A retrospective study on the impact of the number of resected lymph nodes on the survival outcome of stage IV rectal cancer patients after preoperative therapy

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Background: There is no consensus on the optimal number of examined LNs for stage IV rectal cancer patients after preoperative therapy. We aimed to explore the impact of the number of resected lymph nodes (LNs) on the survival outcomes of stage IV rectal cancer patients after preoperative therapy.

Methods: Clinicopathologic data of 556 patients diagnosed with stage IV rectal cancer between 1st January, 2010 and 31st December, 2015 from the Surveillance, Epidemiology, and End Results (SEER) database after preoperative therapy were reviewed. The patients were further divided into two groups: the ≥15 resected LNs group and <15 resected LNs group based on the X-tile software analysis results of the number of resected LNs.

Results: Both univariate and multivariate regression analyses revealed that the number of resected LNs and N status were significantly positively correlated with the survival outcome of the patients. Patients in the ≥15 resected LNs group had a significant better cancer-specific survival (CSS) (P=0.003) than those in the <15 resected LNs group. The 3-year CSS rate was 63.2% for patients with ≥15 resected LNs compared with 55.7% for those with <15 resected LNs. The 5-year CSS rate was 50.2% and 30.5% for patients in the ≥15 resected LNs group and those in the <15 resected LNs group, respectively.

Conclusions: The number of resected LNs is an important independent prognostic factor that influences the survival outcome of stage IV rectal cancer patients after receiving preoperative therapy.

Keywords: Rectal cancer; number of resected lymph nodes; stage IV; Survival, Surveillance, Epidemiology, and End Results database (SEER database)

Introduction

Colorectal cancer is one of the most common cancers in the world based on GLOBOCAN 2018 estimates. Approximately 1.8 million new cases of colorectal cancer are diagnosed yearly (1). The increasing incidence of rectal cancer cases have raised huge concerns within the scientific and health experts. Based on the guidelines of the American Joint Committee on Cancer (AJCC) and the National Comprehensive Cancer Network (NCCN), patients diagnosed with locally advanced rectal cancer (T3/4 or N1/2) should receive neoadjuvant chemoradiotherapy (NCRT) follow by total mesorectal excision (TME) thereafter (2,3). These guidelines suggest that a minimum of 12 lymph nodes (LNs) should be examined for rectal cancer patients regardless of neoadjuvant therapy (4,5). However, several studies report that neoadjuvant chemoradiotherapy decrease the number of LNs retrieved in subsequent surgery resections (6-8). This further disputes the optimal number of examined LNs in rectal cancer patients after neoadjuvant therapy (9,10).

The LN status is an important factor in staging and survival of rectal cancer patients (2). The number of resected LNs is significantly associated with the survival outcome of rectal cancer patients and is thus vital for accurate pN staging (11-14). Several studies have postulated that the higher the number of LNs recovered, the higher the number of LNs metastases is in colorectal cancer (15,16). This largely depend on the criterion of lymphadenectomy used by clinicians. To date, there is no consensus on the optimal number of examined LNs for rectal cancer patients after preoperative therapy.

In clinical practice, some rectal cancer patients receive preoperative therapy followed by TME are confirmed to have stage IV rectal cancer after postoperative pathological diagnosis. For these patients, the standard number of examined LNs suitable for them remains unclear. As such, this study aimed to explore the impact of the number of resected LNs on the survival of stage IV rectal cancer patients who initially received preoperative therapy. Rectal cancer datasets from the Surveillance, Epidemiology, and End Results (SEER) database were used. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jgo-20-175).

Methods

Patient selection

Clinical data of patients diagnosed with stage IV rectal cancer after preoperative radiotherapy between 1st January, 2010 and 31st December, 2015 was retrospectively examined. Patients whose TNM stage information was incomplete as well as those whose radiation method was not beam radiation or unknown were excluded from the study. Patients whose data of examined LNs was unclear or incomplete and those with a second cancer or borderline tumor were also excluded. This was also the case for patients less than 18 years old, patients without chemotherapy, non-adenocarcinoma patients, patients with tumor deposit and patients who died within 30 days after surgery. In addition, patients with no surgical procedure of primary site and or the information of surgery was incomplete as well as those died not due to the cancer were also excluded from the study. Finally, 556 patients were enrolled in the study (*Figure 1*).

