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Original article

Prognostic impact of log odds of positive lymph nodes (LODDS) in the stratification of patients with rectal cancer

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ABSTRACT

Introduction: The use of the N category of the TNM staging system, lymph node ratio (LNR) and log odds of positive lymph nodes (LODDS) in predicting overall survival (OS) and disease-free survival (DFS) in patients with rectal cancer is still controversial.

Material and methods: A retrospective study of 445 patients with rectal cancer who underwent surgery between 2008 and 2017 in the University Complex Hospital of Vigo was performed. Patients were stratified according to number of lymph nodes examined (NLNE), N staging, LNR and LODDS. The analysis was performed using the log-rank test, Kaplan–Meier functions, Cox regression and ROC curves.

Results: Five-year OS and DFS were 73.7% and 62.5%, respectively. No statistically significant differences were observed depending on NLNE. Increased LNR and LODDS were associated with shorter OS and DFS, independently of NLNE.

Multivariate analysis showed that N stage, LNR and LODDS were independently associated with OS and DFS; however, the LODDS system obtained the best area under the curve, with greater predictive capacity for OS (AUC: 0.679) and DFS (AUC: 0.711).

Conclusion: LODDS and LNR give prognostic information that is not related to NLNE. LODDS provides better prognostic accuracy in patients with negative nodes than LNR and N stage.

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Impacto pronóstico del Log Odds de ganglios linfáticos positivos (LODDS) en la estratificación de pacientes con cáncer de recto

Palabras clave:
Cáncer de recto
Estadificación
Afectación ganglionar
N
CGL
LODDS
Supervivencia

RESUMEN

Introducción: La utilidad de la estadificación N del sistema TNM, el cociente de ganglios linfáticos (CGL) y el logaritmo de probabilidades de ganglios linfáticos positivos (LODDS) para predecir la supervivencia global (SG) y la supervivencia libre de enfermedad (SLE) en pacientes con cáncer de recto es aún controvertida.

Material métodos: Se realizó un estudio de cohortes retrospectivo con pacientes intervenidos por cáncer de recto entre 2008 y 2017 en el Complejo Hospitalario Universitario de Vigo. Los pacientes se estratificaron en subgrupos de acuerdo al número de ganglios examinados (NGE), estadificación N del sistema TNM, punto de corte CGL y punto de corte LODDS. Se realizó un análisis mediante Log-Rank test, curvas de Kaplan-Meier, regresión de Cox y curvas ROC.

Resultados: Se incluyeron 445 pacientes. La SG y la SLE, a 5 años, fue de 73.7% y 62.5%, respectivamente. No se encontraron diferencias estadísticamente significativas en la supervivencia según el NGE. A medida que se incrementa el valor de CGL y LODDS disminuye significativamente la SG y la SLE, independientemente del NGE.

En el análisis multivariante la estadificación N, el CGL y el LODDS se mostraron como factores independientes de la SG y SLE; pero el sistema LODDS obtuvo la mejor área bajo la curva, con mayor capacidad predictiva para la SG (ABC: 0.679) y SLE (ABC: 0.711).

Conclusión: LODDS y CGL proporcionan información pronóstica independientemente del NGE. LODDS proporciona un rendimiento predictivo más preciso en los pacientes con ganglios negativos que el CGL y la estadificación N.

Introduction

The number of metastatic lymph nodes (MLN) is a significant prognostic factor associated with survival in patients with colorectal cancer (CRC).[1]

It has been established that at least 12 lymph nodes should be evaluated for safe staging.[2] However, while most scientific societies recommend this cut-off,[3] many series do not follow this recommendation. In some, less than 40% of patients have ≥12 lymph nodes examined.[4]

To overcome the dependence on the number of lymph nodes resected and analyzed, a staging system called the lymph node ratio (LNR) was proposed, which is defined as the quotient obtained from dividing MLN/LNR.[5]

Another system, the log odds of positive lymph nodes (LODDS), defined as the logarithm between the probability of a node being positive and a node being negative when analyzed, has been shown to be useful in reducing the risk of stage migration in gastric, breast, colon and pancreatic cancer. It is calculated using the formula ''log (NPLN + 0.5)/(NDLN − NPLN + 0.5)'', where NPLN is the MLN and NDLN is the total number of dissected lymph nodes. The number ''0.5'' appears twice to avoid results tending to infinity.[4] This has shown a significant predictive impact in stage III colon cancer,[6] but few researchers have applied it to rectal cancer.

The aim of this study is to examine the prognostic reliability of the N, CGD and LODDS systems in terms of survival for patients undergoing resection for rectal cancer. Our objective was to evaluate the efficacy of these systems to differentiate prognoses within the same tumor category, thereby allowing us to more accurately identify patients at higher risk.

Methods

Ours is a retrospective, single-center, observational cohort study of patients diagnosed with adenocarcinoma located ≤15 cm from the anal margin from 2008 to 2017. Patients with synchronous tumors, local resection, R2 resection, stage IV disease, loss to follow-up or deaths during admission were excluded.

