 10 LNs were removed.

De Ridder *et al*[48] directly compared the TNM staging system to the LNR-based staging. The median number of retrieved LNs was 10. The prognostic separation using LNRs was 31% and that using N stages was 26%.

Wang *et al*[27,54] reported on 24 477 stage Ⅲ colon cancer cases. In only 7469 (30.5%) patients, more than 15 LNs could be harvested from the specimen. They categorized the patients into 4 groups; i.e. LNR1 to LNR4, on the basis of the cut-off points 1/14, 1/4, and 1/2, respectively. There was no difference in the survival rate among the stage ⅢA patients in the LNR1 to LNR4 groups ($P = 0.08$). The 5-year survival rate of the stage ⅢB patients in the LNR1, LNR2, LNR3, and LNR4 groups was 63.5%, 54.7%, 44.4%, and 34.2%, respectively ($P < 0.0001$). The 5-year survival rate of the stage ⅢC patients with LNR2, LNR3, and LNR4 was 49.6%, 41.7%, and 25.2%, respectively ($P < 0.0001$). LNR was an independent predictor of survival after adjusting for patient age, tumor size, tumor grade, race, number of positive LNs, and total number of LNs harvested [RR, 2.30; 95% confidence interval (CI), 2.08-2.55].

In a single center analysis, Rosenberg *et al*[26] reported the prognostic impact of LNRs in 3026 CRC patients. In all, 1763 colon and 1263 rectal carcinomas were documented. The mean numbers of retrieved and metastatic LNs for each patient were 18.3 and 2.6, respectively. The mean LNR was 0.14. In multivariate analysis, both LNR and N stage were found to be independent prog-

Table 1 Lymph node ratio (LNR) in colorectal cancer

Author, year	[Reference]	No. of patients	Selection of patients	Cut-off of LNR	5-year overall survival (%)	Uni *P* value	Multi *P* value	HR (95% CI)
Berger *et al*, 2005	[22]	3411	Stage Ⅱ and Ⅲ	< 0.05	79	< 0.0001	[1]NS[a]	-
			colon cancer	0.05-0.19	73		[1]< 0.0001[b]	[1]3.87 (NA)[b]
				0.2-0.39	63		[1]< 0.0001[c]	[1]12.43 (NA)[c]
				0.4-1.0	52			
De Ridder *et al*, 2006	[48]	26181	Node-positive	-0.4	56	-	< 0.0001	-
			colon cancer	0.4-	25			
Schumacher *et al*, 2007	[50]	232	Non-stage Ⅳ	< 0.08	-	< 0.05	-	-
			colon cancer	0.08 ⩽	-			
Lee *et al*, 2007	[51]	201	Stage Ⅲ colon cancer	0.01-0.11	83.6[d]	< 0.0001	< 0.0001	1
				0.12-0.24	61.1[d]			2.973 (1.407-6.280)
				0.25-0.92	20[d]			8.362 (3.739-18.704)
Wang *et al*, 2008, 2009	[27,54]	24477	Stage Ⅲ colon cancer	< 1/14	64.8	< 0.0001	[1]< 0.0001	[1]2.30 (2.083-2.545)
				1/14 ⩽ - < 0.25	56.2			
				0.25 ⩽ - 0.50	45.1			
				0.50 ⩽ - ⩽ 1.0	29.6			
Rosenberg *et al*, 2008	[26]	3026	Colorectal cancer	0	87.1	< 0.001	< 0.001	1 (NA)
				0.01-0.17	60.6			1.92 (NA)
				0.18-0.41	34.4			2.92 (NA)
				0.42-0.69	17.6			3.62 (NA)
				0.70 ⩽	5.3			4.31 (NA)
Peng *et al*, 2008	[52]	318	Node-positive	< 0.14	72.19	0.002	[1]0.003	[1]3.11 (1.47-6.58)
			rectal cancer	0.14-0.49	61.92			
				0.5-1	38.47			
Peschaud *et al*, 2008	[53]	307	Rectal cancer	0	89[e]	0.0013	[1]0.0003	[1]1.019 (1.009-1.029)
				0.01-0.07	92[e]			
				0.07-0.2	71[e]			
				0.2 <	67[e]			
Derwinger *et al*, 2008	[55]	136	Stage Ⅳ	0-0.15	708 d[f]	< 0.0049	[1]< 0.05[g]	2.1 (1.3-3.6)[g]
			colorectal cancer	0.16-0.65	438 d[f]			
				0.66-1	277 d[f]			
Derwinger *et al*, 2008	[56]	265	Stage Ⅲ colon cancer	0-0.125	80[h]	< 0.001	[1]< 0.0002	[1]10.6 (3.2-31.8)
				0.126-0.266	-			
				0.267-0.450	-			
				0.451-1	29[h]			
Vather *et al*, 2009	[57]	2364	Stage Ⅲ colon cancer	Lowest group	55-60	< 0.0001	-	-
				Higher group	10-20			
Chin *et al*, 2009	[34]	490	Stage Ⅲ colon cancer	⩽ 0.4	66.7[d]	< 0.0001		1
			(LN ⩾ 12)	0.4 < ⩽ 0.7	35.1[d]		0.001	2.298 (1.384-3.815)
				0.7 <	0[d]		< 0.001	7.407 (3.153-17.397)
Vaccaro *et al*, 2009	[61]	362	Stage Ⅲ colon cancer	< 0.25	64.9	< 0.0001	0.005	1
				0.25 ⩽	38.3			2.3 (1.3-4.1)
Park *et al*, 2009	[28]	318	Stage Ⅲ colon cancer	< 0.059	83.6[h]	0.0002	-	-
				0.059-0.23	71.1[h]			
				0.23 <	55[h]			
Priolli *et al*, 2009	[58]	113	Colorectal cancer	0	More than 80	0.03	[1]0.003	[1]8.575 (NA)
				0.01-0.2	67.6			
				0.21 ⩽	37.5			
Moug *et al*, 2009	[59]	295	Colorectal cancer	< 0.05	-	< 0.001	[1]< 0.001[i]	[1]11.65 (5.00-27.15)[i]
				0.05-0.19	-		[1]< 0.001[j]	[1]13.40 (3.64-49.10)[j]
				0.20-0.39	-			
				0.40-1.00	-			
Kim *et al*, 2009	[60]	232	Stage Ⅲ rectal cancer	⩽ 0.1	89	< 0.001		1
				0.1 < - ⩽ 0.2	67		0.623	1.260 (0.501-3.173)
				0.2 < - ⩽ 0.4	64		0.0047	2.435 (1.012-5.862)
				0. 4 <	50		0.005	3.701 (1.493-9.178)

