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ABOUT COVER

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ORIGINAL ARTICLE

Retrospective Cohort Study

Impact factors of lymph node retrieval on survival in locally advanced rectal cancer with neoadjuvant therapy

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Author contributions: Mei SW, Chen JN and Wang ZJ designed the research; Wei FZ, Shen HY, Li J and Zhao FQ collected the data; Pei W, Wang Z, Liu Z and Wei FZ analyzed the data; Mei SW drafted the manuscript; Liu Q and Wang XS revised the paper.

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Abstract

BACKGROUND

Conventional clinical guidelines recommend that at least 12 lymph nodes should be removed during radical rectal cancer surgery to achieve accurate staging. The current application of neoadjuvant therapy has changed the number of lymph node dissection.

AIM

To investigate factors affecting the number of lymph nodes dissected after neoadjuvant chemoradiotherapy in locally advanced rectal cancer and to evaluate the relationship of the total number of retrieved lymph nodes (TLN) with disease-free survival (DFS) and overall survival (OS).

METHODS

A total of 231 patients with locally advanced rectal cancer from 2015 to 2017 were included in this study. According to the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) tumor-node-metastasis (TNM) classification system and the NCCN guidelines for rectal cancer, the patients were divided into two groups: group A (TLN ≥ 12, n = 177) and group B (TLN < 12, n = 54). Factors influencing lymph node retrieval were analyzed by univariate and binary logistic regression analysis. DFS and OS were evaluated by Kaplan-Meier curves and Cox regression models.

RESULTS

The median number of lymph nodes dissected was 18 (range, 12-45) in group A

committee of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (Approval No. 17-116/1439).

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and 8 (range, 2-11) in group B. The lymph node ratio (number of positive lymph nodes/total number of lymph nodes) (P = 0.039) and the interval between neoadjuvant therapy and radical surgery (P = 0.002) were independent factors of the TLN. However,TLN was not associated with sex, age, ASA score, clinical T or N stage, pathological T stage, tumor response grade (Dworak), downstaging, pathological complete response, radiotherapy dose, preoperative concurrent chemotherapy regimen, tumor distance from anal verge, multivisceral resection, preoperative carcinoembryonic antigen level, perineural invasion, intravascular tumor embolus or degree of differentiation. The pathological T stage (P < 0.001) and TLN (P < 0.001) were independent factors of DFS, and pathological T stage (P = 0.011) and perineural invasion (P = 0.002) were independent factors of OS. In addition, the risk of distant recurrence was greater for TLN < 12 (P = 0.009).

CONCLUSION

A shorter interval to surgery after neoadjuvant chemoradiotherapy for rectal cancer under indications may cause increased number of lymph nodes harvested. Tumor shrinkage and more extensive lymph node retrieval may lead to a more favorable prognosis.

Key Words: Lymph node retrieval; Survival analysis; Neoadjuvant therapy; Rectal cancer; Tumor-node-metastasis stage; Prognosis

Core Tip: The number of lymph node retrieval and survival on surgery after neoadjuvant therapy in rectal cancer are still under debate. This study analyzes the effects of lymph node retrieval in rectal cancer after neoadjuvant therapy on patient survival. We concluded that a shorter interval to surgery after neoadjuvant chemoradiotherapy for rectal cancer under indications caused increased number of lymph nodes harvested. Tumor shrinkage and more extensive lymph node retrieval may lead to a more favorable prognosis.

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INTRODUCTION

The internationally recognized tumor-node-metastasis (TNM) classification system is widely practiced in the staging of clinical malignant tumors. Since first proposed by a Frenchman, Pierre Denoix, between 1943 and 1952, the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) have gradually established international classification standards, and in 1968, the first edition of the TNM classification of malignant tumors was published[1,2]. Currently, 8 editions of the TNM classification system for colorectal cancer have been developed, and the 8th edition has become a widely used reference for colorectal oncologists globally[3]. With social and economic development, colorectal cancer now ranks third in the world in terms of morbidity and mortality[4]. In China, colorectal cancer is also a serious threat to human health. Locally advanced rectal cancer accounts for the majority of colorectal cancer cases. Positive lymph nodes (pN1-2) suggest a risk of systemic metastasis and unfavorable prognosis[5]. The harvest of fewer than 12 lymph nodes has been identified as a predictor of unfavorable outcomes in rectal cancer according to the National Comprehensive Cancer Network (NCCN) guidelines, and this cut-off is regarded as a standard in surgical treatment[6,7]. With the widespread application of neoadjuvant therapy for rectal cancer, in general, the number of lymph nodes harvested is negatively correlated with tumor regression. The total number of retrieved lymph nodes (TLN) is often less than 12 after neoadjuvant therapy, which has a debatable

