Surgical Oncology 48 (2023) 101908

Contents lists available at ScienceDirect

Surgical Oncology

journal homepage: www.elsevier.com/locate/suronc

The definition of "R1" lymph node dissection status in patients undergoing curative-aim gastrectomy for gastric carcinoma: A proof of concept study

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ARTICLE INFO

Keywords:
Gastric cancer
Lymph node dissection
R0 resection
Radical gastrectomy
Loco-regional recurrence

ABSTRACT

Introduction: The aim of this study was to define and investigate the prognostic impact of "R1-Lymph-node dissection" during gastrectomy.
Methods: This was a retrospective study conducted with 499 patients undergoing curative-aim gastrectomy. We defined R1-Lymph dissection as an involvement of lymph node stations anatomically connected with lymph node stations outside the declared level of dissection (D1 to D2+). The primary outcomes were disease-free and disease-specific survival (DFS and DSS).
Results: At multivariable analysis, the type of gastrectomy, pT and pN were associated with DFS, and the type of gastrectomy, R1-Margin status, R1-Lymph status, pT, pN and adjuvant therapy were associated with DSS. Moreover, pT and R1-Lymph status were the only factors associated with overall loco-regional recurrence.
Conclusions: In this study, we introduced the concept of R1-Lymph-node dissection, which was significantly associated with DSS and appeared to be a stronger prognostic factor for loco-regional recurrence than the R1 status on the resection margin.

1. Introduction

Gastric cancer (GC) is the fifth most frequently diagnosed cancer and the third leading cause of cancer death worldwide [1]. For patients in the advanced stage ($\geq$ T2 and/or N+), the use of multimodal strategies both in the neoadjuvant and adjuvant setting has been demonstrated to benefit survival [2], even though the cardinal treatment for GC remains radical surgery (gastrectomy with proper lymphadenectomy and negative resection margins - R0 resection). However, many studies have demonstrated that the actual benefit of R0 resection is limited to patients with "confined" local (up to T2-3) and regional (up to N1-2) GC [3–5] and that the role of R0 resection seems more relevant in patients with node-negative disease [6,7]. The survival rate of patients with positive resection margins (R1 resection) is significantly worse than that of patients with R0 resection margins [6]; this is mostly due to a higher rate of systemic recurrence. Accordingly, R1 resection is currently more often considered a marker of underlying aggressive tumor biology rather than a risk factor for local recurrence in most patients with locally advanced GC [8].

Lymph node (LN) involvement is another leading prognostic factor for patients undergoing curative-aim gastrectomy. Since the AJCC/TNM 5th edition, a quantitative (numeric-based) LN staging system has been favored over a qualitative one (anatomic based) due to the simplicity and overall prognostic advantage. However, information on the entity and pattern of LN involvement (i.e., lymph-node ratio, involvement of the central node stations or of the second level LN) could improve the prognostic stratification of GC [9–11].

The dismal prognosis associated with extensive LN disease, especially when extraperigastric LN stations are positive, could be due to unresected metastatic lymph nodes beyond the surgically dissected area. Theoretically the prognosis of patients with a risk of unresected metastatic lymph nodes, even after R0 resection, could be considered similar to the prognosis of patients undergoing R1 resection on the gastrectomy margins. This assumption could have relevant implications for the definition of true radical surgery and from a therapeutic point of view in terms of promoting more extensive lymph node dissections and/or the

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https://doi.org/10.1016/j.suronc.2023.101908
Received 9 August 2022; Received in revised form 11 January 2023; Accepted 28 January 2023
Available online 2 February 2023
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administration of postoperative loco-regional therapy. Therefore, the aim of this study was to define and investigate the role of "R1 lymph node dissection" from a prognostic point of view.

2. Materials and methods

2.1. Population of the study

This is a retrospective cohort study that included all cases of gastric adenocarcinoma that underwent gastrectomy with lymphadenectomy between 1988 and 2018 in the General Surgery Unit of the Fondazione Policlinico Universitario "A. Gemelli" IRCCS in Rome, Italy. From an initial population of 845 patients with gastric cancer observed in our unit, we included only patients undergoing gastrectomy in this study. We excluded patients with stump GC, patients with clinical and pathological stage IV disease, patients who died in the postoperative period, patients lost to follow-up, patients alive without recurrence with a follow-up < 18 months, and patients who had insufficient or inconclusive data in medical records (specifically, those who lacked the description of the extent of lymphadenectomy or of the involvement of each lymph node station) from the study.

2.2. Data collection

Information was retrospectively collected from the medical records and included clinical aspects (such as age, sex, gastric location, and macroscopic aspect of the lesion), technical aspects (the type of surgery and type of lymphadenectomy), pathological variables (the depth of the lesion, presence of lymph node metastasis, Lauren classification, presence of SRC, and evaluation of the resection margin) and survival data (the pattern of recurrence, disease-free survival – DFS and disease-specific survival - DSS).

2.3. Outcome measures and definitions

DFS was defined as "the time from surgery to documented cancer recurrence", and DSS was defined as "the time from surgery to cancer-related death". Patients with microscopic involvement of the resection margin were classified as R1 on the specimen (R1-Mar). We attempted to define a "safe margin" of lymphadenectomy as a lymph node dissection that guarantees the removal of a nonmetastatic lymph node station at the upper anatomical level of a metastatic lymph node station.

Then, we defined the following patients as undergoing "lymph node R1" (R1-Lymph) dissection (Fig. 1).

- patients undergoing D1 lymphadenectomy with involvement of first-level lymph nodes (Nos. 1–7), except for Station 3, for whom Station 7 was not involved;
- patients undergoing D2 lymphadenectomy with involvement of second-level lymph nodes (No. 8–12);
- patients with involvement of lymph node stations anatomically connected with lymph node stations outside the declared level of dissection (D1, D1plus, D2 and D2plus), when the next anatomically connected node station was not removed (i.e., patients with Station 5 were involved when Station 12 was not dissected, patients with Station 7 were involved when Station 9 was not dissected, and patients with Station 6 were involved when Station 14v was not dissected) [12].

Loco-regional recurrence (LRR) was defined as any radiologic, laparoscopic, laparotomic or histologic evidence of metachronous recurrence in the proximity of the tumor bed (including anastomotic) and/or lymphatic recurrence within the N2–N3 level (i.e., lower mediastinal nodes, hepatic hilum nodes, or paraortic nodes) during follow-up.

