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Comparison of Different Nodal Staging in Patients With Locally Advanced Mid-low Rectal Cancer After Long-term Neoadjuvant Chemoradiation Therapy

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Abstract. *Background/Aim: The aim of this study was to compare the ability of different lymph nodal staging systems to predict cancer recurrence in a multicenter European series of patients who underwent proctectomy after neoadjuvant chemoradiotherapy for locally advanced rectal cancer. Patients and Methods: Data on 170 consecutive patients undergoing proctectomy after neoadjuvant therapy for cT3-4 or cN+ rectal adenocarcinoma were retrieved from the European MRI and Rectal Cancer Surgery database. The prognostic role of the number of retrieved and examined nodes, nodal ratio, and log odds of positive lymph nodes (LODDS) was analyzed and compared by receiver operating characteristic curves, Pearson test, and univariate and multivariate analysis. Results: At multivariate analysis, ypN, nodal ratio, and LODDS were all significantly associated with disease-free survival, but LODDS showed the strongest association (hazard ratio(HR)=2.39; 95% confidence interval(CI)=1.05-5.48; p=0.039). Conclusion: LODDS appears to be a useful prognostic indicator in the prediction of disease-free survival of patients undergoing neoadjuvant chemoradiotherapy and proctectomy for locally advanced rectal cancer.*

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Key Words: Log odds of positive lymph nodes, LODDS, rectal cancer, neoadjuvant therapy, nodal ratio, disease-free survival.

Lymph node status is a well-known prognostic factor in patients with rectal cancer, determinant for therapeutic decision-making. In the seventh edition of the International Union Against Cancer (UICC)/American Joint Committee on Cancer (AJCC) Tumor Node Metastasis (TNM) staging system, regional lymph nodes in rectal cancer are classified as N1 [metastasis in 1 (N1a), 2-3 regional lymph nodes (N1b), or tumor deposit (s) in the subserosa, mesentery, or non-peritonealized pericolic or perirectal tissues without regional nodal metastasis (N1c)], and N2 [metastasis in 4-6 (N2a) or ≥7 (N2b) regional lymph nodes] (1, 2). The number of retrieved lymph nodes is also recorded, as it represents the staging accuracy. For optimal staging of colorectal cancer, the analysis of 12 or more lymph nodes is recommended by the AJCC (3). However, after neoadjuvant chemoradiation therapy the number of detected nodes is lower: sampling of 12 lymph nodes is rarely achieved, with only 20% of patients having adequate lymph node sampling (4, 5). Inadequate nodal staging due to sub-optimal surgical dissection, inaccurate pathological examination, or a low number of lymph nodes in the specimen related to patient characteristics, may lead to understaging of the cancer and thus to inappropriate treatment. This phenomenon is referred to as stage migration (6-8).

Local recurrence of locally advanced rectal cancer is reported in approximately 5-20% of patients, and distant recurrence in up to 35% (9). Stratification of patients according to the recurrence risk is important in order to establish adjuvant treatments, intensive follow-up and

prompt detection and management of recurrence. Nodal staging has been reported as one of the most important predictive factors for disease-free survival (DFS) (10).

Efforts to provide a more accurate nodal staging system than the pN parameter of TNM have led to the evaluation of novel nodal staging systems. The lymph nodal ratio (LNR) is defined as the ratio of metastatic to examined lymph nodes. The number of retrieved nodes influences the LNR to a lesser extent than does the number of metastatic nodes (11). However, its utility in node-negative patients is the same as the pN of TNM, as N0 patients are included in the same category, regardless of the number of retrieved nodes.

Log odds of positive nodes (LODDS) are defined as the log of the ratio between the number of positive nodes and the number of negative nodes. LODDS has recently been proposed in the setting of colorectal cancer, with studies supporting the role of LODDS as a significant prognostic factor in patients with colon cancer. LODDS has the advantage of predicting prognosis and allowing stratifying patients with similar pN or nodal ratio. However, few data exist on the role of LODDS in the prediction of recurrence (12-17) and as a prognostic factor for rectal cancer.

Concerning rectal cancer, one study was conducted in the US as a single-institution study and three other studies were based on Chinese databases (18). All these previous studies are concordant in asserting that LODDS is a reliable system for predicting prognosis in patients undergoing proctectomy for rectal cancer, with or without neoadjuvant therapy (19-21). Still, the clinical use of LODDS is limited, probably because of few published reports on this topic and the limitations of previous studies. For instance, data on the accuracy of LODDS in predicting DFS are lacking, and the majority of studies described pooled data of patients with and without neoadjuvant therapy (19-21).

