Original Article

Lymph Node Ratio is Not Predictive of Survival in Stage III Colorectal Cancer with Less than 12 Lymph Nodes Examined

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Key Words
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Lymph nodes yield (LNY);
5-year tumor-specific survival (TSS)

Background. Lymph node ratio (LNR) (positive lymph nodes/sampled lymph nodes) is associated with disease-free survival (DFS) and 5-year tumor-specific survival (5-year TSS) in stage III colorectal cancer (CRC). The likelihood of receiving inadequate lymph nodes yield (LNY) (i.e., at least 12 LNs examined), and the influence of accurate predictive factors on LNR evaluation. This study identified predictors of LNR evaluation instage III CRC patients who had different lymph nodes (LNs) sampling status (less than or more than 12 LNs examined).

Methods. From January 2000 to December 2014, the follow-up status of stage III CRC patients who underwent surgery in a single medical center was retrospectively analyzed. These patients were stratified into LNR groups 1 (LNR $\leq$ 0.1), LNR groups 2 (0.1 < LNR $\leq$ 0.2), and LNR groups 3 (0.2 < LNR $\leq$ 0.42), and LNR groups 4 (LNR > 0.42). Prognostic significance with DFS, and 5-year TSS curves were calculated with the Kaplan-Meier survival analysis and Cox proportional hazards regression.

Results. In the study population, including 656 stage III CRC patients with a mean age of 67.06 $\pm$ 14.18 years. Of the 656 patients, an adequate number of lymph nodes (n $\geq$ 12) had been harvested in 495 patients. Right-sided tumor, higher T stage, higher N status and poor differentiated were all associated with higher LNR. A multivariate analysis showed that lower LNR was associated with better DFS when more than 12 LNs were sampling status in stage III CRC patients. However, LNR was not an accurate prognostic factor for DFS and 5-year TSS when fewer than 12 LNs were sampling status in stage III CRC patients.

Conclusions. These results support consideration that lymph node ratio isn't predictive of survival in stage III CRC with less than 12 LNs examined.

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In Taiwan, CRC is the most common cancer and the third most frequent cause of cancer-related death, accounting for an estimated 5698 deaths in 2012.[1,2] With the increase in the symptomatic cases and screening colonoscopies detected case in Taiwan and its incidence is rapidly increasing of stage III CRC cases have been detected, representing an estimated 22-25% of the new CRC cases in our hospital data-

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base. These patients will present with potentially curable disease that is treated by surgical resection. Surgical treatment should include resection of the affected segment of bowel and en bloc resection of the associated draining LNs tothe level of the origin of the primary blood supply to that segment of the bowel.[3]

Although most stage III CRC patients undergo radical surgery, 30% to 50% of patients with stage III tumors inevitably experience tumor relapse manifesting as locoregional recurrence, distant metastasis, or metachronous colorectal lesions within 5 years of follow up.[4] Therefore, postoperative adjuvant chemotherapy (CMT) has been widely recommended as the standard treatment for stage III CRC cancer since the early 1990s, and has resulted in a 30% decrease in the relapse rates compared with surgery alone.[5] The aim of adjuvant CMT is to eradicate micrometastases and increase the 5-year TSS.[5,6] TNM stage III colorectal cancer is different, and the same chemotherapy regimen is prescribed for all stage III CRC patients. However, patient prognosis primarily relieson the tumor stage at diagnosis. In fact, stage IIIA, IIIB, and IIIC CRC patients typically manifest different DFS and 5-year TSS.

Some authors go so far as to suggest that patients deemed LNs positive on the basis of a low number of retrieved LNs should be considered as being at high risk of worse outcome.[7-9] Therefore, the National Comprehensive Cancer Network (NCCN) has recommended a minimum 12-node count as a quality indicator in colorectal cancer surgery. The retrieval of a low number of LNs is also likely to be an indicator of poor-quality surgical or pathologic care. Most clinicians had been proposed that a higher LNY may result in a higher number of positive LNs being detected.[6] To give the best treatment and management for more and more stage III CRC patients, accurate assessment of LNs status is clearly essential.

In most of studies, LNR which means the ratio of involved LNs to the total detected LNs, is an important prognostic factor in malignancies of colon and rectum.[10,11] Two of these series demonstrated that LNR has an independent association with long-term outcome even when the analysis is adjusted to the number of both harvested and positive LNs.[12,13] Besides, some of the aspects regarding the prognostic value of LNR (i.e., different LNs sampling status -- less than or more than 12 LNs examined) remain unclear. The preliminary aim of this study was to discover the effect between patients' survival rates and current guidelines for node harvest as proposed by the AJCC in different CRC stages and LNR on the prognosis of the patients presenting with stage III CRC and to compare the result with the effect of LNs sampling status on their prognosis. Whereas there are limited studies about real impact of the LNR in stage III CRC patients with different LNs sampling status, we decided to investigate the 12 LNs number as adequate LNR evaluation on DFS and 5-year TSS in these patients.

Materials and Methods

Patient selection

From January 2004 to December 2014, a total of 2,809 CRC patients underwent an operation at our hospital (Tri-Service General Hospital, Taipei). The surgical and pathological findings were recorded according to the 6th/7th American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) TNM classification. All operations were performed by colorectal specialists in our hospital.

There were 743 patients with stage III CRC patients in our hospital based on the pathology, according to the 6th/7th AJCC staging system. Those who underwent curative surgery were enrolled in this study. Patients with any of the following criteria were excluded: (1) pathological diagnosis of positive surgical margins; (2) synchronous or metachronous double cancer; (3) synchronous or metachronous multiple CC; (4) inflammatory bowel disease or hereditary colon cancer syndromes; (5) previous history of malignancy; (6) lack of an entire treatment course in our hospital; (7) perioperative (< 30 days post-operation) mortality, (8) lack of follow-up data; or (9) incomplete adjuvant CMT (< 3 months). Data on approximately 9% of patients was incomplete, and hence, these data were removed from the database. A total of

656 patients with stage III CRC were included in this retrospective analysis.

Based on the total number of LNs, they were divided into two non-randomized groups: those with fewer than 12 LNs resected (LN1 < 12) and those with 12 or more nodes resected (LN2 ≥ 12). We further divided the patients into four groups based on the LNR: LNR groups 1 (LNR ≤ 0.1), LNR groups 2 (0.1 < LNR ≤ 0.2), and LNR groups 3 (0.2 < LNR ≤ 0.42), and LNR groups 4 (0.42 < LNR).

All resections were completed with curative intent, which included the primary colonic lesions, removed adjacent organs, and all resected LNs. All surgery was performed by attending surgeons subspecialized in managing CRC. Diagnosis of CRC was established by reviewing the morphology of cancer cells and immunohistochemistry (CK20 or CDX2) of pathological specimens by two independent pathologists. The right colon consists of the cecum, ascending colon, hepatic flexure and the proximal the transverse colon. The left colon consists of the distal transverse colon, splenic flexure, descending colon, and sigmoid. The LNs stage was categorized into 3 levels according to TNM system of cancer staging:[10] N1, 1-3 metastatic lymph nodes; N2a, 4-6 metastatic lymph nodes; N2b, 7 and above metastatic lymph nodes.

