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Lymph Node Yield and Lymph Node Ratio for Prognosis of Long-Term Survival in Gastric Carcinoma

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Simple Summary: Long-term survival of patients with gastric cancer is still poor. Adequate lymphadenectomy is one of the key factors that influence the long-term results of surgery. However, there is still no complete knowledge about factors influencing the lymph node yield. In our study, we analyzed these factors. For many years, the TNM system has allowed estimating long-term survival, but there are many indications that the system, along with UICC/AJCC, should be enriched with additional elements. Lymph node ratio (LNR) seems to be such an element. In this study, we performed a comprehensive analysis of the effect of LNR on long-term survival in patients with gastric cancer.

Abstract: Background: Lymphadenectomy is a fundamental part of surgical strategy in patients with gastric cancer. Lymph node (LN) status is a key point in assessment of prognosis in gastric cancer. The LN ratio (LNR)—number of positive LNs/number of sampled LNs—offers a new approach for predicting survival. The aim of the study was to find factors affecting LN yield and the impact of LNR on 5-year survival. Methods: Prospective multicenter quality assurance study. Only LN-positive patients were included in the LNR calculations. Results: 4946 patients from 149 hospitals were enrolled. The inclusion criteria were met by 1884 patients. Patients were divided into two groups: Group 1 (<16 LN), 456 patients and Group 2 (≥16 LN), 1428 patients. The multivariate analysis found G2 (OR 1.98; 95%CI 1.11–3.54), G3 (OR 2.15; 95%CI 1.212–3.829), UICC-stage II (OR 1.44; 95%CI 1.01–2.06) and III (OR 1.71; 95%CI 1.14–2.57), age < 70 (OR 1.818 95%CI 1.19–2.78) and female gender (OR 1.37; 95%CI 1.00–1.86) as independent factors of ≥16 LN yield. Patients with a LNR ≥ 0.4 have a lower probability of survival (p = 0.039 and <0.001) than patients with a LNR = 0.1. Patients with UICC-II have a lower probability of survival than UICC-I (p = 0.023). Age 70–80 (p = 0.045) and > 80 years (p = 0.003) were negative prognostic factors for long-term survival. Conclusion: Long-term survival is directly related to adequate lymphadenectomy. LNR could be superior to pN-stage for estimating survival and adds remarkable nuances in prognosis compared to UICC-stage. LNR also appears valid, even in the case of insufficient LN yield.

Keywords: gastric cancer; surgery; lymphadenectomy; lymph node ratio; survival

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1. Introduction

One of the most common forms of cancer is gastric carcinoma, with an estimated 1,033,701 new cases being reported in 2018, ranking it No. 6 of all cancers. It is also unfortunately associated with a high mortality rate: a total of 782,685 deaths reported, representing the second leading cause of cancer-related death worldwide [1]. The highest incidence was noted in East Asia, at 35.4 per 100,000 in men, compared to Western Europe, at 8.8 and 3.3 in Western Africa [2]. It is characterized by a relative 5-year survival of 33% in women and 31% in men and relative 10-year survival of 30% in women and 28% in men. The median age of diagnosis in Germany in 2018 was 76 years for women and 71 years for men [3].

A fundamental part of surgical strategy is lymphadenectomy. Regional lymph nodes (LN) can be assigned to compartment I (No. 1–6 along the small and large gastric curvature) and compartment II (No. 7–12 and 14). In carcinomas of the cardia, LN located paraesophageally in the lower mediastinum, in the hiatus and infra- and supradiaphragmatically, are assigned to compartment III (No. 19, 20, 110 and 111) [4]. D1-lymphadenectomy is understood as a dissection of the perigastric LN 1–6 (compartment I), while D2-lymphadenectomy corresponds to an additional dissection of the LN 7–11 (compartment II) along the large arteries of the stomach. An additional lymphadenectomy is designated as D3 (Table 1).

Table 1. The extension of lymphadenectomy in gastric cancer.

