Prognostic Value of Tumor Regression Systems and Lymph Node Regression in Gastric Adenocarcinoma After Neoadjuvant Chemotherapy

Ann. Ital. Chir., 2026 97, 1: 185–195
https://doi.org/10.62713/aic.4201

Özgecan Gündoğar[1], Sibel Bektaş[1], Hüseyin Karatay[2], Esra Paşaoğlu[3], Tevhide Bilgen Özcan[3], Nilsen Yıldırım Erdoğan[2], Pelin Akbaş[1], Emine Yıldırım[4], Sercan Yüksel[5], Özlem Özkul[6]

[1]Department of Pathology, Gaziosmanpaşa Training and Research Hospital, University of Health Sciences, 34255 Istanbul, Turkey
[2]Department of Pathology, Basakşehir Cam and Sakura City Hospital, University of Health Sciences, 34480 Istanbul, Turkey
[3]Department of Pathology, Bağcılar Training and Research Hospital, University of Health Sciences, 34200 Istanbul, Turkey
[4]Department of General Surgery, Istanbul Atlas University, 34203 Istanbul, Turkey
[5]Department of General Surgery, Basakşehir Cam and Sakura City Hospital, University of Health Sciences, 34480 Istanbul, Turkey
[6]Department of Medical Oncology, Bağcılar Training and Research Hospital, University of Health Science, 34200 Istanbul, Turkey

AIM: This study aimed to assess the prognostic significance of various histologic tumor regression grade (TRG) systems (Becker, American Joint Committee on Cancer (AJCC)/College of American Pathologists (CAP), Japanese Gastric Cancer Association (JGCA), JGCA2017, China, Mandard) and lymph node (LN) regression in patients with locally advanced gastric adenocarcinoma who underwent gastrectomy following neoadjuvant chemotherapy (NACT).

METHODS: A retrospective cohort of 134 patients with locally advanced gastric adenocarcinoma from January 2020 to March 2024 who received NACT followed by gastrectomy was analyzed. Due to incomplete records, only the fact that patients received NACT was used, without specific regimen details. Surgical specimens were evaluated by two pathologists according to Becker, AJCC/CAP, JGCA, JGCA2017, China, and Mandard TRG systems. LN regression was categorized as positive/negative and coded as three categories (Code 1: metastasis without regression; Code 2: metastasis with regression; Code 3: regression without metastasis). Clinicopathologic variables, overall survival (OS) and disease-free survival (DFS) were analyzed by Kaplan–Meier curves and log-rank tests. Univariable and multivariable Cox regression models included each TRG subgroup as dummy variables and relevant covariates. Statistical significance was defined as $p < 0.05$.

RESULTS: The median follow-up time was 24 months (range 6–60). The median OS was 18.7 months (95% CI 16.2–21.3), while the median DFS was 16.4 months (95% CI 14.1–18.7). In the univariable analysis, JGCA2017 Score 0 (hazard ratio [HR] 0.28; 95% CI 0.12–0.65; $p = 0.003$), Score 1a (HR 0.36; 95% CI 0.16–0.83; $p = 0.017$), and clinical N3 stage (HR 1.95; 95% CI 1.15–3.30; $p = 0.013$) were significantly associated with both OS and DFS. In multivariable Cox models, independent predictors of OS were JGCA2017 Score 0 (HR 0.25; 95% CI 0.11–0.59; $p = 0.002$), Score 1a (HR 0.33; 95% CI 0.15–0.76; $p = 0.009$), cN3 (vs cN1–2; HR 2.05; 95% CI 1.18–3.56; $p = 0.010$), and positive LN regression (HR 0.42; 95% CI 0.23–0.77; $p = 0.005$). Regarding DFS, JGCA2017 Score 0 (HR 0.30; 95% CI 0.12–0.75; $p = 0.009$), cN3 (vs cN1–2; HR 1.90; 95% CI 1.10–3.30; $p = 0.020$), and positive LN regression (HR 0.50; 95% CI 0.28–0.90; $p = 0.018$) were independent predictors. Other TRG systems' subgroups did not remain significant in multivariable models. Notably, the JGCA2017 Score 0/1a categories independently predicted better OS and DFS, whereas positive LN regression also emerged as a protective prognostic factor.