2.4. Surgical and multimodal treatment

As previously described [13], since 1996, our institution protocol has offered preoperative or perioperative therapy according to the available guidelines to patients with clinically locally advanced (cT3–4 and any N, or $T > 2$ with bulky node-positive disease) potentially resectable GC. Patients outside of the inclusion criteria and patients who refused neoadjuvant therapy underwent upfront gastrectomy. Surgery (upfront or after neoadjuvant therapy) consisted of a total gastrectomy in all proximal tumor locations and of a subtotal gastrectomy in distal tumor locations if a 5- to 6-cm safety margin was present. The dissected lymph nodes were separated and classified according to the Japanese gastric cancer treatment guidelines. In accordance with these guidelines, the extent of lymphadenectomy was classified by the D-level criteria into

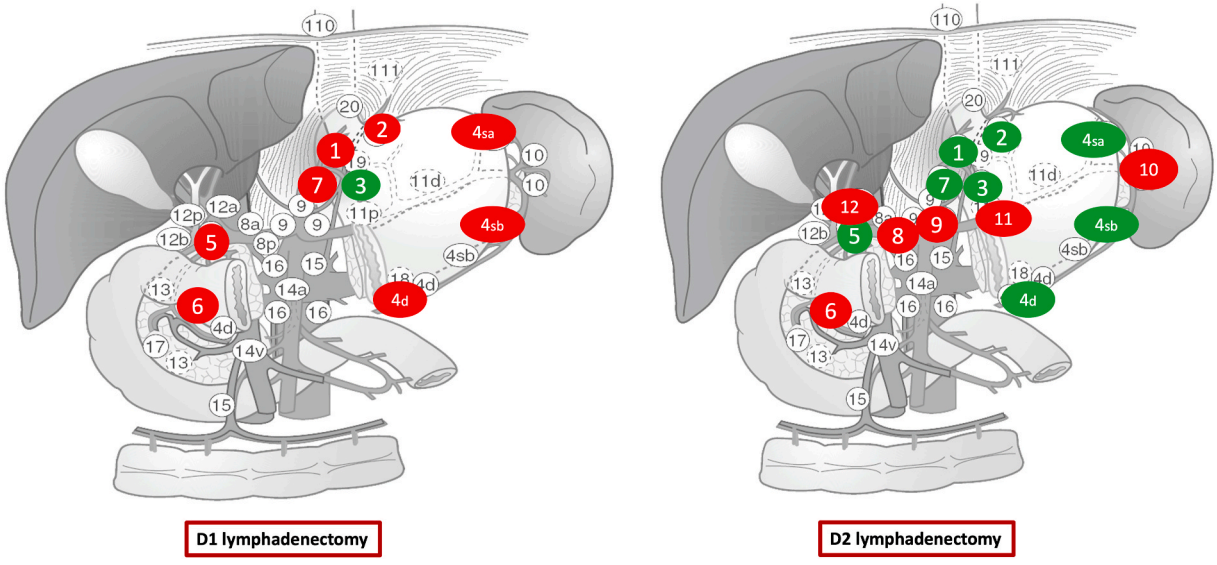

Fig. 1. (A) Patients undergoing D1 lymphadenectomy with involvement of first level LN (No. 1–7), except for station 3 involved with station 7 not involved; (B) Patients undergoing D2 lymphadenectomy with involvement of second level LN (No. 8–12) and patients with involvement of LN stations anatomically connected with LN stations outside the declared level of dissection (No. 6 involved with No. 14v not dissected). According to the level of lymph node dissection the red color indicates metastatic lymph node stations defining a R1-lymph status. The green color indicates a metastatic lymph node station defining a R0-lymph status.

D1, D1+, D2 or D2+. After surgery, patients were administered further courses of the same neoadjuvant chemotherapy regimen for the perioperative chemotherapy group or adjuvant chemotherapy according to the available guidelines. Patients with >N2 disease, >50% lymph node ratio or R1 resection were offered postoperative radiotherapy after the adjuvant chemotherapy regimen.

2.5. Follow-up

For the purposes of this study, we closed the follow-up at 5 years. Postoperative follow-up included a clinical evaluation and detection of biomarkers (every 3 months for 2 years and every 6 months thereafter), an endoscopy (every 6 months for one year and once a year thereafter), an abdominal ultrasound (every 3 months for one year and every 6 months thereafter) and a thoraco-abdominal CT scan (every year for 5 years). Recurrence was determined by biopsy, surgery and/or radiology.

2.6. Statistical analysis

Frequencies and percentages were used for categorical variables, and the means (+- standard deviations) or medians (ranges) were used for continuous variables. Pearson's chi-squared test or Fisher's exact test was used to compare categorical variables, and Student's *t*-test was used to compare continuous variables. The median follow-up was calculated as the median follow-up of survivors. DFS and DSS were calculated from the date of gastrectomy. Disease-specific survival curves for patients undergoing preoperative therapy or upfront gastrectomy were estimated by the Kaplan–Meier method and compared with the log-rank test. We used a Cox multivariable analysis conducted with backward regression (excluding variables with $p > 0,1$ in every new step) to identify variables associated with DFS and DSS. Then, a multivariable logistic analysis (excluding variables with $p > 0,1$ in every step) conducted with backward regression was used to identify variables associated with LRR. A post-hoc analysis comparing the accuracy of R1lymph with those of Lymph Node Ratio (LNR) and LODDS in predicting overall as well as local recurrence was also conducted. Cut-off for LNR and LODDS were chosen based on the median LNR and LODDS values in patients with recurrence (0.19 and −0.59, respectively). All analyses were performed using IBM SPSS for Macintosh, v. 25 (IBM Co., Armonk, NY, USA), Stata for Windows v. 15.0 (StataCorp, College Station, TX, USA) and Microsoft Excel for Macintosh v 16.3.1 (Microsoft Corporation. (2018). Retrieved from https://office.microsoft.com/excel). All tests were 2-sided with a significance level set at 0.05.