The clinical decision of postoperative CMT was based on a discussion with patients about the advantages and disadvantages of receiving adjuvant CMT, the potential complications and side effects after treatments, the existence of high-risk factors that may lead to recurrence and compromise patients' outcome, and finally, their preferences. Over the study period, two options of adjuvant CMT were available: (1) infusional FOLFOX6 -- oxaliplatin/5FU/leucovorin, and (2) infusional XELOX -- oxaliplatin/leucovorin plus oral capecitabine. The FOLFOX-based CMT consisted of oxaliplatin 85 mg/m^2 infusion, leucovorin 400 mg/m^2 infusion for 2 hours on Day 1, followed by 5-FU 2400 mg/m^2 infusion over 46 hours, repeated every 2 weeks for a total of 6 months. The XELOX-based CMT consisted of oxaliplatin 85 mg/m^2 infusion, leucovorin 400 mg/m^2 infusion for 2 hours on Day 1, and oral capecitabine (XELODA) for 10 days, repeated every 2 weeks for a total of 6 months.

The database included (1) patient demographic information, including their name, sex, age, family history; (2) characteristics of the tumor, including the location, gross appearance, TNM stage, and important pathologic prognostic features, such as the number of LNs examined, differentiation, tumor size, and the invasion pattern of the cancerous tissue and mucinous component.

Follow-up

According to the NCCN treatment guidelines, all patients had a regular follow-up consisting of visits at 3-month intervals for the first 2 years, 6-month intervals for up to 5 years, and annually thereafter. The follow-up examinations included a physical examination, rectodigital examination, blood chemistry panel (such as complete blood cell count and liver function tests), radiographs of the thorax and abdominal sonograms. A colonoscopy was performed annually. If recurrence was suspected, further testing, such as a chest computed tomography scan, whole body bone scan, or even a whole body positron emission tomography scan was performed to clarify the site of recurrence. The definition of recurrence included a recurrent lesion that was confirmed pathologically or that was progressively increasing size in image studies.

The 5-year TSS time was measured from the date of the operation to the date of last visit or tumor-specific death. DFS was counted from the date of the operation to the date of confirmation of recurrence.

Statistical analysis

The primary endpoint was to determine whether the LYN to curative surgical resection conferred an improvement in DFS and 5-year TSS for patients with AJCC stage III CRC. In our study we determined the cut-off points by using the 12 LNY to draw the Kaplan-Meier survival curve. Analyzed factors included age (≤ 70 or > 70 years), sex, presence of risk factors, location of primary tumor (cecum, ascending colon, transverse colon, descending colon, sigmoid colon, rectosigmoid, rectum), presence of an obstruction, histopathological classification (well, moder-

ately, or poorly differentiated), tumor size (≤ 49 mm, or > 49 mm), and the number of LNs examined (1-11 or > 12).

IBM SPSS statistics software version 22 (IBM® SPSS® statistics 22) was used for data entry and statistical analysis. Each variable factor of the 5-year TSS and DFS rates was estimated using the Kaplan-Meier method. The significance of the differences between subgroups was calculated using the log-rank test. The variables that reached statistical significance ($p < 0.05$) were entered into multivariate analysis, which was performed using the Cox proportional hazard model. All statistical tests were two-tailed, and a p value of less than 0.05 was considered to be statistically significant.

Ethics statement

This retrospective study has been approved by the Institutional Review Board (IRB) of Tri-Service General Hospital (appropriate in Taiwan). Patients provided written informed consent to participate in this study, and the Ethics Committee of TSGH approved the consent procedure. No informed consent was given, because the data were analyzed anonymously.

Results

Patient demographics

This study investigated the role of LNR in the prognosis of 743 patients with stage III CRC. After the exclusion of 87 patients, 656 individuals with stage III CRC (i.e., any T and N1-N2, M0) were initially enrolled in our study and stratified into two groups: (1) Low LNY group: 161 (24.5%) stage III CRC patients who had lower LNY less than 12; (2) High LNY group: 494 (75.5%) stage III CRC patients who had high LNY more than 12 LNs retrieval improved over time, the proportion of patients receiving adequate LNs evaluation more than 85% since 2006.

The patient population included 340 men (51.8%) and 316 women (48.2%). The mean age was 65.12 ± 13.91 years (range, 24-100 years). Four hundred of the cases were under 70 years and 256 aged 70 years and above. The tumor was mostly located in sigmoid colon. The commonest histologic grade was moderate. With regard to tumor location, 192 (29.3%) were right-side colon carcinomas, 257 (39.2%) were left-side colon carcinomas and 207 (31.5%) were rectal carcinomas. The average follow-up period was 53 months. Thereafter, cases were divided into the following LNR subgroups based on quartiles. Patients were further categorized into four groups: (1) LNR groups 1 (0%-25%): 161 (24.6%); (2) LNR groups 2 (26%-50%): 175 (27%); (3) LNR groups 3 (51%-75%): 155 (23.7%); (4) LNR groups 4 (76%-100%): 162 (24.7%). The general characteristics of the patients are summarized in Table 1.

When the two treatment groups (low LNY group, and high LNY group) were compared, there were no differences in gender, sex, histopathological classification, pre-operative CEA level and with/without adjuvant CMT. There was no postoperative mortality. Clinico-pathological distribution of total stage III CRC patients, included in the analyses stratified by their characteristics and treatment group is shown is Table 2.

The LNR groups did not differ significantly interms of age ($p = 0.285$), sex ($p = 0.623$), tumor size ($p = 0.966$), T stage distribution ($p = 0.168$) and pre-operative CEA ($p = 0.489$). Primary tumor location ($p = 0.022$), poor differentiated ($p < 0.001$), N stage distribution ($p < 0.001$) and AJCC stage ($p < 0.001$) were significantly different between groups with a higher rate in the LNR4 group (Table 3).

LNY sampling status and LNR system were a risk factor for recurrence (Table 4). Patients diagnosed as having LNs fewer than 12 showed a higher recurrence rate than those diagnosed as more than 12 LNs (35 of 161 vs. 71 of 495, $p = 0.036$). The analysis performed on quartiles (< 0.1, 0.11-0.2, 0.21-0.42, and 0.43-1.0) revealed decreasing survival rates with increasing LNR. With regard to LNR evaluation, patients with high LNR showed a higher recurrence (LNR 1 vs. LNR 2 vs. LNR 3 vs. LNR 4 = 15 of 161, 9.32% vs. 27 of 175, 15.43% vs. 28 of 155, 18.06% vs. 36 of 162, 22.22%), although the difference reach statistical significance ($p = 0.015$).

Table 1. Demographic and pathologic features of cases (n = 656)

Variables	Total number of cases
Age (y), mean (SD): 65.12 (13.91)	
≤ 70 years	400
> 70 years	256
Gender	
Male	340
Female	316
Tumor location	
Right	192
Left	257
Rectum	207
LN	
< 12	161
≥ 12	495
Tumor size (mm), mean (SD): 48.90 (24.70)	
< 50	323
≥ 50	297
None (missing)	36
Year of diagnosis	
2004/01/01-2007/12/31	253
2008/01/01-2012/12/31	286
2013/01/01-2014/12/31	117
Histopathological classification	
Not poorly differentiated	511
Poorly differentiated	108
None (missing)	37
T status	
T1	17
T2	53
T3	536
T4	50
N status	
N1	399
N2a	129
N2b	126
None (missing)	2
Adjuvant chemotherapy	
Without	110
With	546
Pre-op CEA	
< 5	449
≥ 5	170
None (missing)	37
AJCC Stage	
3A	53
3B	378
3C	225
Average percentage of LNR	
Number of case in LNR1 (0%-25%)	161
Number of case in LNR2 (26%-50%)	175
Number of case in LNR3 (51%-75%)	155
Number of case in LNR4 (76%-100%)	162
None (missing)	3

SD: standard deviation; LN: lymph node.