The aim of the present study was to compare the ability of different lymph nodal staging systems to predict cancer recurrence in a multicenter European series of patients who underwent proctectomy after neoadjuvant chemoradiotherapy for locally advanced rectal cancer.

Patients and Methods

All consecutive patients undergoing curative-intent proctectomy after neoadjuvant therapy for cT3-4 or cN+ rectal adenocarcinoma were included. The present study consisted of a retrospective analysis of patients data retrieved from the European MRI and Rectal Cancer Surgery (EuMaRCS) Study Group database (22). The EuMaRCS is a multicenter study group involving four European referral hospitals: Henri Mondor University Hospital of Créteil, France; Doctor Peset University Hospital of Valencia, Spain; Geneva University Hospital of Geneva, Switzerland; and Vall d'Hebron University Hospital of Barcelona, Spain. All participating centers contributed to building a database of patients diagnosed with locally advanced rectal cancer who underwent magnetic resonance imaging (MRI) before and after neoadjuvant chemoradiotherapy between January 2010 and January 2016. The study was conducted in accordance with the ethical principles described in the Declaration of Helsinki. Patients' records were analyzed retrospectively and anonymously. Previous results from this population have been reported concerning restaging MRI and pelvimetry (23).

All patients had histologically proven, locally advanced (1) mid or low rectal cancer (up to 12 cm from the anal verge), and had completed a long-course neoadjuvant chemoradiotherapy with a total radiation dose of 45-50.4 Gy delivered in daily fractions of 1.8-2 Gy over a 5- to 6-week period combined with 5-fluorouracil or capecitabine (Xeloda) (24). All patients were evaluated by pretreatment and restaging MRI after neoadjuvant therapy (25). Surgery consisted in elective 'up-to-down' laparoscopic anterior resection with total mesorectal excision (TME) (26, 27), low Hartmann procedure with TME, or laparoscopic abdominoperineal resection.

Indications for radiochemotherapy were cT3-4 tumors and N+ tumors at preoperative staging. Routine lymphoadenectomy included ligation of the inferior mesenteric vein below the inferior aspect of the pancreas and inferior mesenteric artery ligation at 1-1.5 cm from the aorta. All procedures were carried out by senior colorectal surgeons experienced in minimally invasive surgery. Tumor stage was coded according to the TNM system, as described in the seventh edition UICC/AJCC; lymph node

Table I. *Clinicopathological data and univariate disease-free survival (DFS) analysis results of 170 patients undergoing proctectomy for rectal cancer after neoadjuvant radio-chemotherapy.*

Variable	Patients with recurrence (n=34), n (%)	Patients without recurrence (n=136), n (%)	Median DFS (months)	*p*-Value*
Age				
<65 Years	21 (61.8)	86 (63.2)	21.2	0.560
≥65 Years	13 (38.2)	50 (36.8)	13	
Gender				
Male	23 (67.6)	86 (63.2)	17	0.406
Female	11 (32.4)	50 (36.8)	22.7	
BMI				
<30 kg/m^2	29 (85.3)	109 (80.1)	18	0.492
≥30 kg/m^2	5 (14.7)	27 (19.9)	20.5	
Preoperative CEA				
<5 U/ml	17 (50)	103 (75.7)	20	0.003
≥5 U/ml	17 (50)	33 (24.3)	16.45	
LNR				
LNR1	14 (41.2)	109 (80.1)	21.3	>0.0001
LNR2	6 (17.6)	10 (7.4)	16.5	
LNR3	14 (41.2)	17 (12.5)	9	
LODDS				
LODDS1	20 (58.8)	118 (86.8)	20.5	>0.0001
LODDS2	3 (8.8)	9 (6.6)	14.5	
LODDS3	11 (32.4)	9 (6.6)	9	

BMI: Body mass index; CEA: carcinoembryonic antigen; LNR: lymph node ratio; LODDS: log odds of positive lymph nodes. *Log-rank univariate analysis.