Uni: Univariate analysis; Multi: Multivariate analysis; HR: Hazard ratio; 95% CI: 95% Confidence interval; NS: Not significant; NA: Not available; LN, Lymph node; [1]In multivariate analysis, LNR was considered as a continuous variable; [a]In patients with LN < 10; [b]In patients with LN 10-15; [c]In patients with LN > 15; [d]5-year disease-free survival; [e]3-year overall survival; [f]Median survival in days; [g]In patients with LN ⩾ 12; [h]3-year disease-free survival; [i]In colon cancer patients; [j]In rectal cancer patients.

nostic factors. LNR had a better prognostic value than the N stage ($P < 0.05$). The analysis of a subgroup of patients classified into colon and rectal cancer patients confirmed the identified LNRs as an independent prognostic factor ($P < 0.001$).

Peng *et al*[52] demonstrated for the first time the relation-

ship between LNRs and survival rates in rectal cancer patients. The average numbers of retrieved and metastatic LNs for each patient were 12 and 3.8, respectively. The mean LNR was 0.34. Multivariate analysis revealed that LNR was an independent risk factor for local recurrence rate, DFS, and OS; the hazard ratios (HRs) were 8.50 (95% CI, 2.25-32.03; $P = 0.002$), 3.59 (95% CI, 1.83-7.03; $P = 0.0002$), and 3.11 (95% CI, 1.47-6.58; $P = 0.003$), respectively.

Similarly, Peschaud *et al*[53] evaluated the prognostic value of LNRs in rectal cancer. They investigated the relationship between OS, DFS, and LNR in 307 rectal cancer patients. Of the 307 patients, 178 (57.9%) were N0, 67 (21.8%) were N1, and 62 (20.3%) were N2. The mean number of LNs examined was 22. In the multivariate analysis, LNR, and not the presence or absence of metastatic LNs, was found to be a significant prognostic factor for both OS and DFS [HR, 1.019 and 1.016 (95% CI, 1.009-1.029 and 1.008-1.025); $P = 0.0003$ and 0.0002, respectively]. Even in patients with fewer than 12 LNs examined, multivariate analysis confirmed that LNR was an independent prognostic factor for OS and DFS (HR, 1.046 and 1.028; $P = 0.0058$ and 0.0338, respectively).