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effect on the rate of local recurrence and distant metastasis[8,9]. The lymph node ratio (LNR) is also a prognostic factor that is inversely correlated with survival outcomes[8,10,11]. Furthermore, accurate pathological staging plays an important role in determining the postoperative treatment regimen for rectal cancer, and more extensive lymph node retrieval can reduce local recurrence. There have been no large clinical trials investigating whether neoadjuvant chemoradiotherapy affects the TLN.

Various factors influencing lymph node retrieval during surgery make it difficult to determine the influence on the node stage (pN)[12]. Weight, sex, pelvic structure, specimen length and surgical procedure type are factors that may influence the retrieval of lymph nodes[13,14]. Interestingly, a lower N stage can be the result of lymph nodes not being sufficiently dissected by the surgeon or some of the lymph nodes being missed by the pathologist during specimen collection. This phenomenon is due to the neoadjuvant therapy which reduces the size of the tumor and the number of positive lymph nodes[15].

Anatomically, the circumferential margin of involvement of tumors in the rectum is similar to that of tumors in the colon invading the mesocolon, but the rectum is quite different from the colon in terms of the lymph node distribution. This difference leads to a higher recurrence rate of locally advanced rectal cancer (cN+). Therefore, preoperative neoadjuvant therapy plus radical total mesorectal excision (TME) as the standard therapy regimen has been applied in locally advanced rectal cancer[16]. Logically, fewer lymph nodes may be retrieved due to neoadjuvant chemoradiotherapy, and the TLN can thus be influenced by the chemotherapy regimen, radiotherapy dose and tumor response to chemoradiotherapy. A larger TLN may suggest a poorer prognosis.

In the present study, we examined the TLN as an indication for the most suitable neoadjuvant and surgical treatment regimen.

MATERIALS AND METHODS

Patients

We analyzed the data of 231 patients who were clinically diagnosed with locally advanced rectal cancer. All patients were admitted to the Colorectal Surgery Department of the National Cancer Center/National Sciences Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, between November 2014 and August 2017 and enrolled in the treatment regimen, which was preoperative neoadjuvant therapy followed by laparoscopic TME[17]. The cohort was divided into two groups, with 12 lymph nodes as the boundary and the TLN determined by surgeons and pathologists. We investigated the factors that may affect the TLN, as well as factors associated with prognosis, including clinical characteristics, clinical T and N stage, pathological T and N stage, preoperative chemotherapy regimen, radiotherapy dose, TLN, LNR, surgical procedure, pathological outcomes and follow-up data (Table 1). This research was approved by the ethics committee of our institution, and informed consent to collect clinical data was obtained from each patient following the principles of the World Medical Association Declaration of Helsinki. We excluded patients who were diagnosed with clinical TNM stage I and IV disease, other carcinomas or lesions, obstruction, perforation, or bleeding, who were treated with palliative resection and who refused to accept chemoradiotherapy.

Neoadjuvant therapy

According to the AICC/UICC 8th edition TNM classification system[18], patients with stage II and III disease were treated with neoadjuvant chemoradiotherapy. The preoperative radiotherapy dose typically ranged from 45 Gy-50.4 Gy and was administered according to a long-course regimen; some patients were treated with a short-course radiotherapy regimen with a total dose of 25 Gy. Radiation was delivered to the pelvic cavity and tumor bed at an energy of 10 MV. The following chemotherapy regimens were administered concurrently with radiation: XELOX; oral capecitabine alone; and other regimens of fluorouracil combined with other agents.