Table II. *Multivariate analyses of prognostic factors for disease-free survival by Cox proportional hazard method.*

Variable	Model 1			Model 2			Model 3		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
CEA >5 U/ml	3.02	1.4-6.50	0.005	2.63	1.33-5.22	0.005	2.51	1.26-4.98	0.009
LV invasion	1.09	0.37-3.23	0.871	1.05	0.35-3.12	0.935	1.10	0.38-3.17	0.849
Perineural invasion	1.36	0.62-2.98	0.436	1.49	0.70-3.19	0.296	1.62	0.77-3.42	0.198
Tumor deposits	2.18	1.04-4.57	0.038	2.13	1.01-4.49	0.045	2.57	1.25-5.29	0.010
ypT≥3 stage	5.77	1.89-17.62	0.002	6.18	2.04-18.74	0.001	8.13	2.76-23.94	<0.001
Resection margin (R1)	2.82	1.26-6.28	0.011	2.87	1.30-6.34	0.009	2.44	1.13-5.26	0.023
ypN stage	2.23	1.01-4.93	0.046	-	-	-	-	-	-
LNR	-	-	-	1.58	1.04-2.39	0.032	-	-	-
LODDS	-	-	-	-	-	-	2.39	1.05-5.48	0.039

CEA: Carcinoembryonic antigen; CI: confidence intervaI; HR: hazard ratio; LV: lymphovascular; ypT: tumor stage after neoadjuvant therapy; ypN: nodal stage after neoadjuvant therapy; LNR: lymph node ratio; LODDS: log odds of positive lymph nodes.

dissection was considered adequate when at least 12 lymph nodes had been examined. The LNR was defined as the ratio between the number of positive nodes and the total number of lymph nodes examined. Reviewing the previous literature, we chose a system of classification of already validated by Fang *et al*. (14). Three categories of LNR were created based on the following cut-off values: LNR1, ratio <0.10; LNR2, ratio=0.10-0.33; and LNR3, ratio ≥0.34.

LODDS were classified as the logarithm of the ratio between the probability of a node being positive and the probability of a node being negative when the lymph node was harvested. LODDS were estimated by $log\ (pnod + 0.5)/(tnod\text{-}pnod+0.5)$, where *pnod* was the number of positive nodes and *tnod* the total number of examined nodes, and 0.5 is added to both the numerator and the denominator to avoid an infinite number. Cut-offs of LODDS were defined using the classification validated by Fang and colleagues (14). Values of LODDS were classified as follows: LODDS 1: <0.82; LODDS 2: –0.82≤ LODDS <–0.57; LODDS 3: ≥–0.57.

After multidisciplinary discussion, postoperative adjuvant chemotherapy was administered to patients with nodal metastases or ypT3-4 tumors with histologically aggressive characteristics (vascular emboli, perineural invasion). Postoperative complications were reported according to Clavien–Dindo classification (30). All patients were followed up every 3 months in the first 2 years and every 6 months thereafter. Follow-up visits consisted of physical examination, blood tests including tumor markers, computed tomographic scan every 6 months, colonoscopy/rectoscopy at 3 years. The study was conducted in accordance with the ethical principles described in the Declaration of Helsinki.

Statistical analysis. Clinicopathological and follow-up data for each patient were collected in a computerized database by each center, regularly updated for tumor recurrence and survival status, and retrospectively reviewed. Univariate and multivariate analyses were applied to evaluate the prognostic role of clinicopathological variables. Multivariate analysis was performed with the Cox proportional hazard method. Scatter plots of the relationship between LODDS and the number or the ratio of nodal metastases were plotted. Overall survival rates, according to ypN, LNR, and LODDS classifications were evaluated and compared.

Statistical analyses were performed using the SPSS (Statistical Package for Social Science, IBM SPSS Statistics, Version 23 for Macintosh; IBM Corp., Armonk, NY, USA). Group differences were evaluated using *t*-test for continuous variables, chi-square test or Fisher's exact test for categorical variables. Survival was estimated using the Kaplan–Meier method. Differences were assessed by means of the log-rank test. Survival was defined as the time from surgery to disease-related death and censored at the last follow-up date if no events had occurred. DFS was defined as the time from surgery to disease recurrence and censored at the last follow-up date if no events had occurred.

The accuracy of the prognosis assessment of each nodal staging method was compared using the receiver operating characteristic curve (ROC) and the area under the curve (AUC). The correlations between the number of retrieved lymph nodes, number of metastatic lymph nodes, LNR, and LODDS were calculated by the Pearson correlation coefficient. Statistical significance was conventionally defined as $p<0.05$.