Interestingly, Derwinger *et al*[55] investigated whether LNR was a prognostic factor in stage IV CRC patients. It is fairly obvious that stage IV CRC is a heterogeneous group with respect to survival prognosis. LNR groups were formed by dividing the patients into 3 equally sized groups: LNR = 0-0.15, LNR = 0.16-0.65, and LNR = 0.66-1. In a univariate analysis, LNR was found to be a significant marker for survival prognosis ($P < 0.0049$). However, the node stage (N1-N2) had a borderline significance ($P < 0.06$). In a Cox multivariate analysis, the performance status and eligibility for chemotherapy were the most significant markers [HR, 2.2 (95% CI, 1.1-4.3), $P < 0.001$] along with the differentiation grade [HR, 2.0 (95% CI, 1.1-2.8), $P < 0.05$]. Concerning LNs, the LNR was significant as a marker [HR, 2.1 (95% CI, 1.3-3.6), $P < 0.05$], while the N stage was not significant.

In 2009, numerous studies on LNRs in CRC patients were published[28,34,57-61]. Vather *et al*[57] reported the significance of LN evaluation in 4309 stage Ⅱ and stage Ⅲ colon cancer patients. In stage Ⅱ and stage Ⅲ colon cancer patients, the mean numbers of LNs examined were 13.7 and 13.8, respectively. In their study, increased rates of nodal examination were found to be associated with significantly lower 5-year mortality rates for stage Ⅱ and stage Ⅲ colon cancer patients, but this survival advantage appeared to be minimal after the 16-node mark. In 2364 stage Ⅲ colon cancer patients, the 5-year mortality rate showed a clear and steady increase as the LNR increased, with the rate doubling from around 40%-45% in the lowest LNR group to 80%-90% in the higher LNR group. The LNR had a better prognostic discriminative value than the absolute number of positive nodes examined. The LNR has been validated as a powerful predictor of survival in stage Ⅲ cancer patients.

Chin *et al*[34] determined the relationship between LNR and survival in 624 stage Ⅲ colon cancer patients. The mean LNR was 0.2045. It was possible to harvest an adequate number of LNs (LN ≥ 12) in 490 of the 624 patients (78.5%). The rate of adequate lymphadenectomy was significantly lower in patients with cancer of the descending colon and sigmoid colon than in those with cancer involving all the other areas ($P < 0.001$). These 490 patients were stratified into LNR groups: 1 (LNR ≤ 0.4), 2 (0.4 < LNR ≤ 0.7), and 3 (0.7 < LNR). Cox proportional hazards regression analysis revealed that the number of positive LNs was not a significant factor [HR, 1.157 (95% CI, 0.811-1.650), $P = 0.421$] when LNR was taken into consideration. They concluded that LNR is a more precise predictor of 5-year DFS than the number of positive LNs in patients with stage Ⅲ colon cancer [LNR1 *vs* LNR2: HR, 2.298 (95% CI, 1.384-3.815), $P = 0.001$; LNR1 vs. LNR3: HR, 7.407 (95% CI, 3.153-17.397), $P < 0.001$].

Recently, Vaccaro *et al*[61] reported the prognostic value of LNR in stage Ⅲ colon cancer patients who were treated by colorectal surgeons. The median LNR was 0.11. In all, 362 stage Ⅲ colon cancer patients were stratified into LNR groups: LNR1 (LNR < 0.25) and LNR2 (LNR ≥ 0.25). The 5-year DFS, CSS, and OS for the LNR1 group were 68.3%, 74.5%, and 64.9%, respectively, and were 31.5%, 40.1%, and 38.3% for the LNR2 group, respectively ($P = 0.001$ for each variable). Univariate analysis showed that both LNR and N stage were associated with significantly different HRs for DFS [HR, 2.8 and 2.3 (95% CI, 1.9-4.1 and 1.6-3.4), $P < 0.001$, respectively], CSS [HR, 3.1 and 2.3 (95% CI, 2.1-4.7 and 1.6-3.4), $P < 0.001$, respectively], and OS [HR, 2.2 and 2.0 (95% CI, 1.6-3.2 and 1.4-2.9), $P < 0.0001$ and 0.001, respectively]. In a multivariate analysis, LNR was found to be an independent prognostic factor for DFS [HR, 2.6 (95% CI, 1.5-4.8), $P = 0.001$], CSS [HR, 3.8 (95% CI, 1.9-7.4), $P < 0.001$], and OS [HR, 2.3 (95% CI, 1.3-4.1), $P = 0.005$]. However, N stage was not an independent prognostic factor for DFS ($P = 0.41$), CSS ($P = 0.92$), and OS ($P = 0.58$). In addition, the number of harvested LNs was not a prognostic factor for DFS ($P = 0.39$ and 0.72, respectively), CSS ($P = 0.33$ and 0.41, respectively), and OS ($P = 0.23$ and 0.66, respectively) by univariate and multivariate analyses.