Pathological analysis

All surgical specimens were sent for examination and fixation with paraffin in a timely manner after surgery. The pathologists were blinded to the patient information during analysis of the specimens. The final pathological TNM stage was classified using the AJCC/UICC 8th edition classification system. Our institution also uses the tumor

Table 1 Patient characteristics

Variable	TLN ≥ 12 (group A, *n* = 177)	TLN < 12 (group B, *n* = 54)	*P* value
Sex (*n*, %)			0.591
Male	121 (68.4)	39 (72.2)	
Female	56 (31.6)	15 (27.8)	
Age (yr)	60 (51-65)	59.5 (52.75-66.5)	0.544
ASA score (*n*, %)			0.488
1	5 (2.8)	2 (3.7)	
2	139 (78.6)	39 (72.2)	
3	33 (18.6)	13 (24.1)	
BMI (kg/m^2)	23.8 (21.9-26.4)	23.4 (21.5-25.2)	0.423
cT, *n* (%)			0.975
2	2 (1.1)	0 (0)	
3	137 (77.4)	43 (79.6)	
4	38 (21.5)	11 (20.4)	
cN, *n* (%)			0.109
0	44 (24.9)	18 (33.3)	
1	91 (51.4)	28 (51.9)	
2	42 (23.7)	8 (14.8)	
Preoperative CEA (μg/L)	2.99 (1.55-5.57)	3 (1.68-5.57)	0.729
ypT, n (%)			0.140
0	26 (14.7)	14 (25.9)	
1	4 (2.3)	1 (1.9)	
2	37 (20.9)	11 (20.4)	
3	97 (54.8)	24 (44.4)	
4	13 (7.3)	4 (7.4)	
ypN, *n* (%)			0.026
0	90 (50.8)	38 (70.4)	
1	64 (36.2)	10 (18.5)	
2	23 (13)	6 (11.1)	
TRG, *n* (%)			0.312
0	14 (7.9)	4 (7.4)	
1	26 (14.7)	7 (13)	
2	78 (44.1)	22 (40.7)	
3	33 (18.6)	7 (13)	
4	26 (14.7)	14 (25.9)	
No downstaging, *n* (%)	98 (55.4)	20 (37)	0.019
Downstaging, *n* (%)	56 (31.6)	21 (38.9)	0.324
pCR, *n* (%)	26 (14.7)	14 (25.9)	0.057
Positive lymph nodes, *n* (%)	0 (0-1)	0 (0-0)	0.003
LNR	0 (0-0.68)	0 (0-0)	0.012
Radiotherapy dose, *n* (%)			0.557
45-50.4 Gy/28 F	125 (70.6)	39 (72.2)	

< 45 Gy/25 F	34 (19.2)	5 (9.3)	
25 Gy/5 F	18 (10.2)	10 (18.5)	
Preoperative concurrent chemotherapy regimen, *n* (%)			0.376
Capecitabine+ oxaliplatin	54 (30.5)	17 (31.5)	
Capecitabine, oral	108 (61)	37 (68.5)	
Fluorouracil union	15 (8.5)	0 (0)	
Tumor location, DAV (cm)	5 (3-7)	5 (3-7)	0.605
Interval, w (%)	8 (6.5-11)	10 (8-16)	0.001
Surgical procedure			0.018
Miles (*n*, %)	74 (41.8)	26 (48.2)	
Dixon (*n*, %)	93 (52.5)	20 (37)	
Hartmann (*n*, %)	10 (5.6)	8 (14.8)	
LLND (*n*, %)	20 (11.3)	1 (1.9)	0.035
Multivisceral resection (*n*, %)	10 (5.6)	2 (3.7)	0.574
PNI (*n*, %)			0.819
Yes	42 (23.7)	12 (22.2)	
No	135 (76.3)	42 (77.8)	
Intravascular tumor embolus (*n*, %)			0.463
Yes	23 (13)	5 (9.3)	
No	154 (87)	49 (90.7)	
Degree of differentiation, *n* (%)			0.367
Low and low-middle grades	18 (10.2)	9 (16.7)	
Middle, high-middle, and high grades	132 (74.6)	43 (79.6)	
Signet-ring and mucinous adenocarcinoma	4 (2.3)	2 (3.7)	

TLN: Total number of retrieved lymph nodes; BMI: Body mass index; CEA: Carcinoembryonic antigen; ASA: American Society of Anesthesiologists; TRG: Tumor regression grade; LNR: Lymph node ratio; DAV: Distance from anal verge; LLND: Lateral lymph node dissection; PNI: Perineural invasion; pCR: Pathological complete response; F: Fractions.

regression grade (TRG, Dworak), ranging from 0 to 4: TRG0, the tumor tissue showed no significant regression macro- or microscopically; TRG1, the tumor tissue showed < 25% shrinkage microscopically; TRG2, the tumor tissue showed 25%-50% shrinkage microscopically; TRG3, the tumor tissue showed > 50% shrinkage microscopically; and TRG4, no residual tumor cells were observed microscopically. Perineural invasion (PNI) was defined as tumor cells invading any layer of the nerve sheath or tumor cells growing along the nerve wrapping more than 1/3 of the nerve circumference, and intravascular tumor embolus was defined by tumor cell invasion of the lymphatic vessels or vessels of the intestinal wall.