Statistical analysis

The optimal cutoff points of the number of resected LNs were defined using the X-tile software version 3.6.1 (Copyright Yale University 2003). The chi-square test was used to calculate differences in distribution for categorical variables. Moreover, the Kaplan-Meier method was employed to determine the prognostic factors of cancer-specific survival (CSS) using the log-rank test. In the same line, cox univariate and multivariate analyses were used to identify the most significant prognostic factors of CSS. All the statistical analyses were carried out using SPSS software, v25.0 (SPSS Inc., Chicago, IL, USA). A P value less than 0.05 indicated that there were significant differences between groups.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The data in
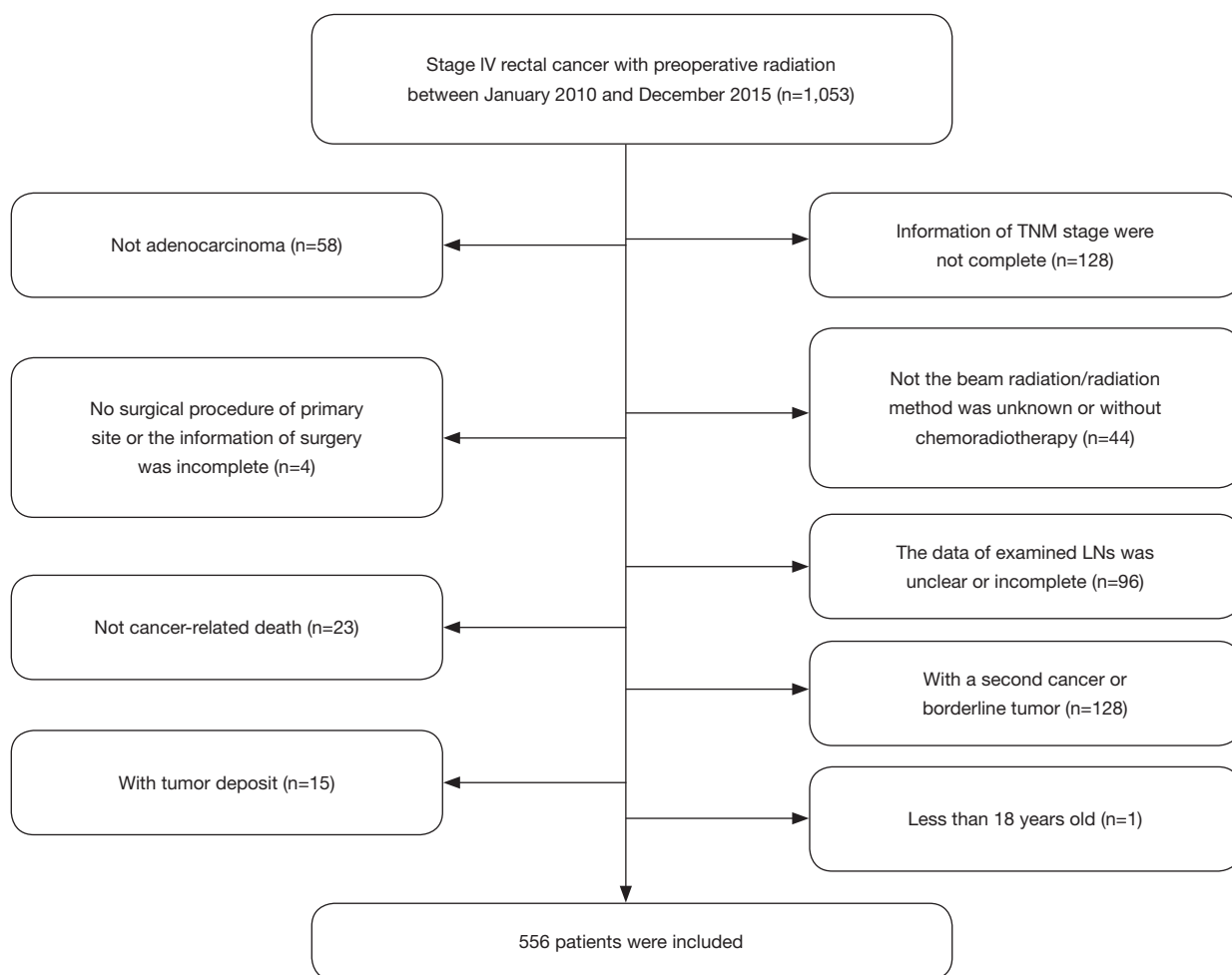
Stage IV rectal cancer with preoperative radiation
between January 2010 and December 2015 (n=1,053)