	Numbers of Lymph Node Stations		
Type of Lymphadenectomy	**Compartment I**	**Compartment II**	**Compartment III**
D1	1, 2, 3, 4, 5, 6	-	-
D2	1, 2, 3, 4, 5, 6	7, 8, 9, 10,11	-
D2-plus	1, 2, 3, 4, 5, 6	7, 8, 9, 10,11	12, 13, 16
D3	1, 2, 3, 4, 5, 6	7, 8, 9, 10,11	12, 13, 14, 15, 16

Lymph node stations: 1: right cardiac nodes, 2: left cardiac nodes, 3: nodes along lesser curvature, 4: nodes along greater curvature, 5: suprapyloric nodes, 6: infrapyloric nodes, 7: nodes along left gastric artery, 8: nodes along common hepatic artery, 9: nodes along celiac trunk, 10: nodes at splenic hilum, 11: nodes along splenic artery, 12: nodes at the hepatoduodenal ligament, 13: retropancreatic nodes, 14: nodes at the root of mesentery, 15: nodes along the middle colic vein, 16: para-aortic nodes.

Some also suggest D2-plus lymphadenectomy (removal of the "posterior" lymph node stations located behind the hepatic artery (no. 8p), the hepatoduodenal ligament (no. 12b/p), the retropancreatic nodes (no. 13), and the para-aortic area (no. 16a2/b1)) with low morbidity and mortality rates and with benefits in survival [4].

A minimum of 25 regional LN should be removed and examined histopathologically. A classification of pN0 is only possible after the excision and histological examination of at least 16 regional LN [5–7]. A curative treatment for gastric carcinoma includes a R0-resection with a D2-lymphadenectomy; however, in selected patients, when necessary, D2-plus or D3 lymphadenectomy should also be considered [4,8].

Survival is determined by patient age, depth of invasion, LN involvement, lymph node ratio (LNR), lymphatic vessel invasion, tumor size, type of surgery, Lauren-classification, and location of infiltrated LN [9]. Early results depend on postoperative course, and anastomotic leak is one of the most important causes of postoperative morbidity and mortality [10]. The 5-year survival rate is estimated to be around 50.4%. However, more specifically, it has been found to be 89.3% for pT1, 72.4% pT2, 36.9% pT3 and 23.7% pT4; for pN0 75.2%, pN1 68.8% pN2 46.7% pN3 and 21.3% [11]; and 93.2% for UICC-stage I, 72.4% stage II, 39.1% stage III and 5.2% stage IV [12].

LN status seems to be a key point in assessment of prognosis in gastric cancer, although the best method to assess LN involvement remains debatable [13]. The LNR, defined as number of positive LNs divided by the number of sampled LNs, offers a new approach for predicting survival, with higher LNR significantly correlating with lower 5-year survival [14]. LNR-based methods allow more accurate estimation of survival compared to TNM classification alone [15,16]. Indeed, its prognostic importance has already been confirmed for colon and pancreatic cancer [17,18].

2. Materials and Methods

2.1. Patients and Data Collection

Data were collected as part of a prospective multicenter quality assurance study (Institute for Quality Assurance in Operational Medicine at the Otto von Guericke University, Magdeburg, Germany); however, taking into account the limitations of our study, we regard the outcomes as preliminary results. P, which have to be confirmed by further research.

Participation was voluntary, and all participants gave their written informed consent to take part. Considering the character of the study design (observational prospective study for quality control), participating hospitals included three levels of care (regional, institute, university).

According to the ethics committee of Otto-von-Guericke University, Magdeburg, no ethical votum was required due to the observational character of the study. All centers were sending their data to the same database form (Quality Assurance Study Protocol Database) built for the study.

The following inclusion criteria were selected:

- Histologically confirmed primary gastric adenocarcinoma;
- Documented lymphadenectomy;
- R0-resection.

Exclusion criteria comprised:

- UICC stage 0;
- UICC stage IV;
- Pre-existing infiltration of neighboring organs (invasion of the duodenum or esophagus alone did not lead to exclusion);
- Postoperative mortality.

Only lymph node-positive patients were included in the LNR calculations. The cohort was then divided into two groups based on German guidelines specifying that an excision of at least 16 LN is necessary for an assignment “pN0” [19].

Based on the available literature, four cut-off values were chosen: 0.1 (0.01–0.1), 0.2 (0.11–0.02), 0.4 (0.21–0.4) and >0.4 [14,20–24].

2.2. Statistical Analysis

All data were integrated into Access databases after being checked for plausibility and completeness. The analysis was performed with IBM® SPSS® Statistics, version 24.0.0; copyright 1989–2016, SPSS Inc. (Chicago, IL, USA).

Continuous variables were described by mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum. Categorical variables were represented by their absolute and relative frequencies and were compared using the chi-square test. To reject the null hypothesis, a p-value < 0.05 was assumed to be statistically significant.