Results

Overall 170 patients were included, with a median age of 61 years (range=27-86 years); 109 (64.1%) were males and 61 (35.9%) were females. The overall median follow-up period was 25.01 months (SD=18.53). Laparoscopic anterior resection with TME with primary anastomosis was performed in 136 patients, low Hartmann procedure with TME in 13, and abdominoperineal resection in 21. Conversion to laparotomy occurred in 6.5% of cases. Twenty-two patients experienced Clavien–Dindo III-IV complications (30). The overall median number of retrieved lymph nodes was 13 (range=3-30) and the median number of metastatic lymph nodes in node-positive patients was two (range=1-22).

Clinicopathological data of 170 patients who underwent laparoscopic proctectomy for rectal cancer after neoadjuvant radiochemotherapy are shown in Table I, according to the occurrence of tumor recurrence during the follow-up. At the univariate analysis, no significant association was found

Table III. *Pearson correlation test between number of retrieved lymph nodes and metastatic nodes, nodal stage after neoadjuvant therapy (ypN), lymph node ratio (LNR), log odds of positive lymph nodes (LODDS).*

	Correlation between the number of retrieved lymph nodes			
	No. of positive lymph nodes	ypN stage	LNR	LODDS
Sample size (n)	170	170	170	170
Correlation coefficient r	0.262	0.210	0.174	−0.181
95% CI for r	0.119-0.391	0.59-0.347	0.020-0.312	−0.391-−0.001
Significance level	0.001	0.006	0.023	0.018

CI: Confidence intervaI.

between cancer recurrence and age, sex, obesity, tumor grading, administration of adjuvant chemotherapy. Univariate analysis identified ypN, LNR and LODDS among the significant predictive factors for DFS, whereas the number of retrieved nodes had no prognostic impact. Other significant predictive factors were preoperative carcinoembryonic antigen (CEA), presence of lymphovascular invasion, perineural invasion, tumor deposits, T-stage and resection margins. At the multivariate analysis, LODDS was found to have the highest hazard ratio (HR=2.39) among the nodal prognostic factors for DFS (Table II). LODDS, ypN and LNR were all significantly associated with DFS. In Figure 1, DFS according to ypN staging is reported, whereas Figure 2 reports DFS according to LNR. Figure 3 shows DFS curves according to LODDS categories. Higher categories of ypN, LNR and LODDS were associated with worse DFS rates. In Figure 4, the ROC curves for ypN, nodal ratio and LODDS are shown. In Table III, the results of the Pearson correlation test between the number of retrieved lymph nodes and the number of metastatic nodes, ypN, LNR, LODDS are reported. All parameters were found to be significantly correlated with the number of retrieved nodes, but LODDS showed a weak negative correlation.

In Figure 5A, the scatter plot distribution of LNR and the number of positive lymph nodes shows that patients with an equal number of positive lymph nodes had different LNRs. In Figure 5B, the scatter plot distribution of LODDS and LNR demonstrates that LODDS permits stratification of patients with the same LNR: for example, patients with LNR of 0 are further stratified by LODDS, which is able to distinguish different prognostic categories even in cases with the same LNR.

Discussion

The evaluation of nodal metastases represents a key factor in assessing prognosis and defining management of patients with rectal cancer. In the absence of distant metastases, the presence of nodal metastases represents an indication for pre-operative/postoperative radiochemotherapy, and is an important determinant of prognosis. The UICC/AJCC staging system stratifies the nodal staging, namely pN, according to the number of metastatic nodes (1). However, this staging system is highly dependent on the number of retrieved nodes, which represents one of its major flaws. Indeed, in the setting of rectal cancer treated with neoadjuvant chemoradiotherapy, adequate sampling of more than 12 lymph nodes is achieved in a minority of cases according to previous studies (4, 5). Thus, this group of patients is particularly exposed to the phenomenon of stage migration, and potentially to understaging and undertreatment. Furthermore, it should be kept in mind that the number of retrieved nodes strongly depends on the accuracy of lymphadenectomy and the pathological examination.

The LNR represents a simple method for nodal staging that is less influenced than the pN by the number of retrieved nodes. A few studies have shown the strong ability of the LNR to predict prognosis in patients with rectal cancer treated by neoadjuvant therapy and surgery (11, 31). However, it is unable to stratify patients without nodal metastases, like pN, and it cannot differentiate patients who had 100% metastatic nodes according to the number of retrieved nodes (they will all have LNR=1).