3. Results

From 697 patients undergoing curative-aim gastrectomy from January 1988 to December 2018, 499 were selected for inclusion in this study (Fig. 2). The median OS of survivors was 77 (13–273) months. According to the definition of R1-Lymph, 243 patients were in the R0-Lymph category, and 256 were in the R1-Lymph category. In the whole population, the rates of R0-Mar and R1-Mar resection were 90.4% and 9.6%, respectively.

3.1. Predictors of DFS and DSS in the whole population

In the multivariable backward Cox regression for DFS (Table 1s) and DSS (Table 2s) conducted on 494 patients undergoing curative-aim gastrectomy, the independent factors that were predictive of DFS were pT (p=<0.001) and pN ($p < 0.001$), and those that were predictive of DSS were sex (female sex protective, $p = 0.049$), type of surgery (subtotal gastrectomy protective $p = 0.003$), R1-lymph margin ($p = 0.039$), R1 margin ($p = 0.032$), pT ($p < 0.001$), pN ($p < 0.001$) and adjuvant therapy (adjuvant therapy protective, $p = 0.010$).

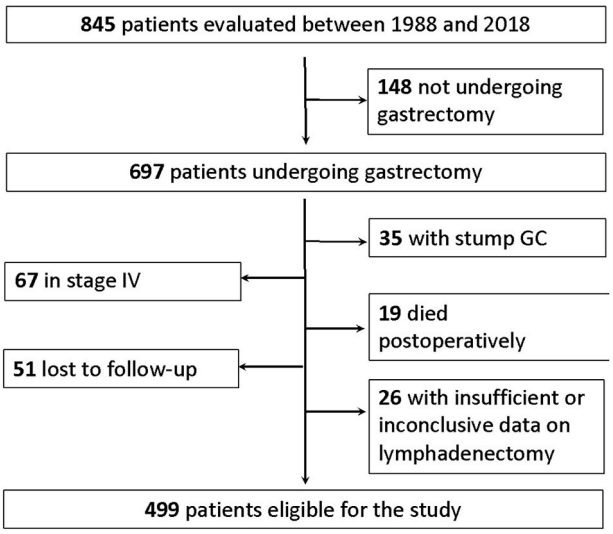

Fig. 2. Flowchart of patients included in the study according to the inclusion and exclusion criteria.

3.2. The R1-Lymph population

From a clinicopathological point of view, different variables were considered in patients undergoing R0-Lymph node dissection and R1-Lymph node dissection. In the comparison between the two populations, age, sex, location of the tumor, and the extent of gastrectomy and lymphadenectomy were not statistically significant (Table 1).

In patients undergoing R0-Lymph node dissection, the most common histotype was the intestinal histotype (59%) according to the Lauren classification. However, a diffuse histotype was found in 30% of patients. Regarding the depth of invasion, 100 patients (41.0%) had T0/Tis/T1 stage gastric cancer, and only 47 of the selected patients (19.3%) had T4 gastric cancer. A total of 194 patients (79.5%) did not have lymph node metastasis, while 50 (20.5%) had lymph node metastasis and of these, only 6 (2,4%) had metastasis in the third compartment. There was no positive resection margin (R0) in 234 patients (95.9%), and only 56 patients (23.0%) underwent adjuvant therapy after surgery. During the follow-up, 45 patients (18.4%) had a recurrence.

In patients undergoing R1-Lymph node dissection, the frequencies of intestinal and diffuse histotypes almost overlapped (43.1% and 39.2%, respectively). Most patients had a T3 or T4 depth of infiltration (34.5% and 45.1%, respectively). There was no positive resection margin in 217 patients (85.1%). Then, 160 patients (62.7%) received adjuvant therapy. More than 50% of the patients experienced recurrence during the follow-up.

3.3. Prognostic significance of R1-Lymph

DFS and DSS were longer in patients with R0-Lymph status than in patients with an R1-Lymph status, as shown in the Kaplan–Meier curves (Fig. 3A and B). The prognostic significance of R1-Lymph was also demonstrated in patients with positive nodes and in patients who underwent R0 and R1 resection (Supplementary Figs. 3C–H).

3.4. Pattern of recurrence in R0-lymph and R1-lymph group

In the R0-and R1-Lymph groups (Table 2), recurrence at the anastomotic site occurred in 36 patients (7.2%). Forty-five patients (9%) had lymph node recurrence, while loco-regional recurrence occurred in 78 patients (15.6%). Moreover, 40 patients (8%) had a liver recurrence, and 48 (9.6%) had a peritoneal recurrence. Recurrences in other sites were observed in 35 patients (7%).

Of patients who underwent R0-Lymph node resection, 7% and 6.1%

Table 1
Clinicopathologic characteristics of patients undergoing R0 lymph node dissection (R0-LYMPH) and R1 lymph node dissection (R1-LYMPH).

VARIABLE	RO-LYMPH (n = 244)	R1-LYMPH (n = 255)	p-value
Age, years (mean ± SD)	66.1 ± 11.7	65.6 ± 12.9	0.661
Gender (n, %)			
Male	150 (61.5%)	151 (59.2%)	0.606
Female	94 (38.5%)	104 (40.8%)	
Location (n, %)			
Upper	41 (16.8%)	49 (19.2%)	0.878
Middle	84 (34.4%)	84 (32.9%)	
Lower	115 (47.1%)	119 (46.7%)	
Linitis	4 (1.6%)	3 (1.2%)	
Extent of gastrectomy (n, %)			
Sub-total	174 (71.3%)	167 (65.5%)	0.162
Total	70 (28.7%)	88 (34.5%)	
Lymphadenectomy (n, %)			
D1	17 (7.0%)	23 (9.0%)	0.867
D1+	8 (3.3%)	8 (3.1%)	
D2	201 (82.4%)	205 (80.4%)	
D2+	18 (7.3%)	19 (7.5%)	
Lauren classification (n, %)			
Intestinal	144 (59.0%)	110 (43.1%)	<0.001
Diffuse	70 (28.7%)	100 (39.2%)	
Mixed	13 (5.3%)	33 (12.9%)	
NA	17 (7.0%)	12 (4.7%)	
SRC (n, %)			
No	177 (72.5%)	166 (65.0%)	0.065
Yes	57 (23.4%)	78 (30.6%)	
NA	10 (4.1%)	11 (4.3%)	
Depth of invasion (n, %)			
pT0/is/1	100 (41.0%)	21 (8.2%)	<0.001
pT2	54 (22.1%)	31 (12.1%)	
pT3	43 (17.6)	88 (34.5%)	
pT4	47 (19.3%)	115 (45.1%)	
Lymph node metastasis (n, %)			
pN0	194 (79.5%)	0 (0.0%)	<0.001
pN1	29 (11.9%)	67 (26.3%)	
pN2	15 (6.1%)	82 (32.2%)	
pN3	6 (2.4%)	106 (41.5%)	
Resection margin (n, %)			
R0-Mar	234 (95.9%)	217 (85.1%)	<0.001
R1-Mar	10 (4.1%)	38 (14.9%)	
Neoadjuvant therapy (n, %)			
No	205 (84.0%)	204 (80.0%)	0.243
Yes	39 (16.0%)	51 (20.0%)	
Adjuvant therapy (n, %)			
No	179 (73.4%)	83 (32.5%)	<0.001
Yes	56 (23.0%)	160 (62.7%)	
NA	9 (3.6%)	12 (5.7%)	
Recurrence (n, %)			
No	195 (79.9%)	109 (42.7%)	<0.001
Yes	45 (18.4%)	136 (53.3%)	
NA	4 (1.6%)	10 (3.9%)	