CONCLUSIONS: JGCA2017 subgroups are the most robust prognostic indicators for OS and DFS in patients with gastric adenocarcinoma following NACT. Positive LN regression is also an independent protective factor. Prospective validation and international standardization of these grading systems are warranted.

Keywords: gastric adenocarcinoma; neoadjuvant chemotherapy; histological tumor regression; lymph node regression; tumor regression grading systems; prognostic factors; survival

Introduction

Gastric adenocarcinoma is the fifth most common cancer and the fourth leading cause of cancer-related mortality worldwide [1]. Neoadjuvant chemotherapy (NACT) has become a pivotal component of treatment for locally advanced disease, improving both resectability and overall survival [2]. The rationale of this multimodal approach is to downstage the primary tumor, eradicate micrometastatic disease, and ultimately increase the likelihood of a complete pathological response, thereby improving long-term prognosis [3,4]. Evaluation of treatment efficacy following NACT is most commonly performed through tumor regression grade (TRG) systems, which histologically quantify residual tumor cells in resected specimens and correlate

Submitted: 8 June 2025 Revised: 22 September 2025 Accepted: 20 October 2025 Published: 10 January 2026
Correspondence to: Özgecan Gündoğar, Department of Pathology, Gaziosmanpaşa Training and Research Hospital, University of Health Sciences, 34255 Istanbul, Turkey (e-mail: ozgecankarahan@hotmail.com).
Editor: Weihua Gong

these findings with clinical outcomes [2]. Several well-established TRG classifications, including those by Mandard, the Japanese Gastric Cancer Association (JGCA), the College of American Pathologists (CAP), and Becker, propose distinct histological criteria; however, their prognostic reliability remains inconsistent [5–10]. Notably, the question of which system provides the most robust and reproducible prognostic insights into gastric adenocarcinoma remains unanswered, underscoring the need for further comparative validation [11].

In addition to primary tumor regression, the response of regional lymph nodes to NACT has emerged as a factor of considerable prognostic relevance. Increasing evidence suggests that lymph node regression may carry independent predictive value beyond that of the primary tumor, refining survival estimates and therapeutic decision-making. Against this background, we conducted a multicenter retrospective analysis that systematically compares six TRG systems in gastric adenocarcinoma. We also integrated a detailed evaluation of lymph node regression without collapsing individual subgroups [12,13]. This study aims to delineate the separate and combined prognostic contributions of primary tumor and nodal regression, thereby advancing the pathological assessment of gastric cancer following NACT and providing insights into more precise risk stratification.

Methods

Patient Selection and Clinical Data

We retrospectively identified 134 patients with clinical stage cT2–cT4a, cN0–3, and cM0–cM1 gastric adenocarcinoma treated at our institutions between January 2020 and March 2024. Representative histological appearance of gastric adenocarcinoma is shown in Fig. 1. All patients received NACT followed by gastrectomy. Clinical demographics (age, sex, tumor location), surgical dates, postoperative pathology reports, recurrence/metastasis data, survival status, and follow-up times were obtained from electronic medical records. Recurrence was defined as radiologically or pathologically confirmed disease relapse after surgery. For each patient, only the first recurrence event was recorded, categorized as either local recurrence or distant metastasis. These categories were mutually exclusive.

Inclusion criteria were as follows:

• Clinical stage cT2–cT4a, cN0–3, and cM0 gastric adenocarcinoma at diagnosis;

• Receipt of neoadjuvant chemotherapy followed by radical surgery, specifically total gastrectomy;

• Availability of baseline clinical and pathological data (demographics, pathology report, survival/follow-up information).

Exclusion criteria were as follows:

• Incomplete or unavailable essential pathological data;

• Patients who did not undergo radical gastrectomy;

• Insufficient follow-up information for survival analysis.