LODDS is a new nodal staging system, which was developed to improve the accuracy of the prognostic assessment. LODDS represents a function of the number of negative nodes, unlike the LNR, which may be regarded as a function of the number of retrieved nodes. LODDS has some theoretical statistical advantages comparing to nodal ratio, as well described by Wang *et al*. (17). One is the ability to differentiate patients with the same nodal ratio of 0 or 1 (for example, patients with 0/4 metastatic nodes from those with 0/40 metastatic nodes; or those with 4/4 metastatic nodes *versus* those with 40/40 metastatic nodes). The role of LODDS has been increasingly investigated for different types of cancer, with the majority of studies confirming its relevance in predicting prognosis (32-34).

In the setting of rectal cancer, three population studies on national databases (19-21) and one single-center report (18) have been published. Their findings are concordant that

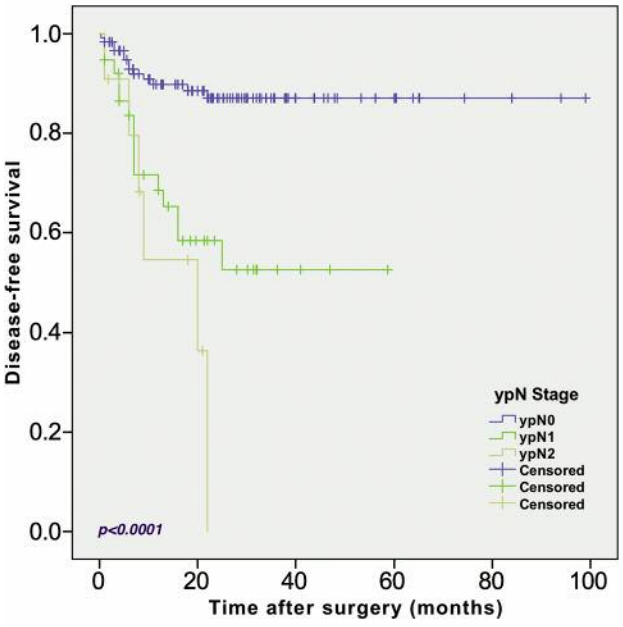

Figure 1. *Disease-free survival according to nodal stage after neoadjuvant therapy (ypN stage).*

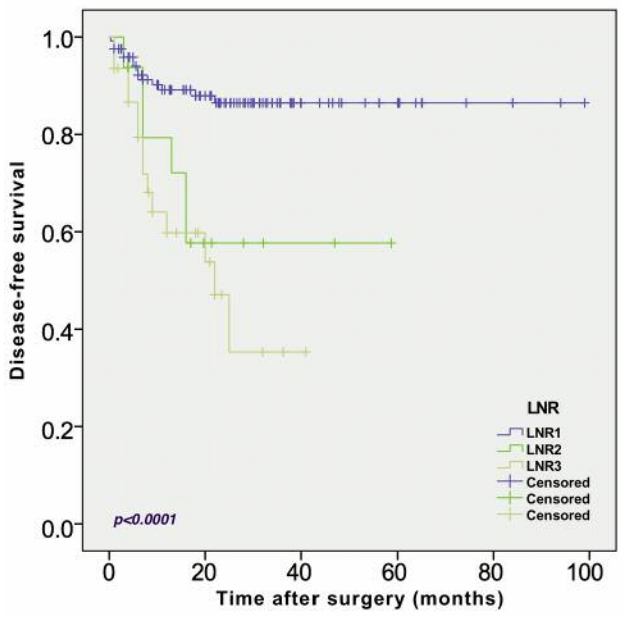

Figure 2. *Disease-free survival according to lymph node ratio (LNR) classes. Three categories of LNR were created based on the following cut-off values: LNR1, ratio <0.10; LNR2, ratio=0.10-0.33; and LNR3, ratio ≥0.34.*