DFS ranged from 4 to 98 months, and TSS ranged from 6 to 104 months. In our data, the 5-year TSS could be more than 84.6% for stage IIIA CRC cancer patients and only 47.8% for stage IIIC CRC patients. There was a significant difference in the DFS between the stage III CRC patients who had low LNY and high LNY ($p = 0.011$; Fig. 1(A)), but not in 5-year TSS ($p = 0.447$; Fig. 1(B)). These results demonstrate statistically significant survival benefit that the increase in LNR, DFS and 5-year TSS falls (DFS, $p = 0.003$; Fig. 2(A); 5-year TSS, $p < 0.001$; Fig. 2(B)).

Among the total stage III CRC patients, we stratified into two subgroups: fewer than 12 LNs group, and more than 12 LNs group. All of the patients were followed up, and they were evaluated in the same manner as the survival benefits for DFS and 5-year TSS. In the subgroup of patients harvested with high LYN, had a significant benefit in terms of DFS and 5-year TSS (DFS, $p = 0.004$; Fig. 3(A); 5-year TSS, $p < 0.001$; Fig. 3(B)). However, a significant survival benefit in terms of 5-year TSS ($p < 0.001$; Fig. 4(B)), it was not statistically significant in terms of DFS with low LYN patients group ($p = 0.545$; Fig. 4(A)).

The univariate and multivariate analysis for DFS and 5-year TSS of stage III CRC was in Table 5 and 6. In univariate analysis and multivariate analysis, only high LNY more than 12 group were good prognostic factors with LNR that significantly influenced DFS and 5-year TSS (Table 5 and 6). In univariate analysis with high LNY group, N2b status (hazard ratio [HR] = 1.74, 95% confidence interval, 0.02-2.99, $p = 0.043$), LNR group 3 (hazard ratio [HR] = 2.43, 95% confidence interval, 1.14-5.19, $p = 0.022$), and LNR group 4 (hazard ratio [HR] = 3.55, 95% confidence interval, 1.70-7.39, $p = 0.001$) were significantly associated with worse DFS (Table 5-2). A multivariate analysis revealed that only LNR group 3 (hazard ratio [HR] = 3.12, 95% confidence interval, 1.39-7.00, $p = 0.033$), and LNR group 4 (hazard ratio [HR] = 6.16, 95% confidence interval, 2.33-16.28, $p < 0.001$) were the only independent prognostic factors with worse DFS (Table 5-2).

In univariate analysis with high LNY group, age >

Table 2. Clinico-pathological distribution of total stage III colorectal cancer patients included in the analyses stratified by their characteristics and treatment group

	LN < 12 (n = 161)	LN ≥ 12 (n = 495)	*p* value[#]
	n (%)	n (%)	
Age (y), mean (SD)	66.12 ± 13.76	64.79 ± 13.96	0.294
≤ 70 years	94 (58.39)	306 (61.82)	0.495
> 70 years	67 (41.61)	189 (38.18)	
Sex			0.068
Male	94 (58.39)	246 (49.70)	
Female	67 (41.61)	249 (50.30)	
Location of primary tumor			< 0.001
Right	19 (11.80)	173 (34.95)	
Left	61 (37.89)	196 (39.60)	
Rectum	81 (50.31)	126 (25.45)	
Location of primary tumor			< 0.001
Cecum	4 (2.48)	51 (10.30)	
Ascending colon	7 (4.35)	98 (19.80)	
Transverse colon	9 (5.59)	28 (5.66)	
Descending colon	12 (7.45)	39 (7.88)	
Sigmoid colon	48 (29.81)	153 (30.91)	
Rectum	81 (50.31)	126 (25.45)	
Tumor size (mm), mean (SD)	42.23 ± 19.43	50.93 ± 25.77	< 0.001
< 50	93 (64.14)	230 (48.42)	0.001
≥ 50	52 (35.86)	245 (51.58)	
Histopathological classification			0.936
Not poorly differentiated	123 (83.11)	388 (82.38)	
Poorly differentiated	25 (16.89)	83 (17.62)	
Adjuvant chemotherapy			0.395
Without	31 (19.25)	79 (15.96)	
With	130 (80.75)	416 (84.04)	
T status			0.001[a]
T1	11 (6.83)	6 (1.21)	
T2	18 (11.18)	35 (7.07)	
T3	120 (74.53)	416 (84.04)	
T4	12 (7.45)	38 (7.68)	
N status			< 0.001
N1	120 (75.47)	279 (56.36)	
N2a	27 (16.98)	102 (20.61)	
N2b	12 (7.55)	114 (23.03)	
Pre-op CEA (ng/mL), mean (SD)			0.503
< 5	38 (77.55)	164 (71.62)	
≥ 5	11 (22.45)	65 (28.38)	
AJCC stage			< 0.001
3A	26 (16.15)	27 (5.45)	
3B	96 (59.63)	282 (56.97)	
3C	39 (24.22)	186 (37.58)	
Average percentage of LNR			0.001
Number of case in LNR1	24 (15.19)	137 (27.68)	
Number of case in LNR2	57 (36.08)	118 (23.84)	
Number of case in LNR3	33 (20.89)	122 (24.65)	
Number of case in LNR4	44 (27.85)	118 (23.84)	

SD: standard deviation; LN: lymph node; [#] assessed by independent-t test or by Chi-square test; [a] *p*-value by Fisher's exact test.

Table 3. Patient characteristics in groups assigned according lymph node ratio (LNR)

Characteristics	Total	Number of case in LNR1 (0-0.1)	Number of case in LNR2 (0.11-0.20)	Number of case in LNR3 (0.21-0.42)	Number of case in LNR4 (> 0.42)	p-value[#]
Age (y), mean (SD)	65.17 (13.89)	65.20 (14.14)	65.76 (12.92)	66.28 (13.84)	63.45 (14.66)	0.285
≤ 70 years	397 (60.80)	96 (59.63)	106 (60.57)	88 (56.77)	107 (66.05)	0.388
> 70 years	256 (39.20)	65 (40.37)	69 (39.43)	67 (43.23)	55 (33.95)	
Sex						0.623
Male	338 (51.76)	78 (48.45)	94 (53.71)	85 (54.84)	81 (50.00)	
Female	315 (48.24)	83 (51.55)	81 (46.29)	70 (45.16)	81 (50.00)	
Primary tumor location						0.022
Right	192 (29.40)	56 (34.78)	57 (32.57)	37 (23.87)	42 (25.93)	
Left	257 (39.36)	63 (39.13)	60 (34.29)	76 (49.03)	58 (35.80)	
Rectum	204 (31.24)	42 (26.09)	58 (33.14)	42 (27.10)	62 (38.27)	
Tumor size (mm), mean (SD)	48.94 (24.73)	49.41 (25.36)	48.27 (29.08)	48.64 (19.93)	49.48 (23.08)	0.966
< 50	322 (52.19)	81 (52.60)	90 (53.57)	74 (52.11)	77 (50.33)	0.950
≥ 50	295 (47.81)	73 (47.40)	78 (46.43)	68 (47.89)	76 (49.67)	
Histopathological classification						< 0.001
Not poorly	509 (82.50)	135 (89.40)	141 (84.43)	129 (87.76)	104 (68.42)	
Poorly	108 (17.50)	16 (10.60)	26 (15.57)	18 (12.24)	48 (31.58)	
Adjuvant CMT						0.771
Without	108 (16.54)	29 (18.01)	28 (16.00)	22 (14.19)	29 (17.90)	
With	545 (83.46)	132 (81.99)	147 (84.00)	133 (85.81)	133 (82.10)	
T status						0.168[a]
T1	15 (2.30)	4 (2.48)	6 (3.43)	2 (1.29)	3 (1.85)	
T2	53 (8.12)	10 (6.21)	24 (13.71)	9 (5.81)	10 (6.17)	
T3	535 (81.93)	135 (83.85)	134 (76.57)	133 (85.81)	133 (82.10)	
T4	50 (7.66)	12 (7.45)	11 (6.29)	11 (7.10)	16 (9.88)	
N status						< 0.001
N1	399 (61.10)	158 (98.14)	159 (90.86)	67 (43.23)	15 (9.26)	
N2a	128 (19.60)	3 (1.86)	15 (8.57)	71 (45.81)	39 (24.07)	
N2b	126 (19.30)	0 (0)	1 (0.57)	17 (10.97)	108 (66.67)	
Pre-op CEA (ng/mL), mean (SD)						0.489
< 5	201 (72.56)	29 (67.44)	27 (72.97)	57 (68.67)	88 (77.19)	
≥ 5	76 (27.44)	14 (32.56)	10 (27.03)	26 (31.33)	26 (22.81)	
AJCC stage						< 0.001
3A	51 (7.81)	14 (8.70)	28 (16.00)	5 (3.23)	4 (2.47)	
3B	378 (57.89)	143 (88.82)	138 (78.86)	81 (52.26)	16 (9.88)	
3C	224 (34.30)	4 (2.48)	9 (5.14)	69 (44.52)	142 (87.65)	