For individual frequencies below 5 and a four-field table, Fisher’s exact test was used. Systematic differences between two groups, such as BMI, sex or ASA-classification, were examined with the t-test if the variables were normally distributed and with the Mann–Whitney U-test if they were not.

Categorical variables with more than two values were compared using analysis of variance, for parametric data, or the Kruskal–Wallis test, for non-parametric data. For normal distribution, the Shapiro–Wilk test was used.

Multivariate logistic regression analysis was performed to predict the relationships between various independent variables and lymph node yield, as the dependent discrete variable. The non-parametric estimates of survival were presented using the distribution-independent Kaplan–Meier curve. All patients who had not died before October 2016 were included in the current survival determination.

Differences were compared in terms of survival using the log-rank test. Median survival and the associated 95% confidence interval were calculated. Survival data were analyzed using Cox regression.

3. Results

From January 2007 to December 2012, 4946 patients from 149 hospitals were enrolled and were followed up until October 2016. The reasons for exclusion: UICC 0, IV: 943 patients; cancer without histological confirmation: 418 patients; invasion of neighboring organs: 489 patients; mortality: 216 patients; resection R1: 372 patients; resection R2: 311 patients; incomplete data: 313 patients. The inclusion criteria were met by 1884 patients. Participating departments reported, on average, 33 (1–217) patients. The median follow-up was 61 months. Of the 1884 patients included, 1118 gave their consent to follow-up; follow-up data were available for 975 patients (87.2%).

A mean of 24.4 $\pm$ 0.65 LN were resected and 2.6 $\pm$ 0.25 were positive. The mean LNR was 0.1068. The patients were divided into two groups for further analysis: Group 1 (<16 LN) comprised 456 patients and Group 2 (16 or more LN) 1428 patients.

3.1. Lymph Node Yield Analysis

A total of 700 women and 1180 men were examined. The mean age was 69.3 ($\pm$1.0) years in Group 1 and 66.9 ($\pm$0.6) in Group 2 ($p < 0.001$). Mean BMI was 26.4 and did not differ between groups. The most common procedure was total (35.1%) or subtotal (25.9%) gastrectomy, performed in 61% of cases, followed by cardiac resection (7.9%), distal gastrectomy with gastrojejunostomy (7.7%) and transhiatal extended gastrectomy (6.6%). The highest numbers of LN were obtained in transhiatal extended gastrectomy. Systematic lymphadenectomy resulted in a significantly higher lymph node yield ($p < 0.001$) compared with limited resection. On average, one lymph node was affected in Group 1, and more than three in Group 2 ($p < 0.001$). Lymphatic invasion (L1) could be detected in 786 (41.9%) specimens (Group 1 n = 160, Group 2 n = 626, $p < 0.001$). Venous invasion (V1) could be detected in 212 (12.5%) patients (Group 1 n = 46, Group 2 n = 166; $p = 0.737$). Information on the histological tissue of the carcinomas was available for 1361 patients. Gastric adenocarcinoma was found in almost 90% of the patients (n = 1236). The tubular and signet ring cell carcinomas accounted for the largest share, with a total of 68%, followed by mucinous and papillary adenocarcinomas. Significantly fewer lymph nodes were removed from mucinous adenocarcinomas ($p = 0.038$), significantly more from signet ring cell carcinomas ($p = 0.026$). Total (52.9%) or subtotal (28.4%) gastrectomy was performed in 81.3% of all patients, followed by proximal resection (3.1%). Total gastrectomy and transhiatal extended gastrectomy were the most successful in terms of lymph node yield. Details are given in Table 2.

Table 2. Effect of patient and tumor-related factors on lymph node yield.