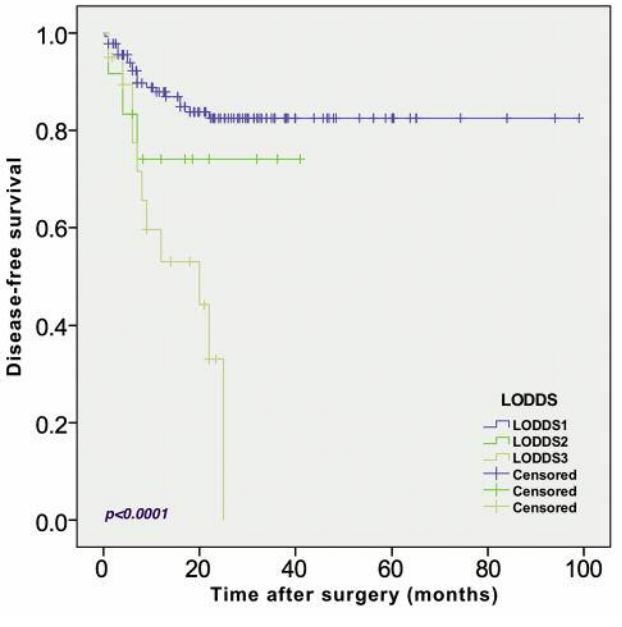

Figure 3. *Disease-free survival according to log odds of positive lymph nodes (LODDS) classes. Cut-offs of LODDS were defined using the classification validated by Fang and colleagues (14). Values of LODDS were classified as follows: 1) LODDS <–0.82; 2) –0.82≤ LODDS <–0.57; 3) LODDS ≥–0.57.*

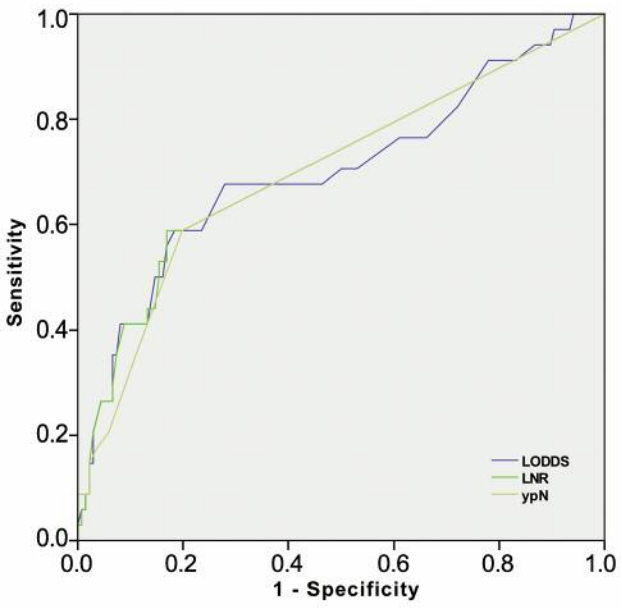

Figure 4. *Receiver operating characteristic curves for TNM nodal stage after neoadjuvant therapy (ypN), lymph node ratio (LNR) and log odds of positive lymph nodes (LODDS).*

LODDS has a strong prognostic ability. Furthermore, superior power of discrimination to predict survival of yp-LODDS over yp-LNR was shown (20). Some limits of these studies should, however, be highlighted. Three of them were population-based studies, which represents an advantage in terms of the number of enrolled patients, but a flaw in terms