SD: standard deviation; LN: lymph node; [#] assessed by one-way ANOVA or by Chi-square test; [a] *p*-value by Fisher's exact test.

70 years (hazard ratio [HR] = 2.34, 95% confidence interval, 1.77-3.09, $p < 0.001$), poor differentiated (hazard ratio [HR] = 1.56, 95% confidence interval, 1.11-2.20, $p = 0.011$), AJCC stage 3B (hazard ratio [HR] = 8.68, 95% confidence interval, 1.21-62.30, $p = 0.032$), AJCC stage 3C (hazard ratio [HR] = 17.07, 95% confidence interval, 2.38-122.26, $p = 0.005$), LNR group 3 (hazard ratio [HR] = 1.87, 95% confidence interval, 1.25-2.8, $p = 0.02$), and LNR group 4 (hazard ratio [HR] = 2.29, 95% confidence interval, 1.54-3.4, $p < 0.001$) were significantly associated with worse 5-year TSS (Table 6-2). A multivariate analysis revealed that age > 70 years (hazard ratio [HR] = 2.34, 95% confidence interval, 1.73-3.12, $p < 0.001$), and AJCC stage 3C (hazard ratio [HR] = 10.66, 95% confidence interval, 1.43-79.58, $p = 0.021$) were the only independent prognostic factors with worse 5-year TSS (Table 6-2).

Table 4. The risk factors with the recurrence rate for both colorectal cancers. Total patient number = 656, recurrent number = 106 (16.2%)

Factors	Recurrent number (%)	Total	*p*-value[#]
Examined lymph node			0.036
< 12	35 (21.74)	161	
≥ 12	71 (14.34)	495	
Age			0.290
< 70	70 (17.50)	400	
≥ 70	36 (14.06)	256	
Sex			0.172
Male	48 (14.12)	340	
Female	58 (18.35)	316	
Location of primary tumor			0.667
Right	28 (14.58)	192	
Left	41 (15.95)	257	
Rectum	37 (17.87)	207	
Tumor size			1.000
< 50	52 (16.10)	323	
≥ 50	47 (15.82)	297	
Histopathological classification			0.104
Not poorly differentiated	74 (14.48)	511	
Poorly differentiated	23 (21.30)	108	
Adjuvant chemotherapy			0.353
Without	14 (12.73)	110	
With	92 (16.85)	546	
T status			0.587[a]
T1	1 (5.88)	17	
T2	7 (13.21)	53	
T3	88 (16.42)	536	
T4	10 (20.00)	50	
N status			0.349
N1	64 (16.04)	399	
N2a	17 (13.18)	129	
N2b	25 (19.84)	126	
Pre-op CEA(ng/mL), mean (SD)			0.506
< 5	24 (11.88)	202	
≥ 5	12 (15.79)	76	
AJCC Stage			0.095
3A	3 (5.66)	53	
3B	64 (16.93)	378	
3C	39 (17.33)	225	
Average percentage of LNR			0.015
Number of case in LNR1	15 (9.32)	161	
Number of case in LNR2	27 (15.43)	175	
Number of case in LNR3	28 (18.06)	155	
Number of case in LNR4	36 (22.22)	162	

[#] assessed by Chi-square test; [a] *p*-value by Fisher's exact test.

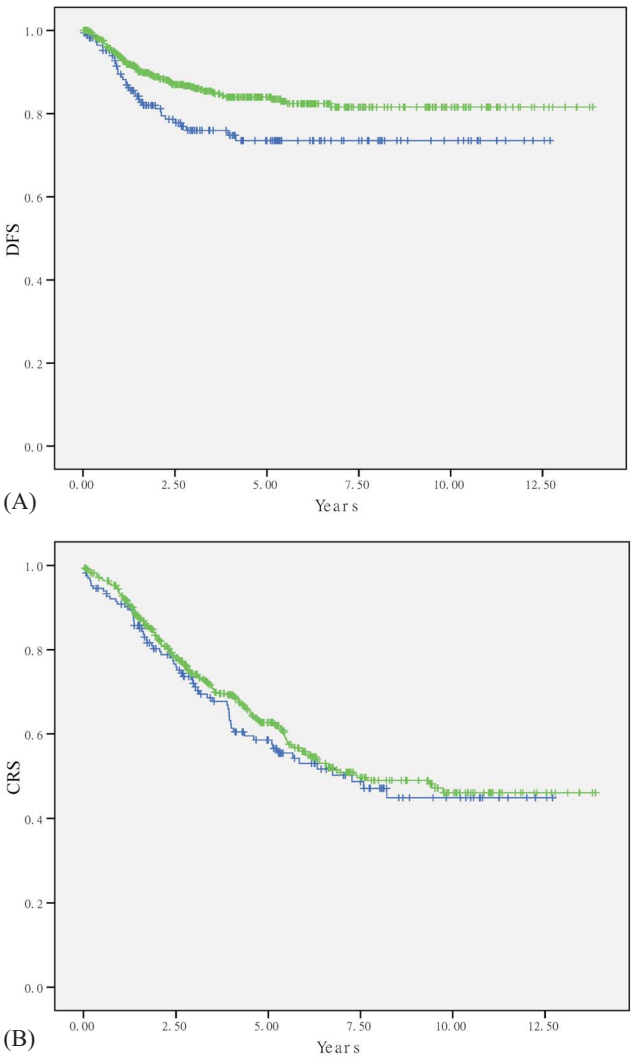

Fig. 1. (A) Disease-free survival (DFS) between lymph node yield (LNY) < 12 and ≥ 12 in patients for stage III colorectal cancer patients (Log rank test, p = 0.011). (B) 5-year tumor-specific survival (TSS) between lymph node yield (LNY) < 12 and ≥ 12 in patients for stage III colorectal cancer patients (Log rank test, p = 0.447).