		Group 1 (n/%)	Group 2 (n/%)	*p*-Value *
Sex	Male	213/68.6	868/60.9	<0.001
	Female	143/31.4	557/39.1	
ASA-classification	ASA I	23/5.1	121/8.6	<0.001
	ASA II	199/44.3	767/54.5	
	ASA III	214/47.7	495/35.2	
	ASA IV	13/2.9	24/1.7	
Grading	G1	39/8.6	59/4.1	<0.001
	G2	159/34.9	429/30.2	
	G3	228/50.1	836/58.8	
	G4	14/3.1	27/1.9	
Histology	Papillary adenocarcinoma	30/6.6	97/6.8	0.874
	Tubular adenocarcinoma	114/25.0	371/26.0	0.677
	Mucinous adenocarcinoma	56/12.3	128/9.0	0.038
	Signet ring cell carcinoma	89/19.5	351/24.6	0.026
	Undifferentiated carcinoma	25/5.5	84/5.9	0.750
	Small cell carcinoma	2/0.4	0/0.0	-
	Squamous cell carcinoma	4/0.9	7/0.5	0.345
	Adenosquamous carcinoma	0/0.0	3/0.2	0.327
Surgical approach	Laparotomy	430/95.2	1411/99.1	<0.001
	Laparoscopic	18/4.0	7/0.5	
Surgical procedure	Proximal resection	36/8.2	22/1.5	<0.001
	Subtotal/distal gastrectomy	166/37.9	364/25.6	0.112
	Total gastrectomy	160/36,4	827/58.1	<0.001
	Transhiatal extended gastrectomy	30/6.8	144/10.1	0.024
	Transthoracic extended gastrectomy	17/3.9	33/2.3	0.101
	Thoraco-abdominal esophagogastrectomy	16/3.6	23/1.6	0.013
	Other gastrectomy	14/3.2	12/0.8	<0.001
Neoadjuvant treatment	No	363/80.3	1054/74.3	0.009
	Yes	89/19.7	365/25.7	
Localization	Gastroesophageal junction	125/27.4	280/19.6	<0.001
	Fundus	19/4.2	45/3.2	0.297
	Corpus	142/31.1	553/38.7	0.003
	Antral/pyloric region	181/39.7	601/41.5	0.366
Invasion depth	pT0	0/0.0	2/0.1	<0.001
	pT1	200/44.0	460/32.3	
	pT2	88/25.1	262/18.4	
	pT3	167/36.7	699/49.1	

Table 2. *Cont.*

		Group 1 (n/%)	Group 2 (n/%)	*p*-Value *
pN-stage	pN0	288/63.6	756/53.0	<0.001
	pN1	81/17.9	239/16.8	
	pN2	52/11.5	203/14.2	
	pN3	32/7.1	228/16.0	
UICC-stage	I	249/54.6	578/40.5	<0.001
	II	117/25.7	427/30.6	
	III	90/19.7	413/28.9	

* Chi^2-Test.

The univariate analysis found the following factors to affect LN yield ≥ 16 LN: neoadjuvant treatment, grading, pT-stage, pN-stage, lymphatic invasion, venous invasion, UICC-stage, Lauren-classification, and localization at the gastroesophageal junction ($p < 0.001$) and the antral/pyloric region ($p = 0.030$) (Table 3).

Table 3. Univariate analysis. Prognostic factors predicting lymph node yield ≥ 16.

		LK-Quotient (Mean ± SD)	*p*-Value
Sex	Male	0.11 ± 0.19	0.132 **
	Female	0.10 ± 019	
Age groups <70, 70–80, >80	<70	0.11 ± 0.19	0.213 *
	70–80	0.11 ± 0.19	
	>80	0.12 ± 0.21	
BMI	<18.5	0.15 ± 0.23	0.682 *
	18.5–24.9	0.11 ± 0.20	
	≥25	0.10 ± 0.18	
Lauren classification	None	0.11 ± 0.18	**<0.001 ***
	Intestinal	0.08 ± 0.16	
	Diffuse	0.14 ± 0.23	
	Mixed	0.10 ± 0.17	
Localization	Fundus	0,12 ± 0.20	0.889 **
	Gastroesophageal junction	0.14 ± 0.20	**<0.001 ****
	Corpus	0.11 ± 0.20	0.923 **
	Antrum/pylorum	0.10 ± 0.20	**0.030 ****
ASA-classification	I	0.10 ± 0.19	0.440 *
	II	0.11 ± 0.20	
	III	0.11 ± 0.19	
	IV	0.05 ± 0.10	
Neoadjuvant treatment	**No**	0.10 ± 0.19	**<0.001 ****
	Yes	0.12 ± 0.19	
Surgical approach	Laparotomy	0.11 ± 0.19	0.548 **
	Laparoscopic	0.07 ± 0.12	

Table 3. *Cont.*

		LK-Quotient (Mean ± SD)	*p*-Value
Grading	G1	0.01 ± 0.07	**<0.001 ***
	G2	0.08 ± 0.16	
	G3	0.13 ± 0.21	
	G4	0.11 ± 0.18	
pT-stage	pT0	0.06 ± 0.08	**<0.001 ***
	pT1	0.02 ± 0.08	
	pT2	0.08 ±0.15	
	pT3	0.17 ± 0.23	
pN-stage	pN0	0.01 ± 0.03	**<0.001 ***
	pN1	0.06 ± 0.05	
	pN2	0.15 ± 0.07	
	pN3	0.47 ± 0.22	
Lymph invasion	**L0**	0.03 ± 0.09	**<0.001 ****
	L1	0.20 ± 0.23	
Venous invasion	V0	0.09 ± 0,17	**<0.001 ****
	V1	0.24 ± 0.27	
UICC-stage	I	0.003 ± 0.01	**<0.001 ***
	II	0.05 ± 0.10	
	III	0.31 ± 0.24	

* Kruskall–Wallis Test, ** Mann–Whitney U-Test.