Not adenocarcinoma (n=58)

Information of TNM stage were
not complete (n=128)

No surgical procedure of primary
site or the information of surgery
was incomplete (n=4)

Not the beam radiation/radiation
method was unknown or without
chemoradiotherapy (n=44)

The data of examined LNs was
unclear or incomplete (n=96)

Not cancer-related death (n=23)

With a second cancer or
borderline tumor (n=128)

With tumor deposit (n=15)

Less than 18 years old (n=1)

556 patients were included

Figure 1 Flow chart for screening enrolled patients.

the SEER database were publicly available and de-identified thereby no ethics approval was required.

Results

Patient characteristics

A total of 556 patients were enrolled in the study. The optimum cutoff values of the number of resected LNs were less than 15 (<15) and more than or equal to 15 (≥15) based on the X-tile analysis results (*Figure 2*). The correlation between patient characteristics and the number of resected LNs is shown in *Table 1*. N status was significantly associated with the number of resected LNs. However, age, gender, race, marital status, grade, tumor size, CEA level, perineural invasion, T status, and metastatic location were not associated with the number of resected LNs.

The distribution of the number of resected LNs in 556 patients is shown in *Figure 3*. The mean and the median number of resected LNs was 14.9 and 14.0, respectively (*Table 2*).

Survival outcomes based on the number of resected LNs

Kaplan-Meier survival analysis and log-rank comparison results revealed that the ≥15 resected LNs group had a significant better CSS (P=0.003) compared to the <15 resected LNs group. The 3-year CSS rate was 63.2% for patients with ≥15 resected LNs compared with 55.7% for those with <15 resected LNs. The 5-year CSS rate was 50.2% and 30.5% for patients in the ≥15 resected LNs group and those in the <15 resected LNs group, respectively (*Figure 4*).
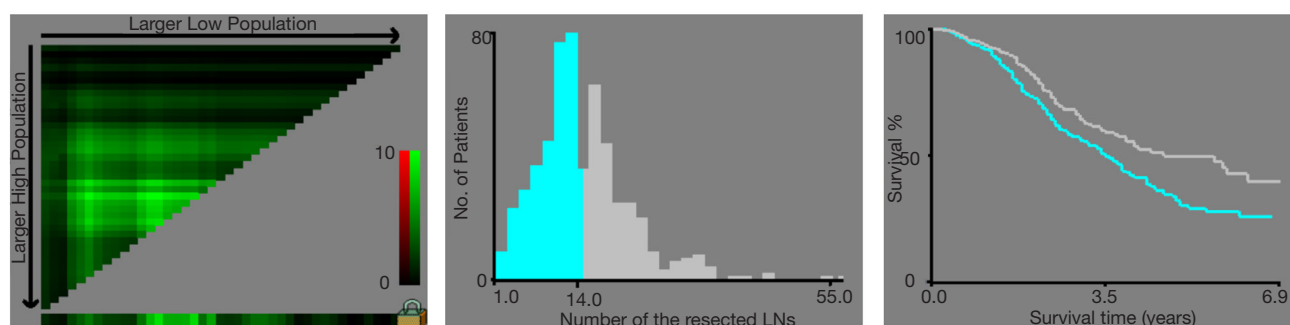
Figure 2 X-tile analysis to determine the cutoff values of the number of resected LNs.

Table 1 Distribution of clinicopathologic characteristics between the two groups (grouped by the number of resected LNs)