Follow-up

Follow-up was conducted in the outpatient clinic or by telephone or email. Clinical and chest, abdominal and pelvic enhanced computed tomography examinations were performed to detect recurrence. Patients were followed up every three months postoperatively for the first two years. If there was no recurrence after two years, patients were followed up every six months once a year. Colonoscopy was performed every six months during the first two years and once a year after the first two years. Disease-free survival (DFS) was analyzed from the day of surgery to the date of tumor-related recurrence. Overall survival (OS) was defined as the time between the date of surgery and cancer-related death. The last date to follow-up was March 22, 2020. The median follow-up was 41 mo.

Statistical analysis

The first part of our statistical analysis focused on factors affecting the TLN. Patient characteristics were analyzed with univariate and binary logistic regression analyses. On univariate analysis, we compared categorical variables with the Chi-squared test or Fisher's exact test, and continuous variables that did not conform to the normal distribution were calculated by Mann-Whitney *U* test and were displayed as the median (range). Variables with *P* values less than 0.05 on univariate analysis were included in the binary logistic regression analysis.

The second part of the analysis examined whether DFS and OS were correlated with the TLN. Factors influencing the prognosis were analyzed by the Kaplan-Meier method and then included in Cox proportional hazards regression models with the aim of determining independent factors affecting DFS and OS.

All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 26.0 for Mac (IBM Corp, NY, United States).

RESULTS

Table 1 shows the clinicopathological features of the patients. There was no significant difference between the two groups except the operating time interval and the lymph node ratio, as shown in Table 2 by binary regression analysis. The median follow-up period was 41 mo (range, 2-62), with no difference between the groups. Fourteen (7.9%) patients in group A and 7 (13%) patients in group B experienced local recurrence ($P = 0.259$). The total number of deaths in the cohort was 27 (15.3%) in group A and 9 (16.7%) in group B ($P = 0.803$). Although there was no significant difference between the two groups, the local recurrence rate and death rate were higher in group B (TLN < 12) than in group A (TLN ≥ 12). More patients in group B than in group A experienced distant recurrence (group A, 19.8% *vs* group B, 37%, $P = 0.009$). Table 3 presents the tumor-related outcomes in both groups.

At the same time, the above potential prognostic factors were analyzed as categorical variables by the Kaplan-Meier method. The cumulative DFS rate, which was determined by the date of tumor recurrence, was higher in group A (TLN ≥ 12) than in group B (TLN < 12) (group A, 68.9% *vs* group, B 40%, $P = 0.006$), but there was no difference between the groups in OS (group A, 79% *vs* group B, 81%, $P = 0.737$) (Figure 1). Other factors leading to a significant difference in DFS included clinical N stage ($P = 0.003$), pathological T stage ($P < 0.001$) and N stage ($P < 0.001$), positive lymph nodes ($P < 0.001$), LNR ($P < 0.001$), interval ($P = 0.044$), multivisceral resection ($P = 0.025$), PNI ($P < 0.001$), intravascular tumor embolus ($P < 0.001$), and degree of differentiation ($P = 0.028$), and factors causing a significant difference in OS included pathological T stage ($P < 0.001$), PNI ($P < 0.001$), and intravascular tumor embolus ($P = 0.004$). All factors affecting survival were incorporated into the Cox proportional hazards regression model for further analysis. Table 4 presents the survival outcomes in both groups. We found that the TLN [$P < 0.001$, odds ratio (OR): 0.302, 95% confidence interval (CI): 0.172-0.531] and pathological T stage ($P < 0.001$) were independent predictors of DFS, while PNI ($P = 0.002$, OR: 3.74, 95%CI: 1.634-8.529) and pathological T stage ($P = 0.002$) were independent predictors of OS, as shown in Table 5.