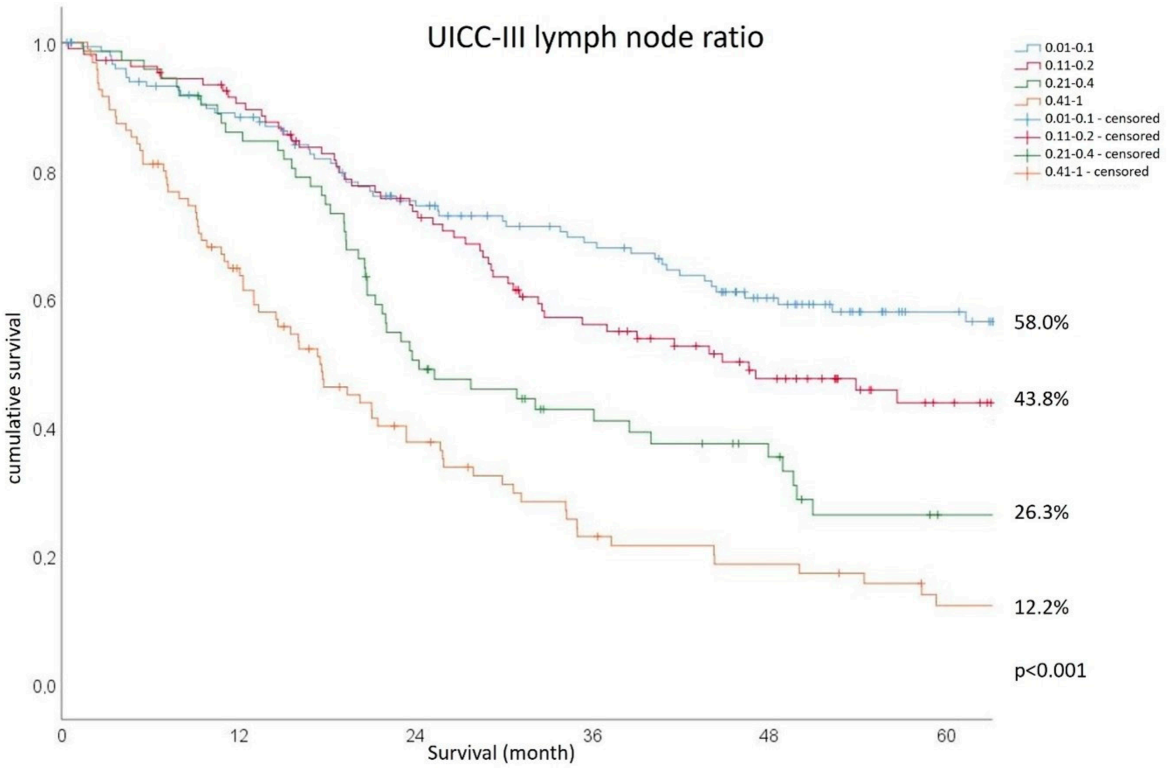
The multivariate logistic regression analysis found grading (grade 2 and 3), UICC-stage, age < 70 years and sex to be independent factors influencing excision of ≥16 LN (Table 4).

Table 4. Factors predicting lymph node yield of ≥16 LN. Results of the logistic regression.