Characteristics	Total, n (%)	<15 resected LNs, n (%)	≥15 resected LNs, n (%)	P
Gender				0.977
Women	219 (39.4)	118 (39.3)	101 (39.5)	
Men	337 (60.6)	182 (60.7)	155 (60.5)	
Age (year)				0.079
≤65	424 (76.3)	220 (73.3)	204 (79.7)	
>65	132 (23.7)	80 (26.7)	52 (20.3)	
Race				0.615
White	440 (79.1)	233 (77.7)	207 (80.9)	
Black	57 (10.3)	32 (10.7)	25 (9.8)	
Others	59 (10.6)	35 (11.7)	24 (9.4)	
Marital status				0.652
Single	111 (20.0)	58 (19.3)	53 (20.7)	
Married	323 (58.1)	170 (56.7)	153 (59.8)	
Widowed/divorced	92 (16.5)	54 (18.0)	38 (14.8)	
Others	30 (5.4)	18 (6.0)	12 (4.7)	
Tumor size (cm)				0.696
<2	35 (6.3)	17 (5.7)	18 (7.0)	
2–5	226 (40.6)	125 (41.7)	101 (39.5)	
≥5	212 (38.1)	110 (36.7)	102 (39.8)	
Unknown	83 (14.9)	48 (16.0)	35 (13.7)	
CEA				0.650
+	300 (54.0)	164 (54.7)	136 (53.1)	
–	125 (22.5)	63 (21.0)	62 (24.2)	
Unknown	131 (23.6)	73 (24.3)	58 (22.7)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Total, n (%)	<15 resected LNs, n (%)	≥15 resected LNs, n (%)	P
Grade				0.378
Well/moderate	400 (71.9)	211 (70.3)	189 (73.8)	
Poor/undifferentiated	95 (17.1)	51 (17.0)	44 (17.2)	
Unknown	61 (11.0)	38 (12.7)	23 (9.0)	
Perineural invasion				0.291
–	342 (61.5)	178 (59.3)	164 (64.1)	
+	139 (25.0)	83 (27.7)	56 (21.9)	
Unknown	75 (13.5)	39 (13.0)	36 (14.1)	
T status				0.990
T1	11 (2.0)	6 (2.0)	5 (2.0)	
T2	37 (6.7)	19 (6.3)	18 (7.0)	
T3	413 (74.3)	224 (74.7)	189 (73.8)	
T4	95 (17.1)	51 (17.0)	44 (17.2)	
N status				0.003
N0	200 (36.0)	122 (40.7)	78 (30.5)	
N1	210 (37.8)	116 (38.7)	94 (36.7)	
N2	146 (26.3)	62 (20.7)	84 (32.8)	
Metastatic location				0.967
Liver	315 (56.7)	170 (56.7)	145 (56.6)	
Lung	84 (15.1)	44 (14.7)	40 (15.6)	
Liver + lung	29 (5.2)	15 (5.0)	14 (5.5)	
Others	128 (23.0)	71 (23.7)	57 (22.3)	

LNs, lymph nodes.

Cox univariate regression analysis revealed that grade, perineural invasion, N status, and number of resected LNs (the cutoff value was 15) were significantly associated with CSS (P values were 0.002, <0.001, <0.001, 0.003, respectively). However, gender, age, race, marital status, tumor size, CEA level, T status, number of resected LNs (the cutoff value was 12), and metastatic location were not correlated with CSS. Similarly, cox multivariate regression analysis revealed that grade, perineural invasion, N status, and number of resected LNs (the cutoff value was 15) were significantly positively correlated with CSS (P values were

0.006, 0.017, <0.001, <0.001, respectively) (*Table 3*).

Discussion

The National Comprehensive Cancer Network (NCCN) recommend that 12 or more LNs should be retrieved for rectal cancer staging. However, many studies have postulated that preoperative chemoradiotherapy reduce the number of LNs examined from the rectal carcinoma specimens (17,18). To date, there is no consensus on an absolute number of LNs that should be recovered for rectal
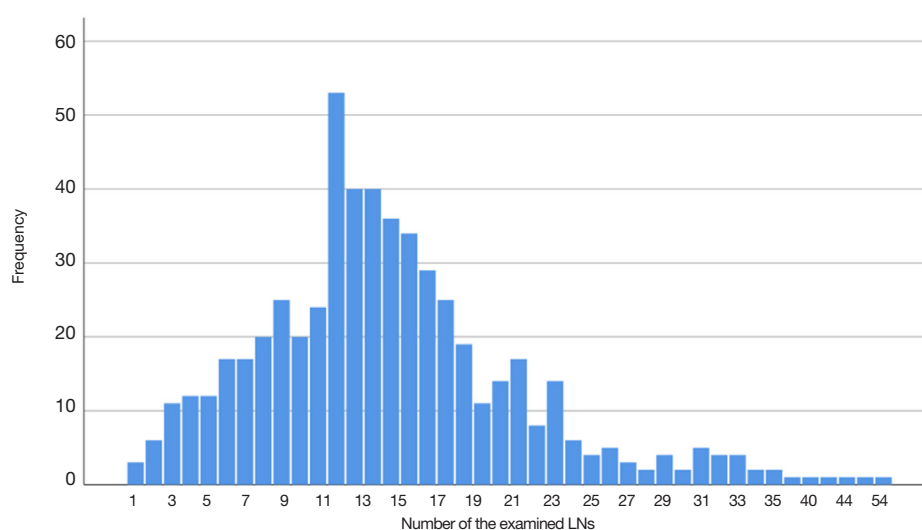
Figure 3 Distribution of the number of resected LNs in 556 patients with stage IV rectal cancer.