We analyzed: sex, age, ASA, neoadjuvant therapy (CRTn), vascular involvement (VI), lymphatic involvement (LI), perineural involvement (PNI), circumferential resection margin (CRM), NLNE, and staging (p/ypT, p/ypN, LNR and LODDS).

We calculated the cut-off point for the LNR group using the mean of all patients with LNR > 0, classifying them into 3 subgroups: LNR0: LNR = 0; LNR1 (low): LNR > 0 and ≤0.238; LNR2 (high): LNR > 0.238.

We calculated LODDS for each patient, who were divided into 3 subgroups by tertiles: LODDS 0: LODDS ≤1.362; LODDS 1: LODDS ≥1.362 and ≤0.854; LODDS 2: LODDS > 0.854.

We used the Kaplan–Meier estimator, making comparisons using log-rank between subgroups. For the multivariate analysis, we used Cox regression to determine the effect of lymph node staging systems on 5-year OS and DFS.

In order to avoid collinearity within the same multivariate model and to identify the classification best related to the prognosis, models were created for each of the staging systems. Model A included all factors that were significant in the univariate analysis and the N classification, excluding

LNR and LODDS. Model B included the LNR classification, but not LODDS. In Model 3, all 3 classifications were included.

The predictive capacity of OS and DFS was evaluated using the area under the curve (AUC) value.

We stratified the N, LNR and LODDS systems and their relationship with the NLNE (high ≥12 or low <12) to try to identify prognostic subgroups.

OS and DFS refer to the time, in months, from surgery to death or until the last check-up and from surgery to the diagnosis of recurrence, respectively.

We performed the statistical analysis with the SPSS 25.0 program for Windows. *P*-values <0.05 were considered statistically significant.

Results

Clinicopathological characteristics

Among the 653 patients diagnosed, 445 (68.15%) underwent elective surgery with curative intent (Supplementary material 1).

The study included 183 women (41.1%). Mean age was 68.4 years (range 25–90). We identified inadequate or low NLNE (<12) in 205 patients (46.1%).

In total, 167 patients (37.5%) received CRTn. Mean NLNE was 13.1, which was higher in patients who did not receive CRTn (14.5 vs 10.6, *P* = 0.001). The percentage of patients with NLNE <12 was higher in patients who received CRTn (61.7% vs 38.3%, *P* < 0.001).

When the NLNE was ≥12, the percentage of patients with affected lymph nodes was lower if they had received CRTn (23.4% vs 29.1%, *P* = 0.304) but significantly higher with surgery alone (48.3% vs 23.5, P < 0.001) (Table 1).

The overall 5-year mortality rate was 26.1%.

The clinical-histopathological characteristics and univariate and multivariate analyses are reflected in Tables 2 and 3.

Staging systems and survival

OS and DFS were 73.7% and 62.5%, respectively. There were no significant differences between patients with NLNE < 12 or ≥12 (71.7% vs 75.14, *P* = 0.346; and 63.9 vs 69.1, *P* = 0.308).

In the N0, N1, and N2 subgroups, OS rates were 78.8%, 60.7%, and 52.5%, respectively. OS rates for the LNR0, LNR1, LNR2 LODDS 0, LODDS 1 and LODDS 2 subgroups were 78.9%, 60.7%, 53.2%, 84.7%, 71.9% and 57%, respectively. Independent risk factors for the N1 and N2 subgroups were: HR 1.83 (1.09–3.08, *P* = 0.023) and HR 1.82 (1.04–3.19, *P* = 0.036); LNR2 subgroup: HR 2.16 (1.25–3.76, *P* = 0.006) and LODDS 1 subgroups: HR 1.91 (1.07–3.41, *P* = 0.029) and LODDS2: HR 2.62 (1.48–4.65, *P* = 0.001).

DFS rates were 76.8%, 53% and 41.6% for the N0, N1 and N2 subgroups, respectively. In the LNR0, LNR1 and LNR2 subgroups, the rates were 76.8%, 57.9% and 38.1% and 82.3%, 70.9% and 47.9% for the LODDS0, LODDS 1 and LODDS 2 subgroups, respectively. The 3 systems were shown to be independent prognostic factors for DFS: N1 with an HR of 2.83 (1.77–4.53, *P* < 0.001), N2 HR 2.89 (1.71–4.87, *P* < 0.001), LNR1 HR 2.46 (1.49–4.06, *P* < 0.001), LNR2 HR 3.48 (2.09–5.81, *P* < 0.001), LODDS1 HR 2.57 (1.43–4.62, *P* = 0.002) and LODDS 2 HR 4.51 (2.53–8.03, *P* < 0.001).

OS and DFS decrease with increasing MLN (N0–N2, *P* < 0.001) and as LNR and LODDS values increase (LNR0–LNR2, *P* < 0.001) (LODDS0–LODDS2, *P* < 0.001) (Fig. 1).

The 3 systems were identified as independent predictors of OS and DFS. LODDS showed a significantly higher predictive capacity for OS (AUC: 0.679; 95% CI 0.612-0.728) and DFS (AUC: 0.711; 95% CI, 0.659-0.763), with *P* = .022, *P* = .034 and *P* = .022, *P* = .007 for the N and LNR systems, respectively (Table 4) (Fig. 2).