DISCUSSION

Comprehensive treatment regimens are constantly updated. Currently, the accepted standard treatment scheme is preoperative neoadjuvant chemoradiotherapy followed by radical surgery, but improvements in treatment are made with the ultimate aim of improving the long-term survival rate and quality of life of patients. The TNM classification system in the AJCC cancer staging manual (8th edition, 2017) is used as the current staging standard for rectal cancer; the TNM stage is not only the most important prognostic predictor in rectal cancer but also critical to the selection of a postoperative treatment regimen. There are few factors affecting the evaluation of the T and M stage, but the N stage is established based on the number of lymph nodes harvested, and both the TLN and number of positive lymph nodes are influenced by the surgical and pathological techniques[19]. In our study, the interval between neoadjuvant therapy and surgery was an independent factor of the number of lymph nodes harvested. This outcome is similar to that of a study performed by Sermier

Table 2 Binary regression analysis

	P value	OR	95%CI
No downstaging	0.640	0.797	0.309-2.061
Positive lymph nodes	0.152	0.873	0.725-1.051
ypN0 *vs* ypN2	0.059	8.239	0.92-73.794
ypN1 *vs* ypN2	0.442	2.228	0.289-17.163
LNR	0.039	66.666	1.239-3587.217
Interval	0.002	1.084	1.029-1.142
LLND	0.086	0.165	0.021-1.287

LNR: Lymph node ratio; LLND: Lateral lymph node dissection; OR: Odds ratio; CI: Confidence interval.

Table 3 Oncologic outcomes

Variable	TLN ≥ 12 (group A, *n* = 177)	TLN < 12 (group B, *n* = 54)	*P* value
Local recurrence, *n* (%)	14 (7.9)	7 (13)	0.259
Distant recurrence, *n* (%)	35 (19.8)	20 (37)	0.009
Death, *n* (%)	27 (15.3)	9 (16.7)	0.803

TLN: Total number of retrieved lymph nodes.

et al[20]; they found that the TLN in abdominoperineal resection was impacted by the interval between neoadjuvant therapy and surgery and the administration of neoadjuvant radiotherapy. Neoadjuvant therapy not only controlled the local recurrence rate after surgery but also reduced the TLN. There are various factors affecting the detection of lymph nodes in rectal cancer after neoadjuvant therapy. Prolonging the interval after neoadjuvant therapy can improve the local pathological response rate[21-23], and neoadjuvant therapy may play a paramount role in treating tumors over time. However, there seems to be a contradiction, as neoadjuvant therapy can also reduce the lymph node retrieval rate and the accuracy of TNM staging. Some studies have indicated that fewer lymph nodes are detected during surgery after neoadjuvant therapy[22,24-26]. Farinella *et al*[22] concluded that small lymph nodes (≤ 5 mm) impacted the N stage. We found that small lymph nodes (≤ 5 mm) accounted for 76.5% of lymph nodes retrieved in our study, which increased the difficulty in accurately identifying the N stage due to atrophy, fibrosis and even necrosis. In a total of 5647 patients who were enrolled in an analysis of the Surveillance, Epidemiology and End Results (SEER) database in 2005, the number of lymph nodes retrieved and the N stage were affected by the administration of neoadjuvant therapy[27]. We analyzed whether neoadjuvant chemoradiotherapy combined with chemoradiotherapy had a sensitization effect on radiotherapy. Theoretically, compared with preoperative radiotherapy, preoperative chemoradiotherapy should significantly reduce the TLN. In this regard, it has also been reported that preoperative chemoradiotherapy has more advantages in terms of tumor shrinkage and tumor persistence than preoperative radiotherapy alone[28].

The effect of the minimum number of harvested lymph nodes on rectal cancer has been discussed between surgeons and pathologists. The effect of the number of lymph nodes harvested in rectal cancer on survival is also a controversial issue. With increasing lymph node dissection and detection, the stage determined according to the TNM classification system becomes increasingly accurate. Considering the effect of neoadjuvant therapy on the accuracy of the N stage, the LNR has been used as a prognostic indicator in some studies[29,30]. Ceelen *et al*[31] performed a systematic review and analysis of a total of 33 984 patients and found that the prognostic value of positive lymph nodes was inferior to that of the LNR. There was another interesting study on the prognostic value of the number of lymph nodes. Sun *et al*[32] reported that the number of negative lymph nodes for ypN+ after neoadjuvant therapy was a prognostic factor for DFS (number of negative lymph nodes ≥ 17, hazard ratio = 0.400,