had recurrence at the anastomotic site and lymph nodes, respectively. Only 7.3% of patients had loco-regional recurrence during the follow-up. Instead, in the R1-Lymph group, recurrence at the anastomotic site and in lymph nodes was observed in 10.2% and 14.5% of cases, respectively, with a frequency of loco-regional recurrence of 23.5%. Peritoneal recurrence was observed in 3.2% of cases in the R0-Lymph group and in 15.7% in the R1-Lymph group. Additionally, 5,7% of patients in the R0-Lymph group and 10,2% of patients in the R1-Lymph group had liver recurrence. The multivariable logistic regression for exclusive loco-regional recurrence confirmed R1-Lymph node dissection as a statistically significant variable for loco-regional recurrence ($p = 0.006$) (Table 3).

3.5. Comparison of the predictive value of R1-Lymph, LNR and LODDS for overall and locoregional recurrence

The comparison of the performance of R1-Lymph, LNR and LODDS

Table 2
Pattern of recurrence in N patients in the R0-LYMPH and R1-LYMPH groups.

SITE OF RECURRENCE	R0-LYMPH (n = 244)	R1-LYMPH (n = 255)	p-value
Anastomotic (n, %)			
No	227 (93.0%)	211 (82.7%)	0.006
Yes	10 (4.1%)	26 (10.2%)	
NA	7 (2.9%)	18 (7.1%)	
Lymph nodes (n, %)			
No	229 (93.9%)	200 (78.4%)	<0.001
Yes	8 (3.2%)	37 (14.5%)	
NA	7 (2.9%)	18 (7.1%)	
Locoregional (n, %)			
No	219 (89.8%)	177 (69.4%)	<0.001
Yes	18 (7.3%)	60 (23.5%)	
NA	7 (2.9%)	18 (7.1%)	
Liver (n, %)			
No	223 (91.4%)	211 (82.7%)	0.047
Yes	14 (5.7%)	26 (10.2%)	
NA	7 (2.9%)	18 (7.1%)	
Peritoneal (n, %)			
No	229 (93.9%)	197 (77.3%)	<0.001
Yes	8 (3.2%)	40 (15.7%)	
NA	7 (2.9%)	18 (7.0%)	
Other (n, %)			
No	227 (93.0%)	212 (83.1%)	0.008
Yes	10 (4.1%)	25 (9.8%)	
NA	7 (2.9%)	18 (7.1%)	

classes in predicting overall recurrence and exclusive locoregional recurrence documented: for overall recurrence, AUCs of 0.694 (0.646–0.743), 0.694 (0.642–0.745) and 0.695 (0.644–0.746) for R1-Lymph, LNR $\geq$ 0.19 and LODDS>=-0.59, respectively; for exclusive locoregional recurrence, AUCs of 0.665 (0.595–0.734), 0.635 (0.553–0.716) and 0.642 (0.561–0.723) for R1-Lymph, LNR $\geq$ 0.19 and LODDS>=-0.59, respectively.

4. Discussion

In this study, we defined the concept of R1-Lymph and analyzed its correlation with disease-specific survival outcomes and recurrence. Among the predictors of survival, the type of gastrectomy, the pathologic tumor staging (pT) and the pathologic node staging (pN) were the factors independently associated with DFS, and the type of gastrectomy, the R1-Mar status, the R1-Lymph status, the pathologic tumor staging (pT), the pathologic node staging (pN) and adjuvant therapy were the factors independently associated with disease specific survival. Moreover, the pT and R1-lymph status were the only factors independently associated with overall loco-regional recurrence. The R1-lymph status was not related to peritoneal or liver recurrence.

In patients with GC, LN involvement is currently considered the main prognostic factor. The AJCC/TNM 4th edition (1987), based on the 13th JGCA classification [14,15], numbered all of the regional LN stations, classifying them into three tiers according to the location of the primary tumor. This classification system was meant to improve the clinical staging and surgical planning. In the corresponding JGCA guidelines for treatment, a dissection of LN one 'level' further than the one involved was advocated. From the 5th edition (1997) [16], the AJCC/TNM staging system converted lymph node staging from an anatomical (location-based) system to a numeric-based system. The new system, based on the number of lymph nodes involved, allowed for a more accurate prediction of the prognosis and a more reliable standardization of the pathological staging. It was also meant to compensate for the missing or incomplete data on the anatomical extent of LN dissection and the involvement of proximal or distal nodes given by the previous classification system. Despite its overall benefit, many authors have questioned the numeric-based lymph node staging system for its specific risk of stage-migration phenomenon, as well as for the notable discrepancy in the prognosis of patients with the same pN stage. This discrepancy has been attributed to the omission of valuable information provided by a