Subgroup stratification

Table 5 shows the OS and DFS of the LNR and LODDS subgroups, stratified according to NLNE and p/ypN staging.

With increasing LNR value, OS decreases, regardless of NLNE < 12 (= 0.019) or ≥12 (*P* < 0.001). The LNR subgroups discriminated different percentages of OS but showed no statistical significance between N1 (*P* = 0.504) and N2 (*P* = 0.752) patients.

The OS of N0 patients was 84.7%, 74% and 61.7% in patients from the LODDS0, LODDS 1 and LODDS 2 subgroups (*P* = 0.023), respectively. The LODDS value discriminated the percentages of OS, although it showed no statistical significance in patients N1 (*P* = 0.609) and N2 (*P* = 0.555).

As the LNR value increases, the DFS decreases regardless of NLNE < 12 (*P* < 0.001) or ≥12 (*P* < 0.001). As the LODDS value increases, the DFS decreases regardless of an NLNE < 12 (*P* = 0.001) or ≥12 (*P* < 0.001).

Comparing the p/ypN1 and p/ypN2 patients of the LNR2 (high) and LNR1 (low) subgroups using a cut-off point of 0.238, we found that the former had worse DFS (*P* = 0.047 and *P* = 0.049, respectively). There were no differences between the LNR2 p/ypN1 and y/pN2 subgroups in OS (*P* = 0.793) and DFS (*P* = 0.828).

DFS was higher in patients with stage p/ypN0 and LODDS0 disease (82.3%) than N0-LODDS1 (72.1%) (*P* = 0.038) and N0-LODDS2 (65.5%) (*P* = 0.039) patients. LODDS 1 and LODDS 2 discriminated different survival rates in high-risk patients (N1 and N2), but with no statistical significance (*P* = 0.181 and *P* = 0.955, respectively)

OS was higher in LODDS0-LNR0 patients (84.7%) than in LODDS1-LNR0 (74.1%) and LODDS2-LNR0 (57.9%) patients (*P* = 0.025 and *P* = 0.018, respectively).

The DFS analysis showed no significant differences between patients with LNR0 and LNR1 in the LODDS1 subgroup (*P* = 0.338), nor between patients with LNR0, LNR1 and LNR2 in the LODDS2 subgroup (*P* = 0.066). In LNR0 patients, the DFS of the LODDS0 subgroup (82.3%) was higher

Table 1 – Lymph node involvement according to the number of resected lymph nodes and option to administer neoadjuvant therapy.

N+			No CRTn N+ (%)		CRTn N+ (%)	
NLNE	n	N+ (%)	n	N+ (%)	n	N+ (%)
<12	205	54 (26.3)	102	24 (23.5%)	103	30 (29.1%)
≥12	240	100 (41.7)	176	85 (48.3%)	64	15 (23.4%)
P value		<0.001		<0.001		0.304

Table 2 – Univariate analysis of overall survival and disease-free survival.

Variable	n	SG (%)	HR (95%CI), P	DFS (%)	HR (95%CI), P
Sex					
Female	183	77.6	Reference	65.6	Reference
Male	262	70.9	1.33 (0.91–1.94), 0.147	60.3	1.14 (0.83–1.56), 0.412
Age (y)					
<70	235	82.9	Reference	69.4	Reference
≥70	210	63.3	2.59 (1.76–3.79), <0.001	54.7	1.62 (1.19–2.20), 0.002
ASA					
I–II	254	83.8	Reference	73.2	Reference
III–IV	191	60.2	3.00 (2.05–4.39), <0.001	48.1	2.37 (1.74–3.23), <0.001
Neoadjuvant CRT					
No	278	73.9	Reference	59.7	Reference
Yes	167	81.4	1.46 (0.83–2.57), 0.194	67.9	0.87 (0.43–1.68), 0.613
VI					
Yes	83	59.8	1.97 (1.31–2.94), 0.001	54.4	1.54 (1.08–2.21), 0.018
No	362	76.9	Reference	67.9	Reference
LI					
Yes	99	61.6	1.96 (1.33–2.89), 0.001	53.5	1.50 (1.07–2.11), 0.019
No	346	77.2	Reference	65.0	Reference
PN					
Yes	66	53.8	2.31 (1.53–3.51), <0.001	41.9	2.16 (1.50–3.10), <0.001
No	379	77.2	Reference	66.1	Reference
CRM+					
Yes	42	46.5	3.06 (1.94–4.83), <0.001	34.9	2.72 (1.81–4.08), <0.001
No	403	76.6	Reference	65.4	Reference
p/ypT					
T0–2	198	83.3	Reference	72.2	Reference
T3–4	247	65.9	2.32 (1.71–3.61), 0.001	54.6	2.88 (1.18–7.04), 0.001
NLNE					
<12	205	71.7	Reference	63.9	Reference
≥12	240	75.4	0.93 (0.65–1.34), 0.705	69.1	0.90 (0.66–1.22), 0.496
p/ypN					
0	291	78.8	Reference	76.8	Reference
1	88	60.7	2.04 (1.31–3.17), 0.002	53.0	1.97 (1.36–2.84), <0.001
2	66	52.5	2.84 (1.82–4.44), <0.001	41.6	2.64 (1.81–3.87), <0.001
LNR					
0	291	78.9	Reference	76.8	Reference
1	78	60.7	1.99 (1.25–3.16), 0.004	57.9	1.99 (1.25–3.16), 0.004
2	76	53.2	2.85 (1.86–4.38), <0.001	38.1	2.85 (1.86–4.38), <0.001
LODDS					
0	154	84.7	Reference	82.3	Reference
1	140	71.9	2.06 (1.20–3.54), 0.009	70.9	2.06 (1.20–3.54), 0.009
2	151	57.0	3.44 (2.09–5.66), <0.001	47.9	3.44 (2.09–5.66), <0.001