		Odds Ratio (95% CI)	*p*-Value
Grading	G1	1	
	G2	1.982 (1.110–3.541)	**0.021**
	G3	2.154 (1.212–3.829)	**0.009**
	G4	0.739 (0.268–2.036)	0.558
UICC-stage	I	1	
	II	1.441 (1.008–2.060)	**0.045**
	III	1.707 (1.135–2.568)	**0.010**
Age groups	>80	1	
	<70	1.818 (1.188–2.783)	**0.006**
	70–80	1.358 (0.874–2.109)	0.173
Sex	Men	1	
	Women	1.365 (1.000–1.863)	**0.050**
Venous invasion	No (V0)	1	
	Yes (V1)	0.647 (0.411–1.016)	0.059

3.2. Long-Term Survival Analyses

Age, pT-stage, UICC-stage and LNR were significant prognostic factors for survival ($p < 0.001$). Postoperative survival was found to decrease with increasing age. Median survival was 65.2 months (<70 year group), 54.7 months (70–80 years) and 44.5 months (>80 years) ($p < 0.001$). Survival also decreased with increasing pT-stage. Overall survival was 95.0 months, but only 56.7 months for patients with pT3 and 103.4 months for pT2. No information for stage pT1 can be given, as the probability of survival at the end of the follow-up was over 50%. Five-year survival also decreased with increasing UICC-stage: 75.2% for UICC-I, 65.6% for UICC-II and 30.8% for UICC-III. It also correlated significantly with LNR ($p < 0.001$), even in the first few months: 5-year survival in UICC-III was found to be 58.0% for LNR 0.1, 43.8% for LNR 0.2, 26.3% for LNR 0.4 and 12.2% for LNR > 0.4 (Figure 1).



LNR.	0 month	12 months	24 months	36 months	48 months	60 months
0.01–0.1	150	127	99	82	61	39
0.11–0.2	107	93	73	52	36	20
0.21–0.4	72	61	35	24	17	9
0.41–1	95	57	30	17	13	7

Figure 1. Five-year survival as a function of lymph node ratio.

The multivariate analysis found patients with a LNR of 0.4 and > 0.4 have a lower probability of survival ($p = 0.039$ and <0.001) compared to patients with a LNR of 0.1. Furthermore, patients with UICC-II gastric cancer have a lower probability of survival than patients with UICC-I ($p = 0.023$). Cox regression also identified age 70–80 years ($p = 0.045$) and over 80 years ($p = 0.003$) as negative prognostic factors for long-term survival (Table 5).

Table 5. Results of Cox regression analysis for 5-year survival.

		Hazard Ratio (95% CI)	*p*-Value
Lymph node ratio	0.01–0.1	1	
	0.11–0.2	1.207 (0.770–1.893)	0.413
	0.21–0.4	1.652 (1.027–2.659)	**0.039**
	0.41–1	2.746 (1.740–4.333)	**<0.001**
UICC-stage	I	1	
	II	0.485 (0.260–0.905)	**0.023**
	III	0.849 (0.436–1.654)	0.630
Age groups	<70	1	
	70–80	1.374 (1.008–1.874)	**0.045**
	>80	1.806 (1.225–2.663)	**0.003**

4. Discussion

This study included one of the largest cohorts in any study about LNR to date. The findings indicate that stratification with a 4 LNR cut-off was statistically valid. LNR allows better differentiation and more precise prediction of outcomes among LN-positive gastric carcinomas.

4.1. Lymph Node Yield

A strong positive correlation was observed between the number of LNs removed and the number of LNs affected ($p < 0.001$). Similar results were obtained by Huang, who reported a mean number of 23.1 ± 8.6 LN removed per patient [25], and in another Chinese study with 1470 patients, where a mean of 25.8 ± 12.8 LN were removed [26]. Even in patients with LN-negative gastric cancer, survival improved when increased numbers of LN were removed [26]. In a Korean study [27], patients with pT1 tumor, pN0-status and UICC-1 stage demonstrated a significantly worse prognosis when fewer than 16 LN were removed compared to those with 16 or more.

The highest numbers of LN were removed in G3 carcinomas, whereas the LN yield in G1 and G4 was particularly poor. Similar results were obtained in a study from Beijing [28], where most patients were found to have G3 (48.2%) and G2 (22.1%); however, G4 carcinomas were more common (26.2%) than in the present study (2.2%), probably mostly due to our exclusion criteria. Grading was also found to be a significant prognostic factor for LN yield in a univariate analysis from Finland [29]. G4 tumors are often marked by fast growth and early tumor spread; as such, in some cases, intraoperative findings may lead to limited resection, resulting in reduced numbers of removed LN. We cannot find the scientific explanation of relations between lymph node yield, grading, venous and lymphatic invasion found in our study; it probably would need more specified research.

UICC-stage is determined by depth of invasion, LN involvement and metastasis. Interestingly, regarding depth of invasion, the most common classification in the present study was pT3, at 46.1% of examined specimens; this was also found to be the most common form in a study by Chen, at 40.8% [27], and a US study, at 36.4% [23]. Our data indicate that the number of LNs removed increased with the depth of invasion. We would hypothesize that size of tumor is correlated with the depth of invasion (pT stage) [11] and thorough this influences the decision to perform, and the extent of, fatty tissue dissection.