In data obtained in our hospital (unpublished data), we investigated the number of LNs retrieved and the effect of N stage (TNM classification versus Japanese classification) on the 5-year OS in 301 stage Ⅲ (TNM classification) CRC patients diagnosed between 1985 and 2000. In our hospital, LN identification was performed according to the Japanese system. Briefly, the mesentery of the excised specimen was dissected away from the bowel and LN identification was performed immediately postoperatively by the surgeon before fixation. In all, 157 colon and 144 rectal cancers were documented. The mean numbers of retrieved and metastatic LNs were 22.9 and 3.2, respectively. Adequate LN evaluation (i.e. examination of at least 12 LNs) was performed in 226 of the 301 (75.1%) patients. As per the TNM classification, the group of patients with N1 ($n = 220$) and N2 ($n = 81$) had a 5-year OS

of 84.9% and 50.1%, respectively, while according to the Japanese classification, the group of patients with N1 (n = 212), N2 (n = 65), and N3 (n = 24) displayed a 5-year OS of 83.0%, 64.0%, and 40.0%, respectively. Hence, the prognostic separation using the Japanese classification system was 43.0% and that using the TNM classification system was 34.8%. In colon cancer, the mean numbers of retrieved and metastatic LNs were 21.7 and 2.9, respectively. Adequate LN evaluation was performed in 117 of the 157 (74.5%) patients. The groups of patients with N1 (n = 121) and N2 (n = 36) (TNM classification) had a 5-year OS of 91.0% and 55.0%, respectively, while that with N1 (n = 116), N2 (n = 33), and N3 (n = 8) (Japanese classification) had a 5-year OS of 90.7%, 62.4%, and 31.3%, respectively. Hence, the prognostic separation using the Japanese classification system was 59.4% and that using the TNM classification system was 36.0%. In rectal cancer, the mean numbers of retrieved and metastatic LNs were 24.3 and 3.5, respectively. Adequate LN evaluation was performed in 109 of the 144 (75.7%) patients. The groups of patients with N1 (n = 99) and N2 (n = 45) (TNM classification) had a 5-year OS of 77.6% and 49.1%, respectively, while that with N1 (n = 96), N2 (n = 32), and N3 (n = 16) (Japanese classification) displayed a 5-year OS of 75.7%, 65.7%, and 35.5%, respectively. Hence, the prognostic separation using the Japanese classification system was 40.2% and that using the TNM classification system was 28.5%. Therefore, in our analysis, N stage using the Japanese classification system was found to be remarkably superior to the TNM classification system for the stratification of prognosis.

CONCLUSION

In the literature on the number of LNs retrieved, as shown in Table 1, 12 of 17 articles assessed 12 or more nodes[26,28,34,50-53,57-61]. In many studies that were reviewed in this editorial, more than 12 LNs were investigated. However, a population-based analysis revealed that only 37% of patients with CRC received adequate LN evaluation (i.e. at least 12 LNs examined)[29]. To correct this, it may be useful for the method of LN identification in the mesenterium be changed to the Japanese system rather than the Western system after adequate lymphadenectomy.

Some reports showed the advantage of using the LNR compared to the absolute number of LNs and/or LN status (N stage or number of positive LNs). With respect to the retrieval number of LNs in stage Ⅲ CRC, when increasing numbers of LNs are examined, an associated improvement in OS and/or DFS was observed[22,26-28]. However, in some reports, an associated improvement in OS and/or DFS was not observed[50,52,56,59-61]. When taking the LNR into consideration, the retrieval number of LNs was not always found to be a prognostic factor. In contrast, for the LN status (N stage or number of positive LNs), as the LN status decreased, there was an associated improvement in the OS and/or DFS[22,27,48,52,56,59,60]. However, in some reports, such an improvement was not observed[51,61]. When the LNR was taken into consideration, LN status was not always found to be a prognostic factor. The clinical significance of LN status as a prognostic factor is not necessarily absolute.

However, these studies vary widely in sample size and tumor background. It is not known whether a systematic examination of LNRs across all patients would yield consistent results. Although the body of literature regarding LNRs is growing, many studies have been performed using diverse patient groups. When LNR is taken into consideration, the cut-off points have not necessarily been discussed adequately or validated in alternative data sets. We believe that systematic LNR analyses from multi-institutional randomized patient data with validation in similar independent data sets are required to clearly demonstrate the importance of LNRs. The cut-off points for LNRs in grouping patients or for recommending adjuvant therapy have yet to be established. It is essential to consider the staging system to include accurate prognostic variables such as LNR. Cut-off points for LNRs were proposed in numerous studies, but the optimal threshold for LNRs has not received consensus. It is still unclear whether LNR has more prognostic validity than N stage or the number of positive LNs. For all these reasons, the potential advantages of LNRs in staging systems should be investigated in large prospective data sets.

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