than that of the LODDS1 subgroup (72.3%) (P = 0.041) and the LODDS2 subgroup (56.3%) (P = 0.015).

Discussion

In this study, both the log odds of positive lymph nodes (LODDS) and the lymph node ratio emerged as crucial independent prognostic factors for survival in patients with rectal cancer, surpassing in importance the number of lymph nodes resected.

The recommendation to analyze at least 12 lymph nodes to ensure correct staging[3] is not fulfilled in all resected specimens. The NLNE will depend on patient-related factors, some of which are unmodifiable, as well as modifiable factors, such as the tumor, use of CRTn, surgical technique and experience of the surgeon and pathologist.[7,8] After its use, an adequate NLNE is not achieved in approximately half of patients, and the percentage of positive lymph nodes collected is controversial.[9–12]

We found a suboptimal NLNE in 46.1% of patients and in 61.7% after CRTn. With surgery alone, the MLN was significantly higher when at least 12 nodes were analyzed. However, this did not occur in patients who received CRTn, confirming (similar to other authors[13,14]) that the use of CRTn decreases the NLNE and the mean number of positive nodes, which could indicate good response to treatment rather than a poor surgical technique or an incorrect histopathological examination.[15,16]

An NLNE ≥ 12 did not significantly improve OS or DFS. Therefore, we suggest that this threshold may be incorrect and should be re-evaluated especially in patients who have been treated with CRTn.[10] However, although the N-stage system significantly discriminates survival between p/ypN0-N+ patients, it has limited capability between p/ypN1–2 patients, and the survival curves of these subgroups are similar.

Table 3 – Multivariate analysis of overall and disease-free survival.

Variable	Overall survival HR (95%CI), P	Disease-free survival HR (95%CI), P
Age (y)		
<70		
≥70	1.574 (0.962–2.577), 0.071	0.936 (0.632–1.385), 0.740
ASA		
I–II		
III–IV	1.626 (1.034–2.557), 0.035	1.577 (1.083–2.293), 0.017
VI		
No		
Yes	1.689 (0.876–3.246), 0.117	1.234 (0.695–2.197), 0.473
LI		
No		
Yes	0.723 (0.383–1.362), 0.316	0.638 (0.361–1.128), 0.123
PNI		
No		
Yes	1.567(0.927–2.645), 0.094	1.558 (1.011–2.403), 0.045
CRM+		
No		
Yes	1.792 (1.002–3.205), 0.049	1.698 (1.046–2.762), 0.032
p/ypT		
T0–2		
T3–4	2.320 (1.202–4.332), 0.007	1.792 (1.149–2.798), 0.006
Model A		
p/ypN		
0		
1	1.83 (1.09–3.08) 0.023	2.83 (1.77– 4.53) < 0.001
2	1.82 (1.04–3.19) 0.036	2.89 (1.71–4.87) < 0.001
Model B		
LNR		
0		
1	1.63 (0.95–2.78) 0.075	2.46 (1.49–4.06) < 0.001
2	2.16 (1.25–3.76) 0.006	3.48 (2.09–5.81) < 0.001
Model C		
LODDS		
0		
1	1.91 (1.07–3.41) 0.029	2.57 (1.43–4.62) 0.002
2	2.62 (1.48–4.65) 0.001	4.51 (2.53–8.03) < 0.001

Table 3. Multivariate analysis. In Models A, B and C, the N-stage, LNR and LODDS classifications are represented separately to avoid collinearity.

LNR is considered an independent prognostic factor of survival since it classifies patients with the same N into different prognostic groups. High LNR is associated with worse OS and DFS, regardless of the NLNE, and has been shown to be very effective even after neoadjuvant treatment.[17,18] Although LNR improves N staging, it has a series of limitations. There is no defined cut-off value, and its reported variability in each study contributes to heterogeneity.[19] For some authors,[5] it loses predictive value when less than 10 nodes are examined; for others, it is independent of the NLNE.[19] Its discriminatory capacity decreases when its value is 0 or 1. When its value is 0, regardless of the NLNE in N0 patients, and when its value is 1, that is, when the NLNE is equal to the MLN, we would potentially be introducing a false prognostic value, and both values of LNR lead to an inevitable risk of stage migration.