The mean age of patients in this study was 66.7 years for men and 69.2 years for women. These were slightly lower than the mean values in the German database from the Robert Koch Institute, listing all gastric cancer patients (71 years for men and 76 years for women) [3]. Age group clearly affected the extent of LN yield, with age 70–80 years having the most LN removed. This was also confirmed in a Chinese study, which found older patients to have more advanced and larger tumors [30]. This might explain the difficulties associated with lymphadenectomy in the elderly. Also, older patients have more comorbidities that might require more limited surgery, i.e., shorter operations with a lower risk of complications. Mayol-Oltra et al. [31] report that the presence of comorbidities in older patients leads to fewer LN being removed. This might be the reason for fewer LN being removed in patients aged > 80 years in our study.

Fewer LNs tend to be removed from male patients. This may be significant, as gastric carcinoma is more common in men. The sex ratio in the present study was 1:1.69 women to men. A similar ratio, i.e., 1:1.65, was noted for 2018 German data from the Robert Koch Institute [3]; however, a study by the Korean Cancer Association found the ratio to fall from 1:1.8 in 2004 to 1:1.5 in 2014 [32]. The numbers of new cases of gastric carcinoma seem to approximate between the sexes.

Neoadjuvant treatment led to a significant increase in harvested LN ($p = 0.009$). In contrast, Li et al. [33] report that preoperative chemoradiotherapy caused a decrease in LN yield (25.5). Chemotherapy alone (31.0) also resulted in a decreased LN yield compared to patients not receiving neoadjuvant treatment (32.0). The extent to which neoadjuvant radiotherapy affects LN excision remains to be investigated, but it has been demonstrated that preoperative radiotherapy can increase the chance of 5-year survival from 19.75% to 30.10% and 10-year survival from 13.30% to 20.26% ($p = 0.0094$). Radiotherapy also reduced the rate of LN metastases from 84.9% to 64.3% [34]. Other studies [20,35] using neoadjuvant chemotherapy demonstrated an increase in free resection margin and a decrease in the number of local LN metastases.

In recent years, there has been a significant shift towards immunotherapy as a promising avenue for the treatment of advanced malignancies. Clinical trials have also demonstrated the efficacy of neoadjuvant immunochemotherapy in patients with locally advanced gastric cancer [36,37]. Zhou P. et al. [38] found that high LNR (≥33%) was an independent prognostic factor for overall survival (HR 6.258, 95% CI 1.798–21.778; $p = 0.004$) and progression-free survival (HR 3.431, 95% CI 1.341–8.780; $p = 0.010$).

Unfortunately, detailed information about neoadjuvant treatment was not included in the protocol and thus was not assessed in the present study. We realize that it could be one of the limitations of our study.

The gastric carcinomas demonstrated similar localizations, as noted in Chinese studies by Chen et al. [28] and Zhao et al. [39]. Most carcinomas were found in the lower third (antrum/pylorus) followed by the middle third (corpus). Our data indicate that tumor location and LN yield are significantly related. Recent studies indicate that tumors may also occur more frequently in the upper third: one Turkish study [40] found cardia carcinomas to be more common than those in other parts ($p = 0.004$).

4.2. Lymph Node Ratio

The univariate and multivariate analyses found age group, depth of invasion, UICC-stage and LNR to be independent prognostic factors for long-term survival. This has been confirmed in other studies [39,41,42]. LNR and intestinal histological type were found to be independent prognostic factors in a Japanese study [20], and pT-stage, pN-stage and extent of surgery in a Polish study [22]. Son et al. found age ≥ 60 years, male sex, pT-stage, pN-stage, insufficient number of examined LN and upper tumor localization to be significant risk factors for survival [27], while age, UICC-stage, resection margin and LNR were indicated as independent prognostic factors in a study from the NYU School of Medicine [21].

While depth of invasion is a component of UICC-stage and can independently predict survival, LNR seems to be better suited to predict survival than pN-stage. LNR appears to effectively predict 5-year survival regardless of cut-off value. It was found to be 63.4% at a cut-off of LNR 0.15, 46.9% at LNR 0.4, and 22.6% at LNR of 0.41–1 in a Chinese study [39]. A meta-analysis of 27 articles comprising 11,441 patients with gastric cancer and radical surgery found higher LNR to be clearly associated with shorter overall survival; however, the studies displayed high heterogeneity [43].