Table 2 Characteristics of examined LNs

Characteristics	Mean	Median	Range	Number of patients, n (%)
Total number of LNs examined	14.9	14.0	1–55	556 (100.0)
<15 LNs	9.81	11.0	1–14	300 (54.0)
≥15 LNs	20.9	19.0	15–55	256 (46.0)
<12 LNs	7.34	8.0	1–11	167 (30.0)
≥12 LNs	18.2	16.0	12–55	389 (70.0)

LNs, lymph nodes.

cancer patients with NCRT. Previous studies postulated that the optimal number of LNs to be examined in rectal cancer patients who receive preoperative chemoradiotherapy range between 7 and 30 LNs (19-21).

In clinical practice, some rectal cancer patients (special group) who receive preoperative chemoradiotherapy followed by TME are confirmed to have stage IV rectal cancer after postoperative pathological diagnosis. Few studies have explored the prognostic role of the number of LNs examined in these patients. Herein, 556 patients with stage IV rectal cancer patients who received preoperative therapy were specially studied to explore the impact of the number of resected LNs on survival. N status were found to influence the number of LNs resected. When the patients were divided into two groups (≥15 resected LNs group and <15 resected LNs group), patients in the ≥15 resected LNs group had a significant better CSS than those in the <15 resected LNs group. However, the survival outcome

between the ≥12 resected LNs group and the <12 resected LNs group was not significantly different. These results suggested that the current standard (≥12 LNs should be resected) might not be suitable for patients of the special group. In this group, more LNs than the current standard should be examined. Moreover, the N status was found to be significantly positively correlated with the survival outcome. Patients with N1 or N2 lymph node metastases had a poorer survival outcome compared with those with N0. These results proved that the LN status was still an important prognostic factor for stage IV rectal cancer patients after receiving preoperative therapy.

Cox univariate regression analysis further revealed that there was no association between metastatic location and CSS. This might be attributed to missing or unclear therapy data such as the number and size of metastatic tumors in SEER database thereby leading to bias.

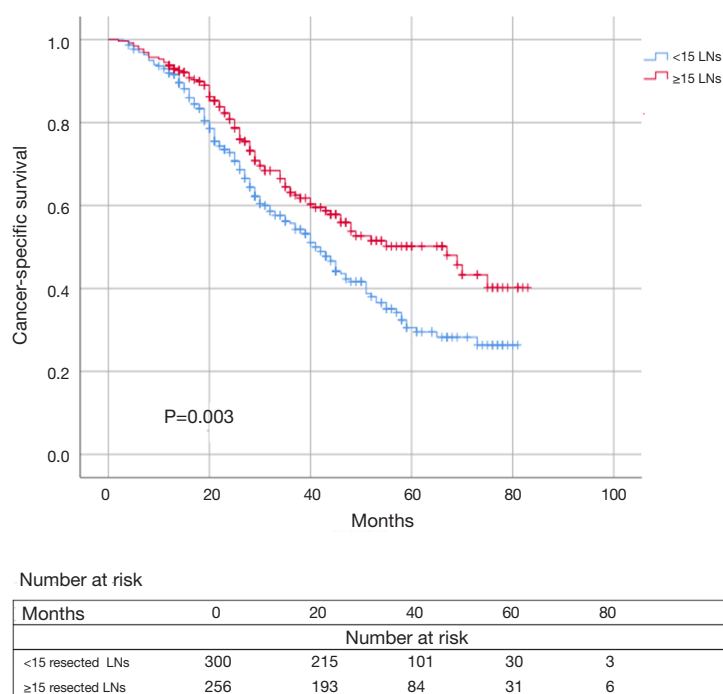Further to this, lymphadenectomy was found to be

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Figure 4 Cancer-specific survival curves for 556 patients with stage IV rectal cancer.