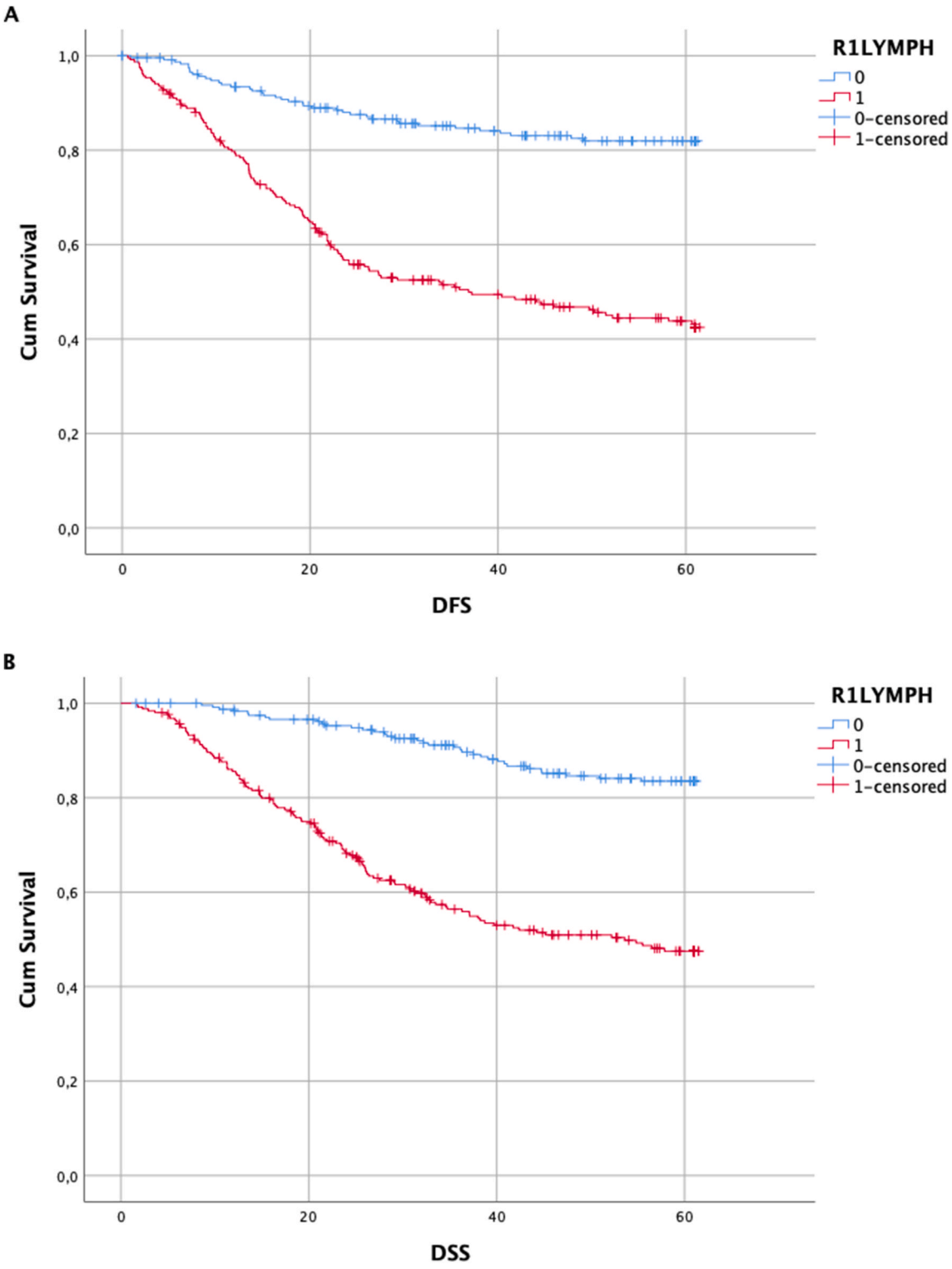

Fig. 3. Kaplan–Meier curves for DFS (A) and DSS (B) of patients with R0-Lymph and R1-Lymph disease in the whole population (both $p < 0.001$), in patients with node positivity - DFS (C) ($p = 0.004$), and DSS (D) ($p = 0.001$), in patients with R0-Mar status - DFS (E) and DSS (G) (both $p < 0.001$) and in patients with R1-Mar status - DFS (F) ($p = 0.002$) and DSS (H) ($p = 0.004$).

qualitative assessment of the extent of LN metastases [17]. Many studies have reported that patients with extraperigastric lymph node involvement had a poorer prognosis than those with perigastric involvement only, both in patients undergoing upfront gastrectomy and neoadjuvant chemotherapy [17,18]. Recently, Ikoma et al. demonstrated that the presence of LN metastases in CnLNs ("central lymph nodes", station nos. 8, 9 and 11p) was a reliable prognostic factor in GC patients who were treated with neoadjuvant chemotherapy [9]. Based on this evidence, hybrid staging systems based on both the number and location of LN metastases have been proposed [10,19]. However, none of the studies on