Discussion

Although, TNM stage III colorectal cancer is different, the same chemotherapy regimen is prescribed for all stage III CRC patients. Accurate staging of CRC is essential for appropriate therapeutic planning. The LNY sampling status is used to determine the stage III CRC staging and is associated with survival outcome.[6] The number of LNs required for adequate

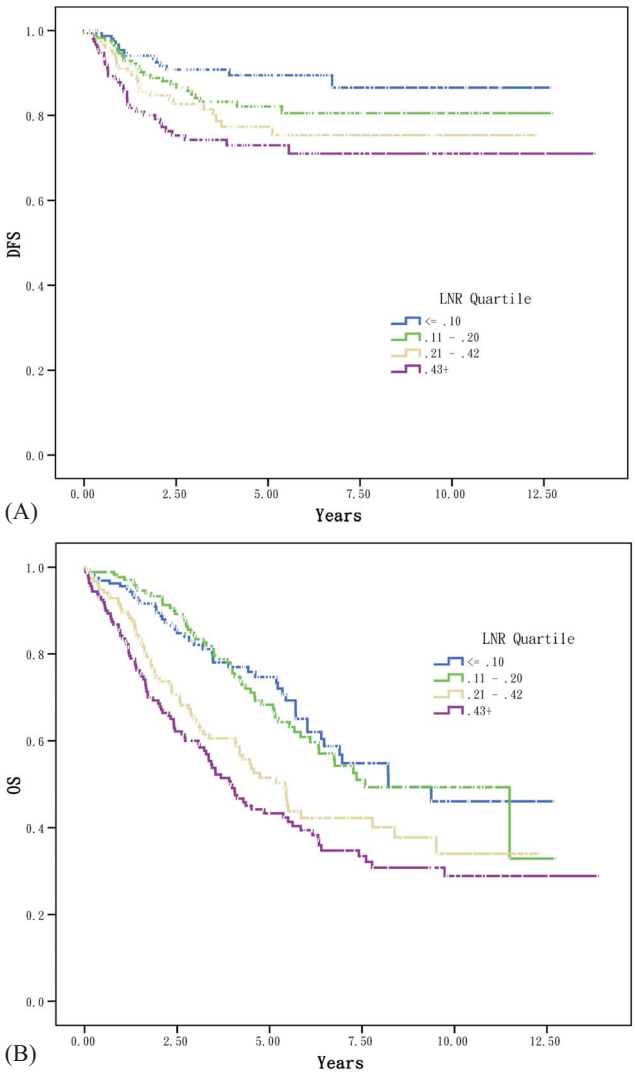

Fig. 2. (A) Disease-free survival (DFS) of stage III colorectal cancer patients according to the LNR (Log rank test, $p = 0.003$). (B) 5-year tumor-specific survival (TSS) of stage III colorectal cancer patients according to the LNR (Log rank test, $p < 0.001$).

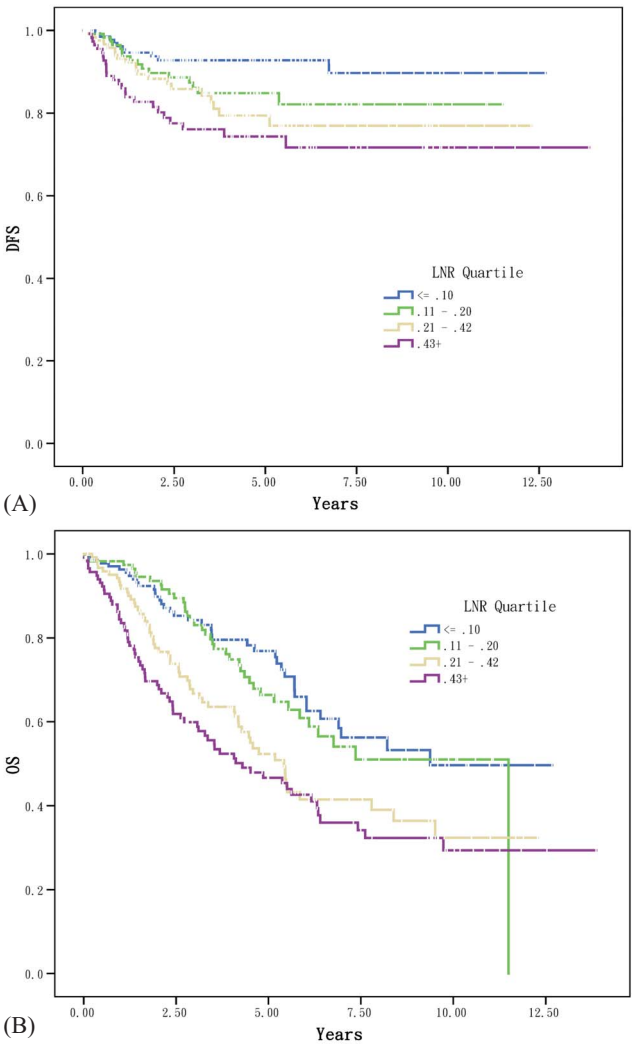

Fig. 3. (A) Disease-free survival (DFS) curves of stage III colorectal cancer patients with LYN more than 12 according to the LNR (Log rank test, $p = 0.004$). (B) 5-year tumor-specific survival (TSS) curves of stage III colorectal cancer patients with LYN more than 12 according to the LNR (Log rank test, $p < 0.001$).

LNs evaluation in patients with CRC has been debated ever since Fielding's 1991 recommendation that a minimum of 12 LNs be evaluated.[14] Now, most authors suggest that LNR was a significantly more variable both in 5-year TSS and in DFS than LNY sampling status. Later, another study confident that the prognostic value of the LNR is independent from the total number of LNY.[15,16] Currently, consensus holds that adequate staging requires the evaluation of as many LNs as possible.[7] In this study of 656 patients with stage III CRC cancer, with an estimated data completeness, we demonstrated that LNR for stage III CRC with the represent the inadequate staging about DFS and 5-year TSS in the LNY less than 12 group. And, the LNR evaluation in stage III CRC patients was significantly affect their DFS and 5-year TSS in the LNY more than 12 group. To our knowledge, this study is the first to examine the prognostic impact of the LNR typically manifest different DFS and 5-year TSS between the LNY ≥ or < 12 in the stage III CRC.

The tumor-node-metastasis (TNM) system devel-

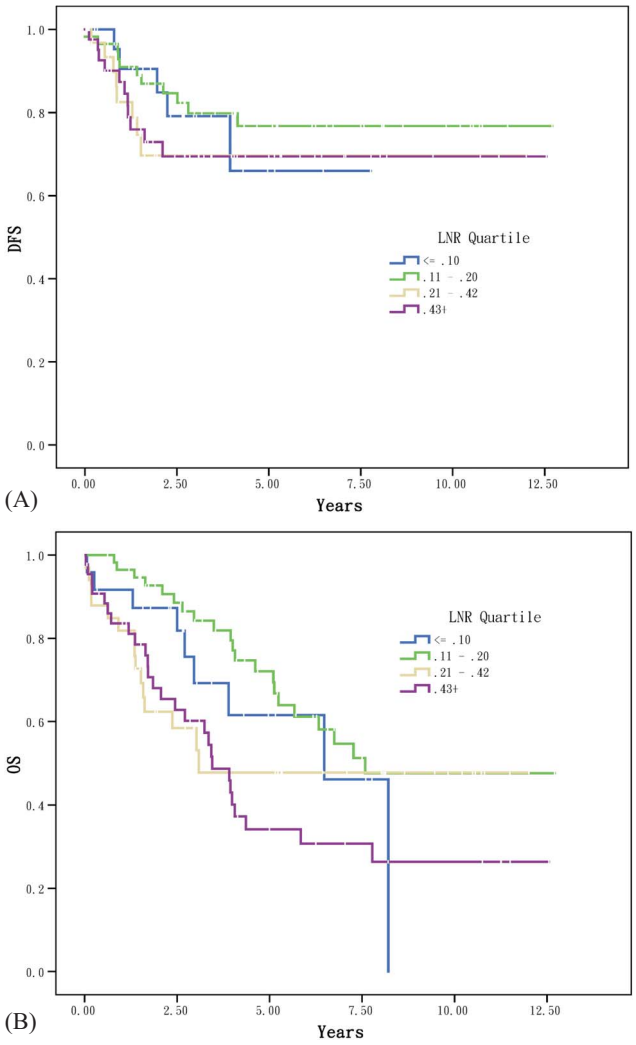

Fig. 4. (A) Disease-free survival (DFS) curves of stage III colorectal cancer patients with LYN less than 12 according to the LNR (Log rank test, $p = 0.545$). (B) 5-year tumor-specific survival (TSS) of stage III colorectal cancer patients with LYN less than 12 according to the LNR (Log rank test, $p = 0.022$).