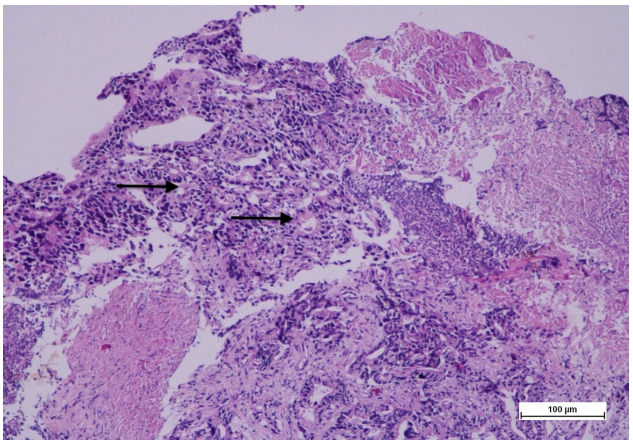

Fig. 1. Gastric adenocarcinoma demonstrating atypical cribriform glandular formations within desmoplastic stroma (hematoxylin and eosin (H&E) ×100) (→: atypical glandular structures).

This study was approved by the Ethics Committee of Basaksehir Cam and Sakura City Hospital, University of Health Sciences, Istanbul, Turkey (Approval No: 2024-15) and conducted in accordance with the Declaration of Helsinki. Due to the anonymization of all patient data, the requirement for informed consent was waived. No personal identifying information was included in the study.

Neoadjuvant Chemotherapy

Due to incomplete documentation, patients were categorized simply as having received NACT. Specific regimen details were unavailable and thus excluded from analysis.

Pathological Assessment

Surgical specimens were independently reviewed by two experienced pathologists (Dr. ÖG, Dr. HK). TRG systems were applied as follows: Becker TRG, American Joint Committee on Cancer (AJCC)/CAP TRG, JGCA TRG, JGCA2017 TRG, China TRG, and Mandard TRG [5–8]. Representative histopathological images illustrating the six tumor regression grading systems are presented in Fig. 2. For each case, regression findings in the lymph nodes—characterized by fibrosis and/or histiocytic aggregation (Fig. 3). Lymph node regression was categorized as Code 1 (metastasis present without regression), Code 2 (metastasis present with regression), and Code 3 (regression present without residual metastasis) [14]. In this classification, Code 1 indicates viable metastatic tumor cells without any histological features of regression. Code 2 refers to metastatic lymph nodes showing regressive changes, such as fibrosis, histiocytic infiltration, or acellular mucin, in addition to residual tumor cells. Code 3 denotes lymph nodes with regressive changes but no viable tumor cells, reflecting a complete nodal response. These definitions were standardized to clarify the biological implications of each category and to ensure reproducibility for multidisciplinary readers.

In this study, the original terminology of each TRG system was preserved. Accordingly, the terms 'Grade' were used for the Becker, Mandard, and China systems, while 'Score' was used for the JGCA, JGCA2017, and AJCC/CAP systems. These terminological differences reflect the inherent definitions of each classification, and we retained them consistently throughout the manuscript.

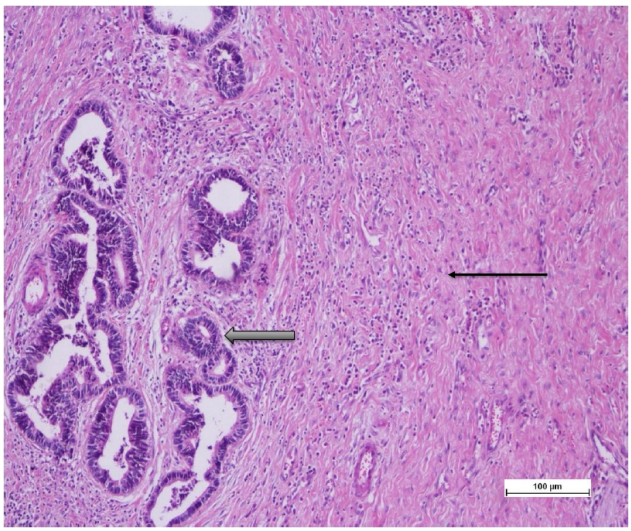

Fig. 2. Regression findings after neoadjuvant therapy. In the tumor bed, extensive fibrosis and desmoplastic stroma (←) were observed, with residual atypical glandular (⇐) structures identified at the periphery. These findings are consistent with partial tumor regression following neoadjuvant therapy (H&E ×100).