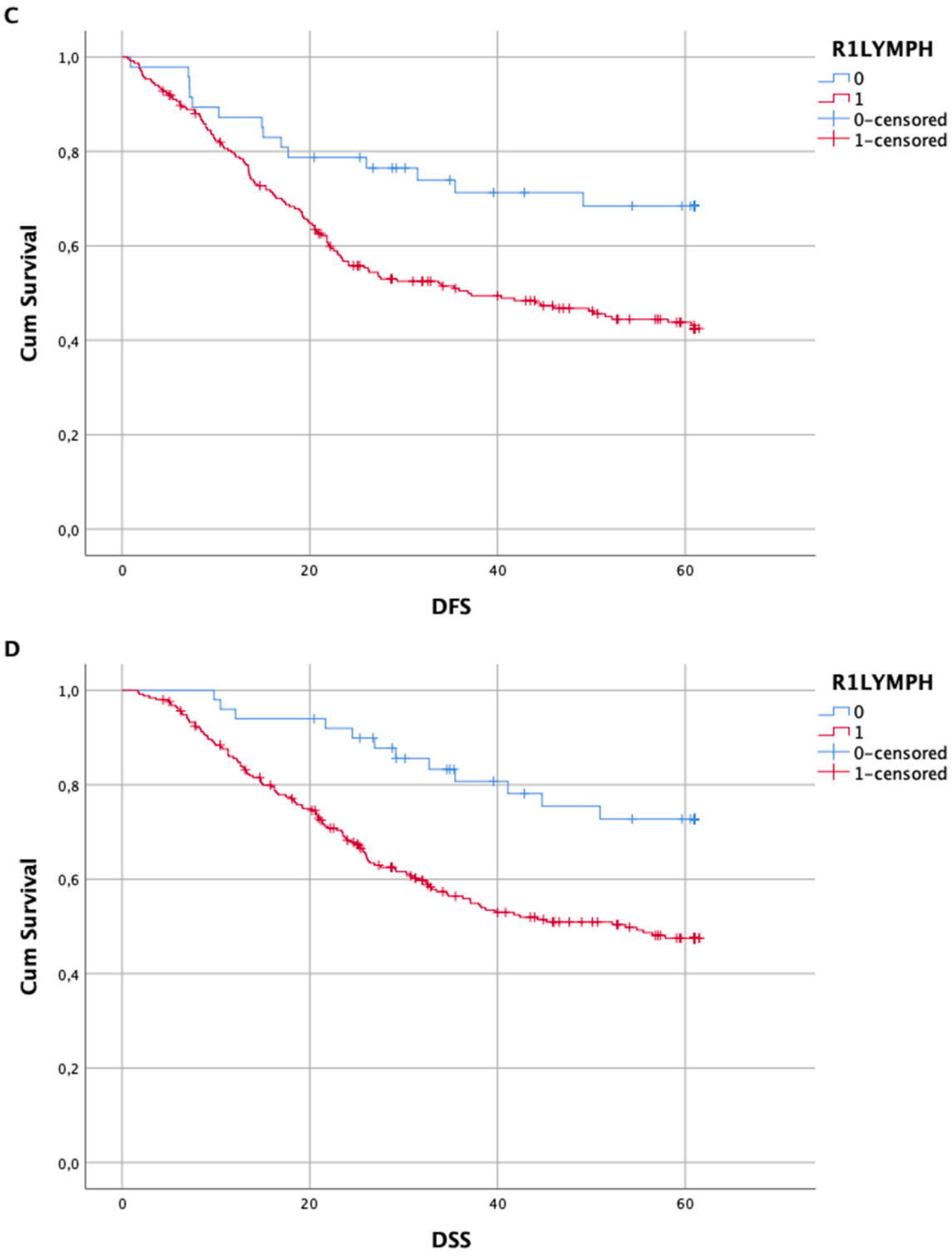

Fig. 3. (*continued*).

this topic have focused on the specific pattern of recurrence in patients with specific types of LN metastases. Our study is the first to define an R1-Lymph concept and to identify a specific pattern of recurrence (increase in the rate of loco-regional recurrence) for these patients. This is in line with the results of other studies that reported lower rates of loco-regional recurrence in patients undergoing more extensive lymphadenectomy [20–23].

Our findings could have relevant implications. From a surgical point of view, they reinforce the theoretical rationale behind the concept of D2 plus lymphadenectomy. Extending the dissection one 'level' further than the LN involved, especially for "border" LN stations where there is no corresponding next level codified in D2 lymphadenectomy, could aid in removing the micro metastatic disease. This concept is not original; it has been extensively investigated in the literature and even codified with the Maruyama computer program, which was created to estimate the risk of residual positive LNM in each of the abdominal nodal stations [24]. However, the use of this program, given its scarce availability, has been nonhomogeneous, which limits its prognostic validation and its use

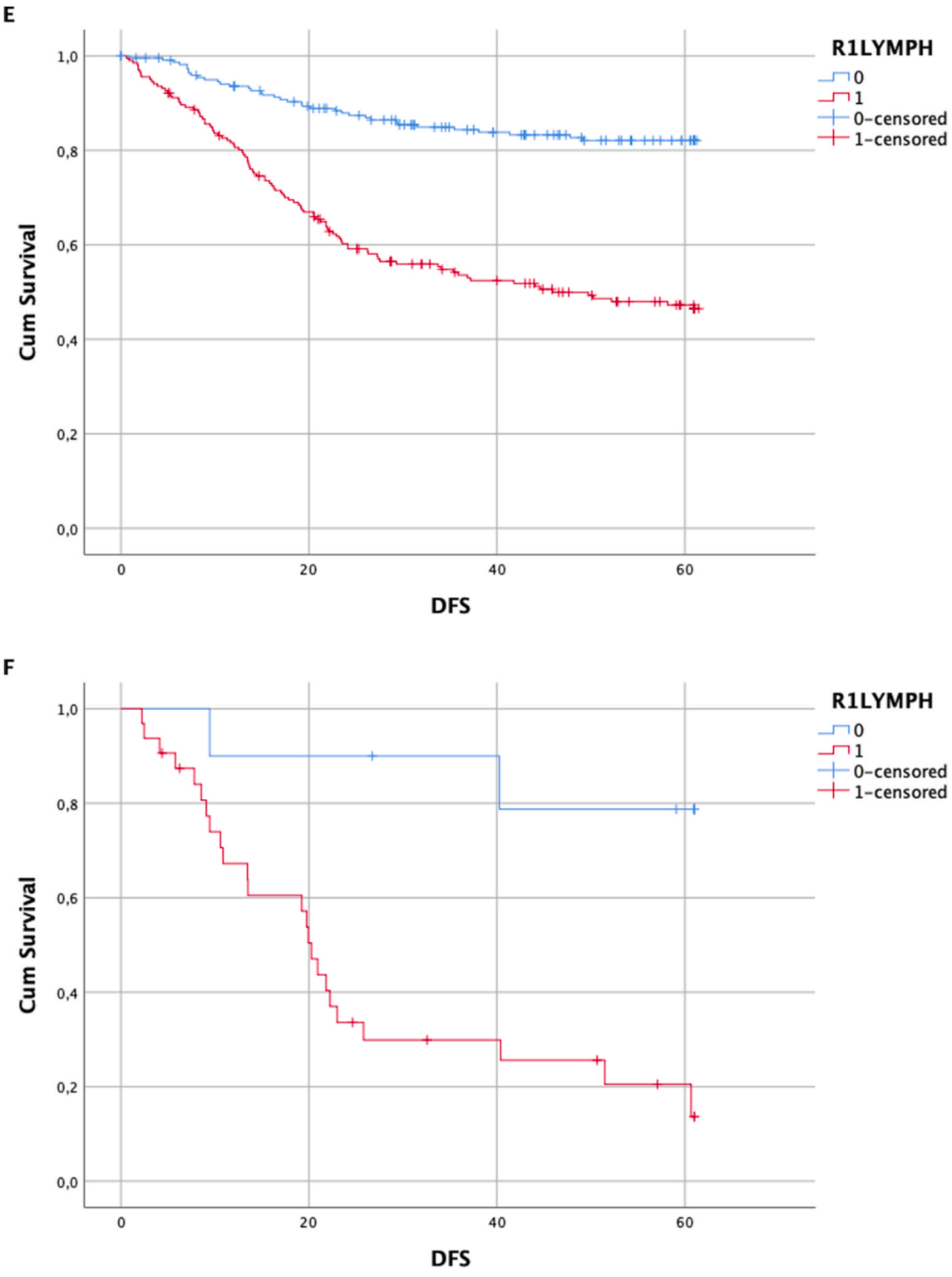

Fig. 3. (*continued*).

in clinical practice.