oped by the AJCC is an internationally recognized method for evaluating staging of CRC.[17] Considering the prevalence of this cancer, knowing the factors influencing the survival rate of the patients is of great importance. The occurrence of metastatic LNs is a strong prognostic factor in CRC, which N staging is based on the number of positive nodes.[17] The seventh edition of the AJCC' s system subdivided stage III disease into IIIA (T1-2N1), IIIB (T3-4N1), and IIIC (any TN2).[17] One of these factors is the involvement of LNs, which can decrease the survival rate.[12] Stage IIIA, IIIB, and IIIC patients typically manifest different DFS and 5-year TSS.

Adequate LNs evaluation is clearly essential for proper staging of nonmetastatic CRC. A complete evaluation of the LNs basin, which collects lymphatic drainage from the affected segment of the bowel, is important for accurately identifying LNs involvements with CRC and for complete resection of disease. LNs status is the strongest predictor of long-term outcome in patients with CRC who do not have metastatic disease, and the current guidelines, the recommended standard number of LNs examined to ensure adequate sampling is 12, is considered essential to avoid underestimation of stage III CRC disease. Inadequate LNs evaluation is associated with worse outcome in terms of tumor recurrence and patient survival, particularly in patients with stage III CRC.[7-9] However, the LNY is a complex factor and has been discussed extensively in the literature. Factors that influence LYN include patient, surgeon oncologist, particularly the size and organization of the individual hospitals, and even the pathologist.[18,19] Despite these issues with regard to the LNY, the association between LNY and CRC surgery outcome has been extensively studied mostly in mixed studies of colon and rectal cancer, where an association between low LNY and adverse prognostic outcomes, especially for stage III CRC disease, has been found.[20-22]

The LNR, defined as the ratio of involved to the total resected LNs, has gained increasing attention. Some study confident that LNR is more precise than positive number of LNs to predict the survival rate in patients presenting with CRC.[15,23] Chin CC et al. determined that LNR is a more precise predictor of 5-year DFS than number of positive LNs (N stage) in patients with stage III CRC cancer.[24] The present study shows that LNR is a prognostic factor for CRC, independent of number of harvested and of positive LNs. Therefore, using LNR along with TNM system may help us more to predict the relapse and survival of the stage III CRC.[25,26] However, LNR can be easily affected by the evaluation of LNs number and their surgical resection; thus, its real value to determine the prognosis remains vague.[27] Whereas, few studies have evaluated real impact of the LNR in survival of pa-

Table 5-1. Univariate analysis and multivariate analysis for DFS in LN < 12 patients with colorectal cancer (n = 161)

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age						
≤ 70 years	1.00					
> 70 years	0.98	0.49-1.94	0.941			
Sex						
Male	1.00			1.00		
Female	2.00	1.03-3.92	0.042	1.80	0.92-3.53	0.088
Location						
Right colon	1.00					
Left colon	1.03	0.34-3.12	0.962			
Rectum	0.83	0.28-2.48	0.741			
Tumor size (mm)						
< 50	1.00					
≥ 50	1.30	0.63-2.69	0.472			
Histopathological						
Non-poor	1.00					
Poor	2.02	0.90-4.52	0.089			
T status						
T1	0.22	0.02-1.94	0.171			
T2	0.16	0.02-1.39	0.096			
T3	0.78	0.27-2.21	0.634			
T4	1.00					
N status						
N1	1.00					
N2a	0.51	0.16-1.69	0.273			
N2b	1.82	0.64-5.23	0.264			
AJCC stage						
3A	1.00			1.00		
3B	4.29	1.02-18.13	0.048	3.79	0.89-16.14	0.072
3C	3.58	0.76-16.88	0.107	3.26	0.69-15.44	0.136
Adjuvant CMT						
Without	1.00					
With	0.95	0.37-2.45	0.916			
Average percentage of LNR						
Number of case in LNR1	1.00					
Number of case in LNR2	0.83	0.29-2.38	0.724			
Number of case in LNR3	1.46	0.48-4.48	0.505			
Number of case in LNR4	1.37	0.48-3.95	0.558			

tients with low LNs, we decided to perform the present study including the patients with less than 12 LNs. Our analysis revealed that there was not a significant difference between LNR1, LNR2, LNR3 and LNR4 in DFS and 5-year TSS for the patients with less than 12 LNs group. Significant differences also were observed by grouping patients according to quartiles of LNs number 12.

Other, Peschaud and coworkers in their study demonstrated that "LNR is the most significant prognostic factor for both overall and disease-free survival in patients with rectal cancer, even in patients with fewer than 12 LNs examined".[23] However, our results cannot support the conclusions of these previous studies, fewer than 12 LNs, and there was no statistical difference for DFS and 5-year TSS.

In this study, we set DFS and 5-year TSS as the primary endpoints of evaluation to determine the ef-

Table 5-2. Univariate analysis and multivariate analysis for DFS in LN ≥ 12 patients with colorectal cancer (n = 495)

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age						
≤ 70 years	1.00					
> 70 years	0.89	0.54-1.46	0.887			
Sex						
Male	1.00					
Female	1.06	0.67-1.70	0.796			
Location						
Right colon	1.00					
Left colon	0.91	0.52-1.57	0.731			
Rectum	1.10	0.61-1.99	0.759			
Tumor size (mm)						
< 50	1.00					
≥ 50	1.00	0.62-1.61	0.994			
Histopathological						
Non poor	1.00					
Poor	1.59	0.90-2.83	0.113			
T status						
T1	--					
T2	0.83	0.27-2.58	0.747			
T3	0.73	0.31-1.68	0.454			
T4	1.00					
N status						
N1	1.00					
N2a	1.07	0.58-1.98	0.838			
N2b	1.74	1.02-2.99	0.043			
AJCC stage						
3A	1.00			1.00		
3B	3.88	0.53-28.22	0.181	3.84	0.53-28.04	0.185
3C	5.24	0.72-38.40	0.103	1.97	0.25-15.47	0.517
Adjuvant CMT						
Without	1.00					
With	0.89	0.44-1.79	0.741			
Average percentage of LNR						
Number of case in LNR1	1.00			1.00		
Number of case in LNR2	1.89	0.86-4.16	0.116	1.95	0.89-4.31	0.097
Number of case in LNR3	2.43	1.14-5.19	0.022	3.12	1.39-7.00	0.006
Number of case in LNR4	3.55	1.70-7.39	0.001	6.16	2.33-16.28	< 0.001

fects conferred by LNY on patients with stage III CRC. Analysis of our data, indicates that LNR is a more precise predictor in the high LYN group for more than 12 LNs significantly improves DFS and 5-year TSS ($p = 0.014$ and $p < 0.014$); however, the results were not statistically significant for 5-year TSS ($p = 0.447$) in the low LYN group. According to our analysis, we believe that achieving a high LNY more than 12 remains important in the accurate LNR evaluation system.