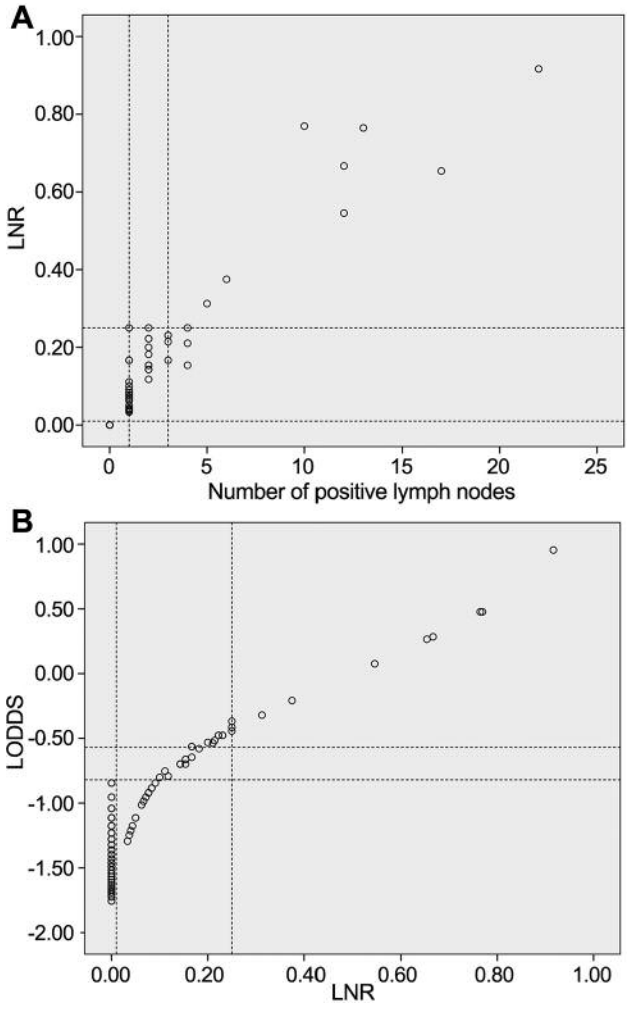

Figure 5. *Scatter plot of the relationship between lymph node ratio (LNR) and the number of positive lymph nodes (A) and log odds of positive lymph nodes (LODDS) (B).*

of the quality of data. Indeed, retrieval of specific information concerning other prognostic factors may be more difficult because it depends on the completeness of the databases, and, more importantly, protocols of treatments, surgical procedures, accuracy in retrieving lymph nodes, are likely to be heterogeneous, given the high number of centers included in the analysis. The study by Lee *et al.* (18), on the other hand, was at a single institution, which guarantees higher data homogeneity. However, in this series, patients who underwent proctectomy without neoadjuvant treatment were also included.

Our study was on a multicenter European series of patients undergoing neoadjuvant therapy and proctectomy for AJCC stage I-IIIc rectal cancer. Protocols of treatment, quality of surgery and nodal retrieval were homogeneous, as all the centers are tertiary referral centers for rectal cancer and followed the same protocols of treatment. In particular, our analysis focused on the ability of LODDS to predict recurrence, which is a less studied aspect, although fundamental in the setting of rectal cancer for both follow-up and treatment purposes. In our patient population, standard lymphadenectomy was performed with ligation of the superior mesenteric artery at 1-1.5 cm from the aorta and ligation of the inferior mesenteric vein at the origin. The mean number of retrieved lymph nodes was 13, which is an indicator of the quality of surgery and pathological examination. The 3-year DFS rate was 72.5% with more than a quarter of patients having recurrence in the first 3 years, highlighting the need for efficient predictive systems. The univariate analysis showed several prognostic factors for DFS, including ypN, LNR and LODDS, whereas the number of retrieved nodes had no prognostic impact. In multiple models for multivariate analysis, LODDS had the highest HR value among the nodal prognostic factors of DFS. Moreover, LODDS was the nodal staging system with a weak, although significant, negative correlation with the number of retrieved nodes. Finally, the scatter plots of the relationship between LODDS and LNR well demonstrated the ability of LODDS to discriminate patients with the same LNR but different prognoses. Thus, even if both LNR and LODDS were found to be significant prognostic factors at multivariate analysis, LODDS appears to be more efficient at discriminating among patients with the same LNR classification with different prognoses, particularly those whose ratio of node metastasis is 0 or 1, as was found by Fang *et al.* (14).

The present retrospective study has strengths and limitations. We analyzed a homogeneous population of patients with locally advanced rectal cancer who received neoadjuvant chemoradiation therapy; we focused on the prediction of cancer recurrence, which, to our knowledge, has not yet been evaluated from European databases. Furthermore, the participating centers were tertiary referral centers for the treatment of rectal cancer, with standardized surgical procedures and pathological analysis, which may also explain the median number of 13 retrieved lymph nodes. Limitations include the number of included patients, which is relatively small compared with population-based studies, and the median follow-up period, which is not long enough to conclude about the prognostic role of LODDS in long-term survival but largely sufficient for our purpose, the analysis of DFS.

Conclusion

The study demonstrated that LODDS is a useful and discriminative prognostic indicator of DFS in patients undergoing neoadjuvant chemoradiotherapy and proctectomy for locally advanced rectal cancer. LODDS is less influenced

by the number of retrieved nodes and allows prognostic stratification of patients with LNR approaching 0 or 1. At the multivariate analyses, LODDS had the highest HR for predicting recurrence compared to the other nodal staging systems. For these reasons, LODDS appears to have a clinical utility in patients with rectal cancer treated with neoadjuvant therapy and surgery, and may add significant information to ypN and LNR evaluation, especially in cases with inadequate lymphadenectomy.

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Competing Interests

The Authors declared no competing interests in regard to this study.

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