We calculated the LNR individually[9] and, after finding the median of the patients with LNR > 0, we divided them into 3 subgroups. Our results indicate that, as the LNR increases, the OS and DFS decrease significantly, regardless of the high or low NLNE group. LNR0 patients and p/ypN0 patients, by definition, have a similar OS and DFS; therefore, the LNR classification does not add prognostic value to patients with negative lymph nodes. Like other authors,[19–21] we can confirm that the LNR significantly discriminates different percentages of DFS in high-risk patients with metastatic lymph nodes and the same p/ypN category, suggesting that it has a higher stratification power than N-staging and could be used in patients with metastatic lymph nodes, in the follow-up strategy, and/or in adjuvant treatment.

LODDS has been identified in several cancers as a prognostic factor with a greater impact on survival than LNR and N-staging.[22,23] In this study, the 3 systems were identified as independent prognostic factors, but LODDS was shown to have a more favorable AUC. Survival was significantly reduced as LODDS values increased. LODDS 2 patients had a risk of 2.62- and 4.41-times worse OS and DFS compared to LODDS 0.

The predictive value of LODDS was independent of NLNE, and its prognostic power is preserved even when NLNE is <12. LODDS 2 patients had worse OS and DFS, regardless of being classified in the high or low NLNE group, and this may indicate that the assignment of these subgroups alone is insufficient to provide

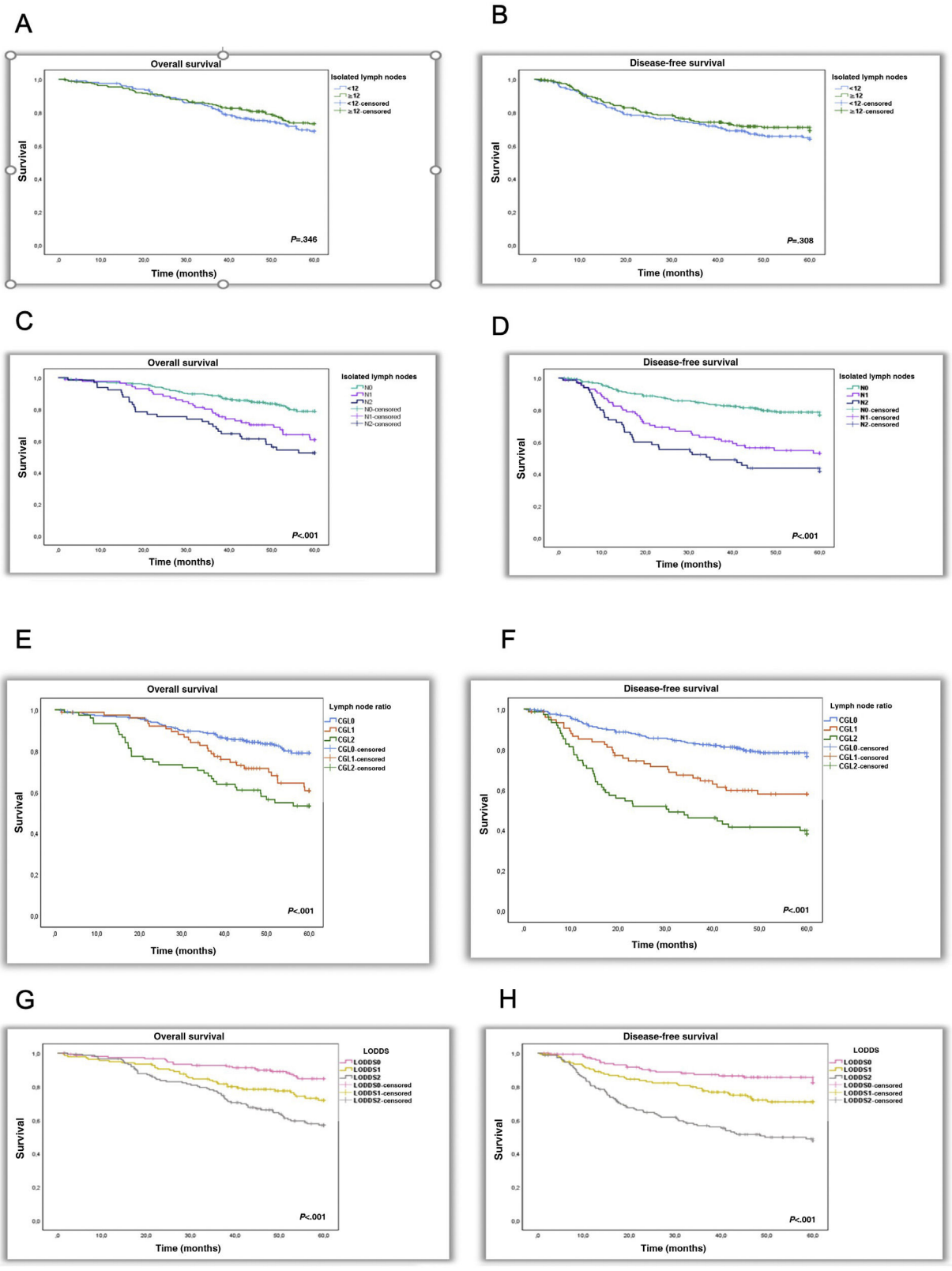

Fig. 1 – Kaplan–Meier estimations with OS and DFS of the staging systems: (A and B) according to NGE; (C and D) according to the N classification of the TNM; (E and F) according to the CGL expressed in tertiles; (G and H) according to LODDS.