In the present study, the UICC-III patients demonstrated 5-year survival values of 58.0% (LNR 0.01–1), 43.8% (0.11–0.2), 26.3% (0.21–0.4) and 12.2% (0.41–1). LNR allows a more accurate and detailed prognosis estimation for pN-positive gastric cancer patients compared to AJCC/TNM-staging alone [44,45]. In a population-based study by Huang et al. [46], a total of 13,027 patients with IIIA category (8th AJCC) were classified into subgroups rIIB, rIIIA, rIIIB and rIIIC with the help of LNR; the patients demonstrated a similar 5-year overall survival rate to our present cohort, i.e., from 66.7% to 5.1%. Combined TNM and LNR seem also more reliable for prognosis in patients with neoadjuvant treatment compared to TNM-classification alone, as shown in a large population-based study from Chen et al. [16] with 1791 patients.

The distribution of LN involvement in this study roughly corresponds to that observed in an US review comprising 9357 patients. In both cases, the largest group included patients without local LN metastases: 45.1% in the US study compared to 55.5% in this study. Individual pN1–pN3 stages differed by only a few percent between studies (pN1: 19.5% vs. 17.0%; pN2: 16.9% vs. 13.6%; pN3: 18.5% vs. 13.8%) with slightly higher values noted in all groups in the American study [23]. A Chinese study [41] (935 patients) comparing three different LN staging systems in survival prognosis following D2 lymphadenectomy in gastric cancer found LNR to be superior to pN-stage.

Our data indicate a significant positive relationship between the number of positive LNs and the numbers of LN removed ($p < 0.001$). Similar results were found in a Chinese study by Zhao [39], in which 858 patients were classified as free of metastases (pN0), 511 were assigned to pN1, 494 to pN2 and 712 to pN3. It is important to note that care should be taken to completely remove the individual LN compartments; this is particularly important for carcinomas with a low UICC-stage. It was also found that removing higher numbers of LN was also related to improved overall survival [47].

Our data indicate that LNR was a significant prognostic factor for long-term survival. This has also been confirmed in several other studies [14,20,22,23,39,41,42,45,46,48] using a variety of cut-off points ranging from LNR 0 to 0.8. The numbers of patients in these studies range from 73 to 9357. Our classification with LNR cut-off values of 0.1, 0.2, 0.4 and >0.4 was found to give a precise survival prognosis for patients with 16 or more LN removed and who are lymph node-positive.

Interestingly, retrospective data from Sun Yat-sen University Hospital in China [46] (2205 patients) displayed no difference in survival prognosis for patients with ≥16 LN removed (C-index: 0.77) compared to patients with ≤15 LN removed (C-index: 0.75). Also, among patients with ≥UICC-2 stage, Son et al. [27] found no difference in overall survival between patients with <16 removed LN and those with 16 or more. As such, it may be that LNR could be a useful indicator even in the event of insufficient LN harvest.

4.3. Limitations of the Study

We realize that our study has several limitations. Participating hospitals were not obliged to follow any specific pathological and surgical protocol. The decisions (surgical and pathological) were made only according to current guidelines. We realize that the lack of a uniform protocol might have influenced our results. In the database protocol, the only ASA classification was included to describe patient general stage and, indirectly, comorbidities. Information on particular comorbidities was not collected. The obtained data concerned the neoadjuvant therapy without information on the details of the therapy (type of treatment, time of duration). For that reason, we were not able to provide the precise impact of individual elements of neoadjuvant therapy but only its overall impact on lymph node yield.

5. Conclusions

Long-term survival of patients with gastric carcinoma is directly related to adequate lymphadenectomy. LNR is superior to pN-stage for estimating survival and adds remarkable nuances in prognosis compared to UICC-stage. LNR also appears valid even in the case of insufficient LN yield. We hence recommend that LNR should be incorporated into staging systems (UICC/AJCC) and into the decision process for adjuvant strategies.

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Conflicts of Interest: Authors Martin Schwanz, Ronny Otto, Hans Lippert and Pawel Mroczkowski were employed by the company Institute for Quality Assurance in Operative Medicine Ltd. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

LNR	Lymph Node Ratio
TNM	Tumor Nodes Metastasis
LN	Lymph Node
BMI	Body Mass Index
UICC	Union for International Cancer Control
AJCC	American Joint Committee on Cancer
ASA	American Society of Anesthesiology

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