In this study, we also found that right-side tumor were significantly different between groups with a higher rate in the higher LNY. Other, the DFS and 5-year TSS of stage III left-side colon cancer patients with yield LNs metastasis who more or less than 12 was significantly different, but not in right-side colon. It is not known whether there are fundamental variations in the density of LNs within different regions of

Table 6-1. Univariate analysis and multivariate analysis for 5-year TSS in LN < 12 patients with colorectal cancer (n = 161)

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age						
≤ 70 years	1.00					
> 70 years	1.53	0.96-2.43	0.074			
Sex						
Male	1.00					
Female	1.26	0.79-2.00	0.337			
Location						
Right colon	1.00					
Left colon	0.69	0.34-1.44	0.325			
Rectum	0.62	0.30-1.25	0.177			
Tumor size (mm)						
< 50	1.00					
≥ 50	1.34	0.83-2.17	0.239			
Histopathological						
Non poor	1.00			1.00		
Poor	1.82	1.04-3.21	0.038	1.44	0.81-2.57	0.216
T status						
T1	--					
T2	0.19	0.05-0.72	0.014			
T3	0.67	0.32-1.41	0.281			
T4	1.00					
N status						
N1	1.00					
N2a	1.41	0.80-2.50	0.234			
N2b	2.66	1.30-5.45	0.008			
AJCC stage						
3A	1.00			1.00		
3B	15.74	2.17-114.11	0.006	15.24	2.09-111.06	0.007
3C	19.67	2.66-145.53	0.004	21.11	2.78-160.47	0.003
Adjuvant CMT						
Without	1.00			1.00		
With	0.53	0.31-0.91	0.022	0.38	0.21-0.68	0.001
Average percentage of LNR						
Number of case in LNR1	1.00					
Number of case in LNR2	0.72	0.33-1.57	0.406			
Number of case in LNR3	1.43	0.63-3.27	0.397			
Number of case in LNR4	1.67	0.78-3.55	0.185			

the normal mesocolon; this is currently being investigated by our group. It has been hypothesized that the greater length of right-sided surgical resections.[28] Right-sided colon cancer has consistently been shown to have a higher LNY than left-sided colon cancer. Another potential explanation relates to the underlying molecular pathogenesis of colon cancer. Chromosomal instability is the most common pathway for the development of left-sided tumors whereas microsatellite instability, which is associated with more immunogenic tumors that have a higher LNY,[29-31] is more common in right-sided tumors.[32] In our study, the anatomic site of the tumor strongly influenced the adequacy of LNs examination. It may actually be necessary to examine more LNs in right-sided colon specimens to accurately determine the LNR evaluation system of patients.

In this study, we found that LNR was positively

Table 6-2. Univariate analysis and multivariate analysis for OS in LN ≥ 12 patients with colorectal cancer (n = 495)

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age						
≤ 70 years	1.00			1.00		
> 70 years	2.34	1.77-3.09	< 0.001	2.34	1.73-3.12	< 0.001
Sex						
Male	1.00			1.00		
Female	0.67	0.51-0.89	0.005	0.77	0.58-1.03	0.075
Location						
Right colon	1.00					
Left colon	0.72	0.52-1.00	0.050			
Rectum	1.02	0.73-1.44	0.898			
Tumor size (mm)						
< 50	1.00					
≥ 50	1.02	0.77-1.35	0.893			
Histopathological						
Non poor	1.00			1.00		
Poor	1.56	1.11-2.20	0.011	1.26	0.88-1.79	0.205
T status						
T1	--					
T2	0.15	0.05-0.45	0.001			
T3	0.62	0.40-0.95	0.030			
T4	1.00					
N status						
N1	1.00					
N2a	1.58	1.12-2.23	0.009			
N2b	2.20	1.59-3.05	< 0.001			
AJCC stage						
3A	1.00			1.00		
3B	8.68	1.21-62.30	0.032	6.48	0.90-46.66	0.063
3C	17.07	2.38-122.26	0.005	10.66	1.43-79.58	0.021
Adjuvant CMT						
Without	1.00			1.00		
With	0.37	0.26-0.52	< 0.001	0.42	0.30-0.60	< 0.001
Average percentage of LNR						
Number of case in LNR1	1.00			1.00		
Number of case in LNR2	1.13	0.72-1.76	0.600	1.04	0.66-1.66	0.858
Number of case in LNR3	1.87	1.25-2.80	0.002	1.26	0.75-2.12	0.380
Number of case in LNR4	2.29	1.54-3.40	< 0.001	1.47	0.81-2.69	0.207

correlated with the number of LNs sample status more than 12. According to our analysis, we believe that achieving a high LNY more than 12 remains important in the accurate LNR evaluation system.

Conclusions

LNR is an accurate prognostic factor for both DFS and 5-year TSS in the patients with stage III CRC cancer with LNY more than 12. Based on its improved survival profile, LNY more than 12 had accurate prognostic factor for DFS and 5-year TSS in the patients with stage III CRC. In this study, our data did not confirm the same results in the 5-year TSS in the fewer than 12 LNs group; it is certain whether the number of 12 LNs or a higher number should be aimed in the accurate LNR evaluation system.

Limitations

The present study had some limitations. It was conducted at a single center, had a retrospective design and lacked randomization. There are also a number of limitations to our study. There was a bias towards the inclusion of more recent patients from the national data set because of the greater proportion of patients with missing information in the earlier years of the study period. Whether or not standard LNs was evaluated after a curative operation depended on the clinical surgeon technique and pathologist volumes, and with several clinicopathological variables. An additional randomized study is necessary to clarify the role of LNY in stage III CRC patients.

Author Contribution

Conceived and designed the experiments: JMH, CCW, CWH, CCL, TYL, SIH, SWY, and YCC. Performed the experiments: JMH, CCW, and YCC. Analyzed the data: JMH andYCC. Contributed reagents/materials/analysis tools: JMH and YCC. Wrote the paper: JMH, CCW, CWH, SWY, YCC.

Disclaimers

The authors declare no conflicts of interest.