Table 4 – Comparison of the area under the curve for overall and disease-free survival among the 3 systems.

Overall survival	AUC (95%CI)	AUC comparison; *P* value		
		p/ypN	LNR	LODDS
p/ypN	0.627 (0.566–0.689)	–		
LNR	0.632 (0.571–0.694)	0.328	–	
LODDS	0.679 (0.612–0.728)	0.022	0.034	–
Disease-free survival				
p/ypN	0.665 (0.602–0.717)	–		
LNR	0.668 (0.611–0.726)	0.075	–	
LODDS	0.711 (0.659–0.763)	0.002	0.007	–

AUC: area under the curve; p/ypN: N stage of the TNM classification; LNR: lymph node rate; LODDS: log odds of positive lymph nodes.

Table 5 – Overall and disease-free survival according to the subgroup stratification.

____ NLNE _____	_____ p/ypN _____	_____ LNR_____					
OS	<12 (%)	≥12 (%)	N0 (%)	N1 (%)	N2 (%)	LNR0 (%)	LNR1 (%)	LNR2 (%)
LNR0	74.7	65.4	78.9					
LNR1	63.3	54.1		61.1	57.1			
LNR2	52.4	53		59.6	51.4			
P value	0.019	<0.001		0.504	0.752			
LODDS0	100	83.4	84.7			84.7		
LODDS1	75.3	66.7	74	63.8	50	74.1	61.2	
LODDS2	54.9	56.7	61.7	59.5	52.8	57.9	60.5	53.2
P value	0.003	<0.001	0.023	0.609	0.555	0.018	0.994	
DFS	<12 (%)	≥12 (%)	N0 (%)	N1 (%)	N2 (%)			
LNR0	71.4	82.2	76.4					
LNR1	49.0	62.9		57.8	57.1			
LNR2	33.7	40.4		36.0	38.5			
P value	<0.001	<0.001		0.047	0.049			
LODDS0	83.9	82.2	82.3			82.3		
LODDS1	72.3	64.9	72.1	67.9	50.0	72.3	64.9	
LODDS2	47.4	47.7	65.5	48.3	41.4	56.3	55.2	38.1
P value	0.001	<0.001	0.039	0.181	0.955	0.015	0.570	

NLNE: number of lymph nodes examined; p/ypN: N stage of the TNM classification; LNR: lymph node ratio; LODDS: log odds of positive lymph nodes. OS and DFS were evaluated after 5 years.

good prognostic information, and it is the LODDS that provides us with this information among patients in the NLNE groups.

Some authors[24] report that LODDS could explain the differences in survival found in the LNR groups. One of its advantages over LNR is that it can differentiate risk subgroups within the N0 category, as well as differentiate risk groups within the N1 and N2 categories.[25]

Our results are consistent with those of Persiani et al.[26] and Li et al.[27] in that, in N0 patients, only LODDS has a predictive performance. LODDS discriminates survival in N0 patients and allows for better stratification than N and LNR in patients who would have been classified as low risk. It delineates different survival rates in individual groups, not only of LNR1–2 and N1–2, but also between patients considered to be low

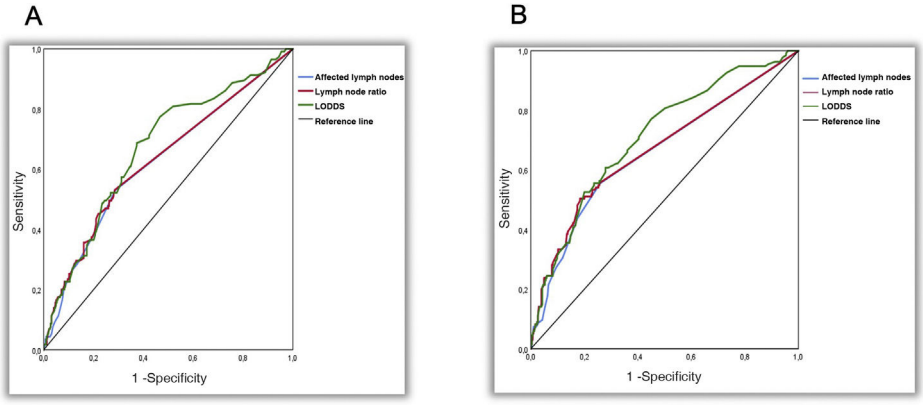

Fig. 2 – ROC curves of the 3 systems: (A) OS; (B) DFS. The lines representing N+ and CGL overlap.

risk. Therefore, like other authors,[9] we believe that LODDS avoids singularities in the case where none or all of the examined nodes are involved, discriminates between patients with negative lymph nodes but with a different number of nodes examined, and minimizes the bias that could occur in other systems.

Similar to the findings of Arslan et al.[28] in colon cancer, we found that N- and LNR-staging do not adequately classify patients with negative lymph nodes. LODDS provides more valuable information than LNR regardless of NLNE and should be included in patients with node-negative rectal cancer.