The concept of R1-Lymph node dissection, which seems to be a specific prognostic factor for loco-regional recurrence, has even more relevant implications. There has been great interest in defining the specific risk factors for loco-regional recurrence after gastrectomy, as the prevention of this type of recurrence seems to be the most coherent indication for postoperative chemoradiotherapy (CRT) instead of chemotherapy alone [25]. One such factor, both in patients undergoing upfront gastrectomy and in those undergoing preoperative chemotherapy, is the ypN stage [7,26]. According to the current Western guidelines, postoperative CRT is recommended only for LAGC undergoing upfront surgery without preoperative chemotherapy or in the case of D1 gastrectomy or no lymphadenectomy [27,28], but they also recommend CRT for pT2N0 patients undergoing R0 resection with high-risk features (poorly differentiated or higher grade cancer, lymphovascular and/or neural invasion, age <50 years, or LN dissection <

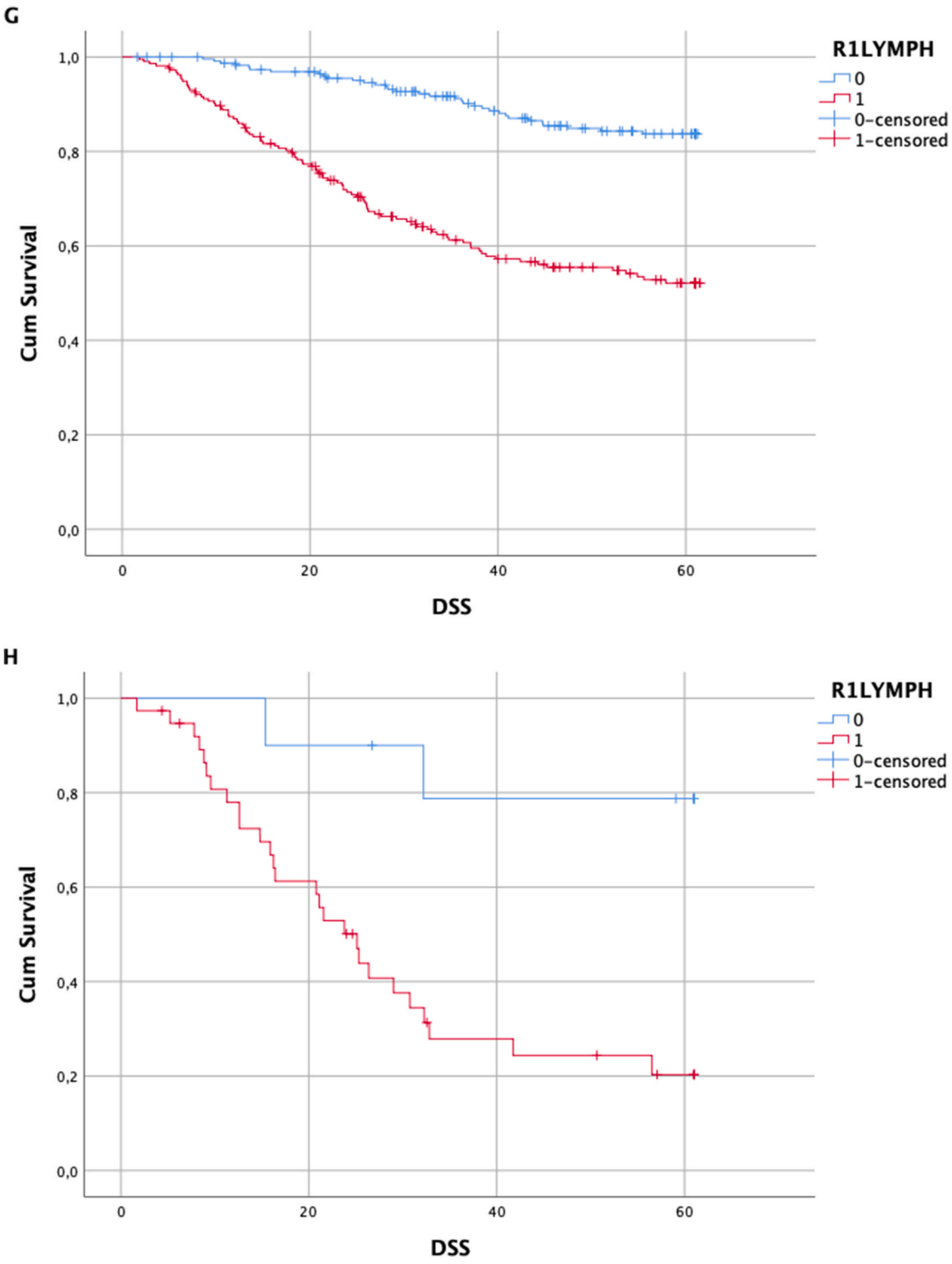

Fig. 3. (*continued*).

D2) [28].