Table 4 Results of Kaplan-Meier analysis

Variable	No. of cases	DFS *P* value	OS *P* value
Sex (*n*, %)		0.708	0.655
Male	160 (69.3)		
Female	71 (30.7)		
Age (yr)		0.86	0.968
< 60	111 (48.1)		
≥ 60	120 (51.9)		
ASA score (*n*, %)		0.912	0.951
1	7 (3)		
2	178 (77)		
3	46 (19.9)		
BMI (kg/m^2)		0.519	0.512
< 25	149 (64.5)		
≥ 25	82 (35.5)		
cT, *n* (%)		0.606	0.476
2	2 (0.9)		
3	180 (77.9)		
4	49 (21.2)		
cN, *n* (%)		0.003	0.063
0	79 (34.2)		
1	112 (48.5)		
2	40 (17.3)		
ypT, *n* (%)		< 0.001	< 0.001
0	36 (15.6)		
1	6 (2.6)		
2	50 (21.6)		
3	122 (52.8)		
4	17 (7.4)		
ypN, *n* (%)		< 0.001	0.097
0	128 (55.4)		
1	74 (32)		
2	29 (12.6)		
TLN, *n* (%)		0.006	0.737
< 12	54 (23.4)		
≥ 12	177 (76.6)		
Positive lymph nodes, *n* (%)		< 0.001	0.063
< 2	182 (78.8)		
≥ 2	49 (21.2)		
LNR		< 0.001	0.058
≤ 0.03			
> 0.03			
Preoperative concurrent chemotherapy regimen, *n* (%)		0.148	0.561

Capecitabine+ oxaliplatin	58 (25.1)		
Capecitabine, oral	140 (60.6)		
Oxaliplatin combination	22 (9.5)		
Postoperative chemotherapy		0.933	0.869
Yes	153 (66.2)		
No	78 (33.8)		
Interval, w (%)		0.044	0.567
≤ 8 wk	139 (60.2)		
> 8 wk	92 (39.8)		
Surgical procedure		0.168	0.662
Miles (*n*, %)	100 (43.3)		
Dixon (*n*, %)	113 (48.9)		
Hartmann (*n*, %)	18 (7.8)		
LLND (*n*, %)	21 (9.1)	0.868	0.994
Multivisceral resection (*n*, %)	12 (5.2)	0.025	0.948
Preoperative CEA (μg/L)		0.344	0.663
< 5	166 (71.9)		
≥ 5	65 (28.1)		
PNI (*n*, %)		< 0.001	< 0.001
Yes	54 (23.4)		
No	177 (76.6)		
Intravascular tumor embolus (*n*, %)		< 0.001	0.004
Yes	28 (12.1)		
No	203 (87.9)		
Degree of differentiation, *n* (%)		0.028	0.152
Low and low-middle grades	32 (13.9)		
Middle, high-middle, and high grades	193 (83.5)		
Signet-ring and mucinous adenocarcinoma	6 (2.6)		

DFS: Disease-free survival; OS: Overall survival; BMI: Body mass index; ASA: American Society of Anesthesiologists; LLND: Lateral lymph node dissection; TLN: Total number of retrieved lymph nodes; CEA: Carcinoembryonic antigen; PNI: Perineural invasion.

P = 0.022). Persiani *et al*[33] conducted a study involving 345 patients treated with neoadjuvant therapy followed by surgery, and they indicated that more lymph nodes were retrieved in cases of a less extensive tumor response and a shorter interval between neoadjuvant therapy and surgery. Hall *et al*[34] indicated that the TLN was strongly correlated with OS, with a cut-off value of 8 lymph nodes. Onitilo *et al*[35], in a retrospective cohort study of 708 patients with rectal cancer treated over the past 10 years, divided the 708 patients into the surgery alone group (279, SURG) and the neoadjuvant therapy plus surgery group (479, NEO) for comparison; the TLN showed a significant difference between the two groups (NEO 10.8 *vs* SURG 15.5, P < 0.001). In contrast, the disease-specific survival in the SURG group was not superior to that in the NEO group. The conclusion of this study explained that neoadjuvant therapy may eliminate the potential positive lymph nodes, leading to a decrease in the retrieval of lymph nodes after radical surgery, and that neoadjuvant therapy plays a concurrent role in controlling local recurrence. In our study, even with neoadjuvant therapy followed by radical resection for rectal cancer, TLN < 12 remained unfavorable in terms of DFS. Considering that the number of lymph nodes detected is affected by many factors, it is important to establish an effective system that re-evaluates the true number of positive lymph nodes harvested for accurate staging after neoadjuvant therapy. This is difficult because there is no method to evaluate the true rate of lymph