References

1. Lin CC, Lin JK, Chang SC, Wang HS, Yang SH, Jiang JK, et al. Is adjuvant chemotherapy beneficial to high risk stage II colon cancer? Analysis in a single institute. *Int J Colorectal Dis* 2009;24:665-76.
2. Patel S. The benevolent tyranny of biostatistics: public administration and the promotion of biostatistics at the National Institutes of Health, 1946-1970. *Bull Hist Med* 2013;87: 622-47.
3. Nelson H, Petrelli N, Carlin A, Couture J, Fleshman J, Guillem J, et al. Guidelines 2000 for colon and rectal cancer surgery. *J Natl Cancer Inst* 2001;93:583-96.
4. O'Connell JB, Maggard MA, Ko CY. Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging. *J Natl Cancer Inst* 2004;96:1420-5.
5. NIH consensus conference. Adjuvant therapy for patients with colon and rectal cancer. *JAMA* 1990;264:1444-50.
6. Goldstein NS. Lymph node recoveries from 2427 pT3 colorectal resection specimens spanning 45 years: recommendations for a minimum number of recovered lymph nodes based on predictive probabilities. *Am J Surg Pathol* 2002;26: 179-89.
7. Le Voyer TE, Sigurdson ER, Hanlon AL, Mayer RJ, Macdonald JS, Catalano PJ, 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;21:2912-9.
8. Prandi M, Lionetto R, Bini A, Francioni G, Accarpio G, Anfossi A, et al. Prognostic evaluation of stage B colon cancer patients is improved by an adequate lymph adenectomy: results of a secondary analysis of a large scale adjuvant trial. *Ann Surg* 2002;235:458-63.
9. Tepper JE, O'Connell MJ, Niedzwiecki D, Hollis D, Compton C, Benson AB, 3rd, et al. Impact of number of nodes retrieved on outcome in patients with rectal cancer. *J Clin Oncol* 2001;19:157-63.
10. Lee SM, Shin JS, Choi HJ, Park KJ, Roh YH, Kwon HC, et al. Prognostic implication of metastatic lymph node ratio in node-positive rectal cancer. *J Korean Surg Soc* 2011;80: 260-6.
11. Lee HY, Choi HJ, Park KJ, Shin JS, Kwon HC, Roh MS, et al. Prognostic significance of metastatic lymph node ratio in node-positive colon carcinoma. *Ann Surg Oncol* 2007;14: 1712-7.
12. Berger AC, Sigurdson ER, Le Voyer T, Hanlon A, Mayer RJ, Macdonald JS, et al. Colon cancer survival is associated with decreasing ratio of metastatic to examined lymph nodes. *J Clin Oncol* 2005;23:8706-12.
13. Schumacher P, Dineen S, Barnett C, Jr., Fleming J, Anthony T. The metastatic lymph node ratio predicts survival in colon cancer. *Am J Surg* 2007;194:827-31; discussion 31-2.
14. Fielding LP, Arsenault PA, Chapuis PH, Dent O, Gathright B, Hardcastle JD, et al. Clinicopathological staging for colorectal cancer: an International Documentation System (IDS) and an International Comprehensive Anatomical Terminology (ICAT). *J Gastroenterol Hepatol* 1991;6:325-44.
15. Vaccaro CA, Im V, Rossi GL, Quintana GO, Benati ML, Perez de Arenaza D, et al. Lymph node ratio as prognosis factor for colon cancer treated by colorectal surgeons. *Dis Colon Rectum* 2009;52:1244-50.
16. Chen SL, Steele SR, Eberhardt J, Zhu K, Bilchik A, Stojadinovic A. Lymph node ratio as a quality and prognostic indicator in stage III colon cancer. *Ann Surg* 2011;253:82-7.
17. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 2010;17:1471-4.
18. Lykke J, Roikjaer O, Jess P. The majority of surgical departments adhere to national Danish guidelines for surveillance after colorectal cancer surgery. *Dan Med J* 2013;60:A4664.

19. Morris EJ, Maughan NJ, Forman D, Quirke P. Identifying stage III colorectal cancer patients: the influence of the patient, surgeon, and pathologist. *J Clin Oncol* 2007;25:2573-9.
20. Chen SL, Bilchik AJ. More extensive nodal dissection improves survival for stages I to III of colon cancer: a population-based study. *Ann Surg* 2006;244:602-10.
21. Amajoyi R, Lee Y, Recio PJ, Kondylis PD. Neoadjuvant therapy for rectal cancer decreases the number of lymph nodes harvested in operative specimens. *Am J Surg* 2013;205:289-92; discussion 92.
22. Lykke J, Roikjaer O, Jess P, Danish Colorectal Cancer G. The relation between lymph node status and survival in stage I-III colon cancer: results from a prospective nationwide cohort study. *Colorectal Dis* 2013;15:559-65.
23. Peschaud F, Benoist S, Julie C, Beauchet A, Penna C, Rougier P, et al. The ratio of metastatic to examined lymph nodes is a powerful independent prognostic factor in rectal cancer. *Ann Surg* 2008;248:1067-73.
24. Chin CC, Wang JY, Yeh CY, Kuo YH, Huang WS, Yeh CH. Metastatic lymph node ratio is a more precise predictor of prognosis than number of lymph node metastases in stage III colon cancer. *Int J Colorectal Dis* 2009;24:1297-302.
25. Ng M, Roy-Chowdhury S, Lum SS, Morgan JW, Wong JH. The impact of the ratio of positive to total lymph nodes examined and outcome in colorectal cancer. *Am Surg* 2009;75:873-6.
26. Wang J, Hassett JM, Dayton MT, Kulaylat MN. Lymph node ratio: role in the staging of node-positive colon cancer. *Ann Surg Oncol* 2008;15:1600-8.
27. Shimomura M, Ikeda S, Takakura Y, Kawaguchi Y, Tokunaga M, Egi H, et al. Adequate lymph node examination is essential to ensure the prognostic value of the lymph node ratio in patients with stage III colorectal cancer. *Surg Today* 2011;41:1370-9.
28. Willaert W, Mareel M, Van De Putte D, Van Nieuwenhove Y, Pattyn P, Ceelen W. Lymphatic spread, nodal count and the extent of lymph adenectomy in cancer of the colon. *Cancer Treat Rev* 2014;40:405-13.
29. Belt EJ, te Velde EA, Krijgsman O, Brosens RP, Tijssen M, van Essen HF, et al. High lymph node yield is related to microsatellite instability in colon cancer. *Ann Surg Oncol* 2012;19:1222-30.
30. Vilar E, Gruber SB. Microsatellite instability in colorectal cancer-the stable evidence. *Nat Rev Clin Oncol* 2010;7:153-62.
31. Guidoboni M, Gafa R, Viel A, Doglioni C, Russo A, Santini A, et al. Microsatellite instability and high content of activated cytotoxic lymphocytes identify colon cancer patients with a favorable prognosis. *Am J Pathol* 2001;159:297-304.
32. Gervaz P, Bucher P, Morel P. Two colons-two cancers: paradigm shift and clinical implications. *J Surg Oncol* 2004;88:261-6.

原　著

當術中淋巴結摘取數目少於 12 顆時，轉移淋巴結及淋巴結摘取數目比率在第三期大腸直腸癌病患無法當做預後指標

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目的　轉移淋巴結數目及淋巴結摘取數目比率，目前被認為與第三期大腸直腸癌的無疾病存活期與五年存活率有關係。然淋巴結摘取數目大於 12 顆已被國際視為治療大腸癌病患品質的指標之一。本研究的目的在於評估轉移淋巴結數目及淋巴結摘取數目比率對第三期大腸直腸結腸癌病患預後的預測價值，是否有受淋巴結摘取數目有無大於 12 顆影響。

方法　從 2000 年 1 月至 2014 年 12 月間，第三期大腸直腸癌在本院接受根治性手術。第三期病患依淋巴結摘取數目 (≥ 12 或 < 12) 及依轉移淋巴結目與淋巴結摘取數目比率 (LNR ≤ 0.1; 0.1 < LNR ≤ 0.2; 0.2 < LNR ≤ 0.42; LNR > 0.42) 進行存活影響分析。

結果　在本實驗中，共 656 病患第三期大腸直腸癌病患收案，平均年齡 67.06 ± 14.18 歲。術中淋巴結摘取數目大於 12 顆的人數有 495 位。右側大腸、侵略性 T 及 N 分期、低度分化與轉移淋巴結數目及淋巴結摘取數目高比率有關係。在多變數分析中，當術中淋巴結摘取數目 ≥ 12 時，轉移淋巴結數目及淋巴結摘取數目低比率的第三期大腸直腸癌病患，有較好無疾病存活期。然而，術中淋巴結摘取數目 < 12 時，轉移淋巴結數目及淋巴結摘取數目比率，與第三期大腸直腸癌的無疾病存活期與五年存活率預測，無統計學上意義。

結論　術中淋巴結摘取數目 < 12 顆時，轉移淋巴結數目及淋巴結摘取數目比率，無法對第三期大腸直腸癌預後，提供精準的預測。

關鍵詞　轉移淋巴結數目及淋巴結摘取數目、無疾病存活期、存活率、第三期大腸直腸癌腸。