According to the CRITICS trial, in patients undergoing preoperative chemotherapy followed by surgery with curative intent, postoperative CRT did not improve OS compared with postoperative chemotherapy [29]. The ARTIST trial compared patients with completely D2-resected GC receiving capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy [30]. In this trial, there were no overall benefits for postoperative CRT, but the findings in the subgroup analysis suggested that patients with node-positive disease had a statistically significant improvement in DFS. These findings led to the conduction of the ARTIST-2 trial, where node-positive stage II/III GC patients receiving gastrectomy with D2 lymphadenectomy and who received chemotherapy and chemoradiation were compared in terms of DFS. Nevertheless, the results of this trial showed that the addition of radiotherapy did not significantly reduce the rate of recurrence [31]. However, in all these trials, all patients with N+ disease (without distinction between N1, N2 and N3 disease) were included. Additionally, no quality indicators of the type of lymph node involvement were

Table 3a
Multivariable backward logistic regression for exclusive locoregional recurrence conducted on 499 patients (434 selected due to missing data) undergoing curative-aim gastrectomy.

VARIABLE	OR	Lower 95% CI	Higher 95% CI	p-value
R1 LYMPH				
0	ref	–	–	,006
1	2695	1323	5490	
pT.VII				
1–2	ref	–	–	,002
3–4	3804	1604	9020	
Constant	,029	–	–	,000

Table3b
Multivariable backward logistic regression for exclusive liver recurrence conducted on 499 patients (434 selected due to missing data) undergoing curative-aim gastrectomy.

VARIABLE	OR	Lower 95% CI	Higher 95% CI	p-value
Lauren type				
- intestinal	ref			,005
- mixed	,284	,061	1325	,109
- diffuse	,045	,006	,354	,003
pN Stage				
- pN0	ref			,129
- pN1	,541	,098	2987	,481
- pN2	2200	,628	7708	,218
- pN3	2986	,826	10,794	,095
pT3-4	5676	1155	27,888	,033
Constant	,019			,000

Table 3c
Multivariable backward logistic regression for exclusive peritoneal recurrence conducted on 499 patients (434 selected due to missing data) undergoing curative-aim gastrectomy.

VARIABLE	OR	Lower 95% CI	Higher 95% CI	p-value
Lauren type				
- intestinal	ref			,035
- mixed	2242	,572	8785	,246
- diffuse	3708	1368	10,048	,010
pN Stage				
pN0	ref			,046
pN1	1054	,138	8043	,960
pN2	2828	,508	15,732	,235
pN3	5540	1109	27,683	,037
pT3-4	8815	1045	74,344	,045
Constant	,002			,000

Variable(s) entered on step 1: neoadjuvant therapy, sex, age, location of the tumor (upper, middle, lower or linitis), type of gastrectomy, R1-Mar, R1 LYMPH, Lauren, pT, pN, adjuvant therapy.

considered.

Another indication for the administration of postoperative RT in the current guidelines is R1-Mar status due to its significant association with worse survival [32] and to the improved local recurrence rate and overall survival in patients treated with adjuvant CRT in a retrospective study [33]. However, the evidence in this regard is somewhat limited and controversial. Other studies have shown that in GC patients treated with CRT after surgery, the 3-year recurrence-free survival and overall survival did not significantly differ between patients undergoing R0 or R1 resection, and only pT and pN were independent prognostic factors for survival [34]. In general, R1-Mar has been regarded as a controversial entity that seems to be more related to systemic recurrence than to loco-regional recurrence [7]. Furthermore, it loses its prognostic significance in patients with advanced disease because of the more dominant negative survival effect of advanced stage than margin status [3–5]. In these patients, the benefit of loco-regional control brought by adjuvant RT has not directly translated to increased survival. The role of R1-Mar gives consistent results. In our study, it was indicated to be a significant factor for predicting disease-specific survival but was not a significant factor for predicting loco-regional recurrence. However, R1-Lymph was indicated as a much more powerful predictive factor of loco-regional recurrence.

Another consideration associated with our results is linked to the fact that in the current postoperative chemoradiation protocols, the CTV (clinical target volume) usually includes the anastomoses, gastric bed/remnant and draining regional lymph nodes using two large parallel opposed radiation fields, which cover both the tumor bed and regional lymph nodes [27,29]. Such treatment has a high rate of poor compliance, and therefore few patients completed the planned chemoradiotherapy regimen (64% in Macdonald, 82% in the ARTIST, 51% in the CRITICS). Moreover, the radiation fields do not routinely include the periaortic nodes (16a2 and 16b1), even though they are the “next level” for many patients with node-positive disease, according to the R1-Lymph concept. Accordingly, they are regarded as the most frequent sites of LRR regardless of the primary tumor location. In administering postoperative chemoradiotherapy, the identification of precise targets, such as specific LN stations at risk (such as the positive ones involved and the “next ones” that have the risk of harboring micrometastatic disease), could lead to more focused treatments with a minimal radiation dose to normal healthy tissues, leading to increased tolerance [25,35].

The main limitations of this study are its retrospective and single-center design and the fact that the data on the specific types of adjuvant therapy were not available in detail. Therefore, based solely on our results, it would not be possible to recommend specific adjuvant treatments. However, the results of this study, conducted on a study population treated in a high-volume Italian institution, are valuable for improving the prognostic stratification of GC patients undergoing curative-aim gastrectomy with lymph node metastases. In fact, these results could improve the existing nomograms predicting LRR and guide future clinical research.

5. Conclusions

In this study, we introduce the concept of R1-Lymph node dissection, which was significantly associated with disease-specific survival and appeared to be a stronger prognostic factor than the R1 status on the resection margin for LRR. This new concept of an R1-Lymph status reintroduces a qualitative evaluation of LN involvement alongside the quantitative evaluation given by the pathological node status. The R1-Lymph status should be further investigated as a prognostic factor and, eventually, to direct the surgical strategy and the administration of postoperative multimodal treatments.

CRediT author statement

Alberto Biondi: Conceptualization, Methodology, Investigation, Original draft preparation. **Annamaria Agnes**: Conceptualization, Investigation, Formal Analysis, Original draft preparation. **Antonio Laurino**: Investigation, Data curation, Writing- Original draft preparation, Visualization. **Pasquale Moretta***:* Investigation, Data curation, Writing- Original draft preparation Visualization. **Laura Lorenzon:** Conceptualization, Supervision, Writing- Reviewing and Editing **Domenico D’Ugo**: Conceptualization, Supervision, Writing- Reviewing and Editing. **Roberto Persiani:** Conceptualization, Supervision, Writing- Reviewing and Editing.

Funding/financial support

None.

Declaration of competing interest

None of the authors has any potential financial conflict of interest.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2023.101908.

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