Table 5 Results of Cox regression analysis of disease-free survival and overall survival

	Disease-free survival			Overall survival		
	P value	HR	95%CI	*P* value	HR	95%CI
cN0 *vs* cN1	0.620	0.794	0.318-1.978	0.801	0.84	0.217-3.249
cN0 *vs* cN2	0.496	1.281	0.628-2.610	0.296	1.712	0.625-4.693
ypT0 *vs* ypT4	< 0.001	0.074	0.019-0.288	0.011	0.11	0.02-0.607
ypT1 *vs* ypT4	0.338	0.46	0.094-2.253	0.494	0.464	0.051-4.202
ypT2 *vs* ypT4	< 0.001	0.097	0.032-0.301	0.002	0.035	0.004-0.305
ypT3 *vs* ypT4	0.014	0.418	0.209-0.837	0.011	0.309	0.125-0.761
ypN0 *vs* ypN1	0.745	0.823	0.254-2.664	0.805	1.245	0.219-7.086
ypN0 *vs* ypN2	0.706	1.178	0.504-2.756	0.816	1.156	0.341-3.92
TLN (≥ 12 *vs* < 12	< 0.001	0.302	0.172-0.531	0.606	0.8	0.342-1.871
LNR (≤ 0.03 *vs* 0.03)	0.840	0.914	0.379-2.20	0.768	1.228	0.314-4.799
Positive lymph nodes (≥ 2 *vs* < 2)	0.828	1.1	0.466-2.593	0.978	0.982	0.271-3.562
Interval (≤ 8 wk *vs* > 8 wk)	0.236	1.369	0.814-2.303	0.626	0.836	0.408-1.715
Multivisceral resection	0.119	1.875	0.851-4.13	0.792	0.816	0.181-3.69
PNI	0.051	1.8	0.998-3.248	0.002	3.747	1.634-8.592
Intravascular tumor embolus	0.244	1.479	0.766-2.858	0.584	1.292	0.517-3.23
Degree of differentiation						
Low and low-middle grades *vs* signet-ring and mucinous adenocarcinoma	0.695	0.739	0.163-3.354	0.811	0.76	0.08-7.221
Middle, high-middle, and high grades *vs* signet-ring and mucinous adenocarcinoma	0.929	0.930	0.19-4.564	0.913	1.141	0.106-12.243

TLN: Total number of retrieved lymph nodes; LNR: Lymph node ratio; DFS: Disease-free survival; OS: Overall survival; PNI: Perineural invasion; HR: Hazard ratio; CI: Confidence interval.

node positivity. However, to deal with the issue of inaccurate N staging, two methods can be utilized. First, as more lymph nodes are harvested to be assessed, the accuracy of staging node-positive disease progressively increases[35-38]; thus, the rate of positive lymph node detection becomes infinitely closer to the true value. Additionally, DFS would seem to improve partly because of shift in staging. Second, a systematic review of many studies can be performed to identify factors affecting DFS on the basis of lymph node dissection. A study of the cohort of patients from the randomized EORTC trial 22921 indicated that DFS was not improved by postoperative adjuvant chemotherapy in patients treated with neoadjuvant chemoradiotherapy[39]. On the other hand, the EORTC trial suggested that the accuracy rate of N staging after neoadjuvant therapy followed by surgery may need to be improved to better plan for postoperative care.

Our study has several limitations. The first limitation is its retrospective nature. Second, there may be bias in the information collected, but the cohort showed acceptable homogeneity. A future multicenter, randomized controlled or cohort trial with a larger sample size may be needed to verify factors of lymph node retrieval after neoadjuvant therapy. Third, the radiotherapy dose administered to patients in our cohort varied because of discrepancies in clinical practice.

CONCLUSION

The TLN may help to predict the prognosis in colorectal cancer. Neoadjuvant therapy caused decreased number of lymph nodes detected, leading to inaccurate staging. The retrieval of more lymph nodes may improve the accuracy of TNM staging and result in a more favorable prognosis.