Table 3 Univariate and multivariate Cox regression analyses results for cancer-specific survival of the 556 patients

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Gender		0.304		
Women	Reference			
Men	1.144 (0.885–1.478)			
Age (year)		0.294		
≤65	Reference			
>65	1.166 (0.875–1.555)			
Race		0.895		
White	Reference			
Black	1.017 (0.680–1.521)	0.933		
Other	1.105 (0.728–1.677)	0.639		
Marital status		0.756		
Single	Reference			
Married	0.931 (0.677–1.281)	0.662		
Widowed/divorced	1.080 (0.724–1.611)	0.705		
Others	0.809 (0.432–1.516)	0.508		

Table 3 (*continued*)

Table 3 (*continued*)

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Tumor size (cm)		0.719		
<2	Reference			
2–5	0.900 (0.546–1.483)	0.678		
≥5	0.798 (0.481–1.324)	0.383		
Unknown	0.792 (0.449–1.399)	0.422		
CEA		0.186		
+	Reference			
–	0.776 (0.563–1.069)	0.120		
Unknown	0.807 (0.594–1.097)	0.171		
Grade		0.002		0.006
Well/ moderate	Reference		Reference	
Poor/undifferentiated	1.748 (1.285–2.378)	<0.001	1.699 (1.247–2.315)	0.001
Unknown	1.232 (0.830–1.828)	0.301	1.104 (0.743–1.640)	0.624
Perineural invasion		<0.001		0.017
–	Reference		Reference	
+	1.681 (1.273–2.219)	<0.001	1.465 (1.103–1.946)	0.008
Unknown	0.862 (0.575–1.292)	0.471	0.884 (0.589–1.326)	0.551
T status		0.098		
T1	Reference			
T2	0.625 (0.199–1.966)	0.422		
T3	1.262 (0.468–3.402)	0.645		
T4	1.432 (0.514–3.988)	0.492		
N status		<0.001		<0.001
N0	Reference		Reference	
N1	1.721 (1.255–2.361)	0.001	1.602 (1.161–2.211)	0.004
N2	2.264 (1.627–3.150)	<0.001	2.280 (1.625–3.199)	<0.001
Number of resected LNs (n=12)		0.167		
<12	Reference			
≥12	0.831 (0.639–1.081)			
Number of resected LNs (n=15)		0.003		<0.001
<15	Reference		Reference	
≥15	0.679 (0.525–0.878)		0.619 (0.476–0.806)	
Metastatic location		0.460		
Liver	Reference			
Lung	0.904 (0.624–1.309)	0.592		
Liver + lung	1.455 (0.866–2.444)	0.156		
Others	1.034 (0.761–1.405)	0.830		

still meaningful and necessary for stage IV rectal cancer patients after receiving preoperative therapy based on the number of resected LNs and N status. This finding might be important in developing viable treatment strategies for patients of the special group despite the unfactored effect of the missing and incomplete clinicopathologic information of patients that would ultimately affect their survival. Given that only few previous studies have discussed the role of lymphadenectomy on the survival outcome of stage IV rectal cancer patients after receiving preoperative therapy, this study provided baseline information and direction for future research in this area.

Nevertheless, this study was limited by several factors. Data bias was inevitable because of its retrospective nature. The SEER database did not record surgery treatment details which could have influenced survival outcomes. The radiotherapy field design and dose were unknown which might influence disease recurrence. In addition, the sequence between chemotherapy and surgery was unknown in the SEER database thereby might influence the selection of enrolled patients. Cognizant to this, large prospective studies should be conducted in the future to verify these results.

Conclusions

Indeed, the number of resected LNs is an important independent prognostic factor that influences the survival outcomes of stage IV rectal cancer patients after receiving preoperative therapy. These patients should have 15 or more LNs resected in this study. Nevertheless, large prospective studies should be conducted to further verify the accuracy of this standard.

Acknowledgments

Footnote

Reporting Checklist: The authors present the study in accordance with the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/jgo-20-175

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.

org/10.21037/jgo-20-175). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The data in the SEER database were publicly available and de-identified thereby no ethics approval was required.

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