Although the calculation of LODDS may be performed by any physician, a computer system that automatically calculates LODDS would be a very advantageous tool, thus making its use more feasible in our daily practice.

This study has limitations. The sample is relatively small, and the study is retrospective, based on prospective data collection over a period of 9 years, during which our protocols have not changed substantially, but perioperative care has. Follow-up data were not available for a small percentage of patients lost to the study, making it very unlikely that these missing values caused any sort of bias that would significantly modify our results. Their exclusion from the analysis is the simplest approach to handle these data.

A large, prospective study would be necessary to determine the optimal cut-off point of LODDS and its predictive value in survival.

Conclusions

The results suggest that the predictive value of the LNR and LODDS systems is independent of NLNE, with a significance superior to that of the N-system, especially when the NLNE is <12.

LODDS is superior in low- or high-risk patient groups as a predictor of OS and DFS and provides a more accurate predictive performance in N0 patients than the N and LNR systems.

LODDS identifies high-risk patients who could benefit from closer follow-up or adjuvant treatment.

Ethical considerations

All patients signed an Informed Consent form. The study was conducted in accordance with the Declaration of Helsinki.

According to the ethical requirements of our institution, the use of anonymized data and the prior approval given for use of the database (Viking Project of the AEC) obviated the need for authorization by the Research Ethics Committee.

Funding

Not required.

Conflicts of interest

None.

STROBE declaration

This study adhered to the criteria of the STROBE Declaration[29] (Supplementary material 2).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cireng.2024.09.010.

REFERENCES

1. Compton CC, Greene FL. The staging of colorectal cancer: 2004 and beyond. CA Cancer J Clin. 2004;54:295–308. http://dx.doi.org/10.3322/canjclin.54.6.295.
2. 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. http://dx.doi.org/10.1111/j.1440-1746.1991.tb00867.x.
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 [PMID: 11309435 DOI: 10.1093/jnci/93.8.583].
4. Pei JP, Zhang CD, Fan YC, Dai DQ. Comparison of different lymph node staging systems in patients with resectable colorectal cancer. Front Oncol. 2019;8:671. http://dx.doi.org/10.3389/fonc.2018.00671.
5. Berger AC, Sigurdson ER, LeVoyer T, Hanlon A, Mayer RJ, Macdonald JS, et al. Colon cancer survival is associated with decreasing ratio of metastatic to examined lymph nodes. Clin Oncol. 2005;23:8706–12. http://dx.doi.org/10.1200/JCO.2005.02.8852.
6. Wang J, Hassett JM, Dayton MT, Kulaylat MN. The prognostic superiority of log odds of positive lymph nodes in stage III colon cancer. J Gastrointest Surg. 2008;12:1790–6. http://dx.doi.org/10.1007/s11605-008-0651-3.
7. Mekenkamp LJ, van Krieken JH, Marijnen CA, van de Velde CJ, Nagtegaal ID. Pathology Review Committee and the Co-operative Clinical Investigators. Lymph node retrieval in rectal cancer is dependent on many factors—the role of the tumor, the patient, the surgeon, the radiotherapist, and the pathologist. Am J Surg Pathol. 2009;33:1547–53. http://dx.doi.org/10.1097/PAS.0b013e3181b2e01f.
8. Li Destri G, Di Carlo I, Scilletta R, Scilletta B, Puleo S. Colorectal cancer and lymph nodes: the obsession with the number 12. World J Gastroenterol. 2014;20:1951–60. http://dx.doi.org/10.3748/wjg.v20.i8.1951.
9. Lee CW, Wilkinson KH, Sheka AC, Leverson GE, Kennedy GD. The log odds of positive lymph nodes stratifies and predicts survival of high-risk individuals among stage III rectal cancer patients. Oncologist. 2016;21:425–32. http://dx.doi.org/10.1634/theoncologist.2015-0441.
10. Lin Z, Li X, Song J, Zheng R, Chen C, Li A, Xu B. The effect of lymph node harvest on prognosis in locally advanced middle-low rectal cancer after neoadjuvant chemoradiotherapy. Front Oncol. 2022;15:816485. http://dx.doi.org/10.3389/fonc.2022.816485.
11. Hamza A, Sakhi R, Khawar S, Alrajjal A, Edens J, Khurram MS, et al. Role of ''second look'' lymph node search in