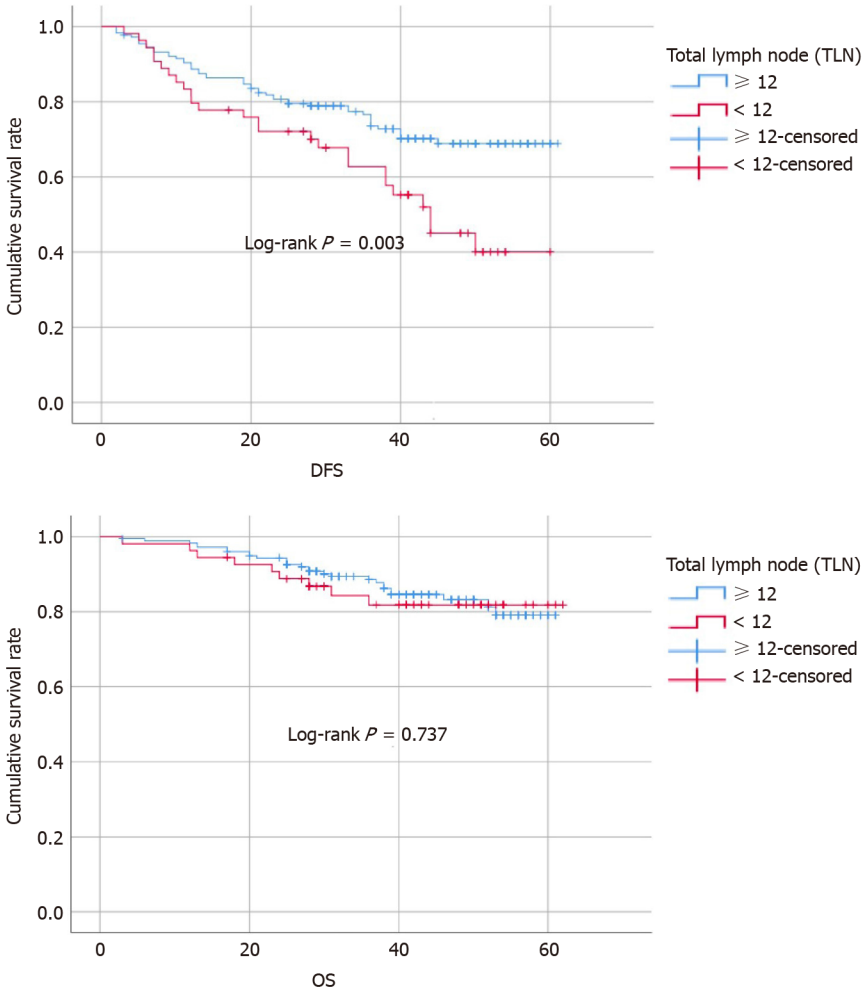

Figure 1 Cumulative disease-free survival rate determined by the date of tumor recurrence, was higher in group A (total number of retrieved lymph nodes, TLN ≥ 12) than in group B (TLN < 12), but there was no difference between the groups in overall survival. DFS: Disease-free survival; OS: Overall survival.

ARTICLE HIGHLIGHTS

Research background

Surgery with total mesorectal excision following neoadjuvant therapy is a standard regime for locally advanced rectal cancer. The number of lymph node retrieval and survival on surgery after neoadjuvant therapy in rectal cancer are still under debate.

Research motivation

There is a lack of consensus concerning the actual number of lymph node retrieval in surgery after neoadjuvant therapy. Whether less or more 12 lymph nodes should be retrieved is controversial. Data are limited regarding outcomes of different number of lymph node retrieval.

Research objectives

The main aim of this study is to investigate whether different number of lymph node retrieval affects the rate of pathological complete response, preoperative outcomes and survival status.

Research methods

This was a retrospective cohort study to collect the data of patients after neoadjuvant therapy for locally advanced rectal cancer. According to the clinicopathological characteristics and other data, the influence of neoadjuvant therapy on the number of lymph node dissection was analyzed.

Research results

A shorter interval to surgery after neoadjuvant chemoradiotherapy for rectal cancer under indications may cause increased number of lymph nodes harvested. Tumor shrinkage and more extensive lymph node retrieval may lead to a more favorable prognosis.

Research conclusions

The TLN may help to predict the prognosis in colorectal cancer. Neoadjuvant therapy caused a decrease in the number of lymph nodes detected, leading to inaccurate staging. The retrieval of more lymph nodes may improve the accuracy of TNM staging and result in a more favorable prognosis.

Research perspectives

Prospective randomized trials are required to evaluate the optimal number of lymph node retrieval that is needed to achieve minimum morbidity, and minimum disease recurrence.

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