harvesting optimal number of lymph nodes for staging of colorectal carcinoma. Gastroenterol Res Pract. 2018;1985031. http://dx.doi.org/10.1155/2018/1985031.
12. Billakanti R, Seshadri RA, Soma S, Makineni H, Sundersingh S. Lymph node harvest after neoadjuvant treatment for rectal cancer and its impact on oncological outcomes. Indian J Surg Oncol. 2020;11:692–8. http://dx.doi.org/10.1007/s13193-020-01162-y.
13. Rullier A, Laurent C, Capdepont M, Vendrely V, Belleannée G, Bioulac-Sage P, et al. Lymph nodes after preoperative chemoradiotherapy for rectal carcinoma: number, status, and impact on survival. Am J Surg Pathol. 2008;32:45–50. http://dx.doi.org/10.1097/PAS.0b013e3180dc92ab.
14. Doll D, Gertler R, Maak M, Friederichs J, Becker K, Geinitz H, et al. Reduced lymph node yield in rectal carcinoma specimen after neoadjuvant radiochemotherapy has no prognostic relevance. World J Surg. 2009;33:340–7. http://dx.doi.org/10.1007/s00268-008-9838-8.
15. Gurawalia J, Dev K, Nayak SP, Kurpad V, Pandey A. Less than 12 lymph nodes in the surgical specimen after neoadjuvantm chemo-radiotherapy: an indicator of tumor regression in locally advanced rectal cancer? J Gastrointest Oncol. 2016;7:946–57. http://dx.doi.org/10.21037/jgo.2016.09.03.
16. Destri GL, Maugeri A, Ramistelle A, La Greca G, Conti P, Trombatore G, et al. The prognosis impact of neoadjuvant chemoradiotherapy on lymph node sampling in patients with locally advanced rectal cancer. Updates Surg. 2020;72:793–800. http://dx.doi.org/10.1007/s13304-020-00841-3.
17. Karjol U, Jonnada P, Chandranath A, Cherukuru S. Lymph node ratio as a prognostic marker in rectal cancer survival: a systematic review and meta-analysis. Cureus. 2020;12:e8047. http://dx.doi.org/10.7759/cureus.8047.
18. Kang J, Hur H, Min BS, Lee KY, Kim NK. Prognostic impact of the lymph node ratio in rectal cancer patients who underwent preoperative chemoradiation. J Surg Oncol. 2011;104:53–8. http://dx.doi.org/10.1002/jso.21913.
19. Zhang MR, Xie TH, Chi JL, Li Y, Yang L, Yu YY, et al. Prognostic role of the lymph node ratio in node positive colorectal cancer: a meta-analysis. Oncotarget. 2016;7:72898–907. http://dx.doi.org/10.18632/oncotarget.12131.
20. Koo T, Song C, Kim J-S, Kim K, Chie EK, Kang S-B, et al. Impact of lymph node ratio on oncologic outcomes in ypstage III rectal cancer patients treated with neoadjuvant chemoradiotherapy followed by total mesorectal excision, and postoperative adjuvant chemotherapy. PLoS One. 2015;10:e0138728. http://dx.doi.org/10.1371/journalpone.0138728.
21. Park IJ, Yu CS, Lim SB, Yoon YS, Kim CW, Kim TW, et al. Ratio of metastatic lymph nodes is more important for rectal cancer patients treated with preoperative chemoradiotherapy. World J Gastroenterol. 2015;21:3274–81. http://dx.doi.org/10.3748/wjg.v21.i11.3274.
22. Calero A, Escrig-Sos J, Mingol F, Arroyo A, Martinez-Ramos D, de Juan M, et al. Usefulness of the log odds of positive lymph nodes to predict and discriminate prognosis in gastric carcinomas. J Gastrointest Surg. 2015;19:813–20. http://dx.doi.org/10.1007/s11605-014-2728-5.
23. Chen L-J, Chung K-P, Chang Y-J, Chang Y-J. Ratio and log odds of positive lymph nodes in breast cancer patients with mastectomy. Surg Oncol. 2015;24:239–47. http://dx.doi.org/10.1016/j.suronc.2015.05.001.
24. Scarinci A, Di Cesare T, Cavaniglia D, Neri T, Colletti M, Cosenza G, et al. The impact of log odds of positive lymph nodes (LODDS) in colon and rectal cancer patient stratification: a single-center analysis of 323 patients. Updates Surg. 2018;70:23–31. http://dx.doi.org/10.1007/s13304-018-0519-3.
25. Fortea-Sanchis C, Martinez-Ramos D, Escrig-Sos J. The lymph node status as a prognostic factor in colon cancer: comparative population study of classifications using the logarithm of the ratio between metastatic and nonmetastatic nodes (LODDS) versus the pN-TNM classification and ganglion ratio systems. BMC Cancer. 2018;18:1208. http://dx.doi.org/10.1186/s12885-018-5048-4.
26. Persiani R, Cananzi FCM, Biondi A, Paliani G, Tufo A, Ferrara F, et al. Log odds of positive lymph nodes in colon cancer: a meaningful ratio-based lymph node classification system. World J Surg. 2012;36:667–74. http://dx.doi.org/10.1007/s00268-011-1415-x.
27. Li T, Yang Y, Wu W, Fu Z, Cheng F, Qiu J, et al. Prognostic implications of ENE and LODDS in relation to lymph nodepositive colorectal cancer location. Transl Oncol. 2021;14:101190. http://dx.doi.org/10.1016/j.tranon.2021.101190.
28. Arslan NC, Sokmen S, Canda AE, Terzi C, Sarioglu S. The prognostic impact of the log odds of positive lymph nodes in colon cancer. Colorectal Dis. 2014;16:O386–92. http://dx.doi.org/10.1111/codi.12702.
29. Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. PLoS Med. 2007;4(10):e297. http://dx.doi.org/10.1371/journal.pmed.0040297.