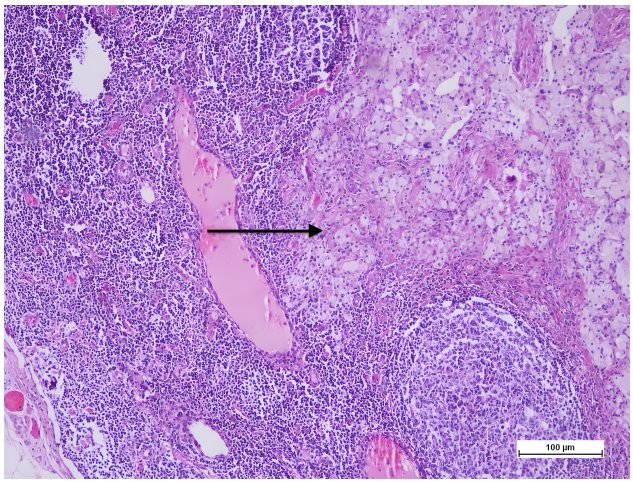

Fig. 3. Metastatic lymph node regression findings after neoadjuvant therapy. Fibrosis and prominent histiocytic reaction were identified within the lymph node, consistent with treatment-related regression (→) (H&E ×100).

Statistical Analysis

Analyses were performed using SPSS v25.0 (IBM Corp., Armonk, NY, USA). The normality of data distribution was assessed using the Shapiro–Wilk test. Continuous variables were expressed as mean ± standard deviation (SD) when normally distributed and compared using Student's *t*-test. Non-normally distributed continuous variables were expressed as median (range) and compared using the Mann–Whitney U test. For comparisons involving more than two independent groups, the Kruskal–Wallis test was applied, followed by Dunn–Bonferroni post hoc tests when appropriate.

Categorical variables were summarized as counts (%) and compared using the chi-square test, Fisher's exact test, or Fisher–Freeman–Halton test, as applicable. No formal adjustment for multiple testing was applied in the log-rank and Cox regression analyses, as the study was exploratory in nature and aimed to compare different TRG systems; therefore, *p* values should be interpreted with caution.

Survival analyses were performed using the Kaplan–Meier method, with comparisons assessed by the log-rank test. Univariable and multivariable Cox proportional hazards models were used to identify potential prognostic factors. Variables included in the multivariable models were selected based on clinical relevance and a stepwise approach to reduce overfitting. Each TRG system was evaluated in a separate model to avoid collinearity. Hazard ratios (HR) with 95% confidence intervals were reported, and statistical significance was defined as $p < 0.05$. For lymph node status, lymph node (LN)-negative (pN0) served as the reference category; HR values >1 indicated worse prognosis.

Results

Patient Demographics and Clinical Characteristics

Baseline characteristics of 134 patients are summarized in Table 1. Median age was 61.5 ± 9.8 years (range, 30–80); 99 (73.9%) were male and 35 (26.1%) were female. Clinical T stage: cT2, 20 (14.9%); cT3, 79 (59.0%); cT4a, 35 (26.1%). Clinical N stage: cN0, 13 (9.7%); cN1–2, 73 (54.5%); cN3, 48 (35.8%). All patients received NACT. Postoperative pathology: mean number of lymph nodes examined, 34 (range, 2–87); median number of metastatic nodes, 2 (range, 0–85).

Lymph node regression was categorized as Code 1 (metastasis present without regression), Code 2 (metastasis present with regression), and Code 3 (regression present without metastasis). A total of 117 patients had lymph nodes evaluated histologically. However, according to the lymph node regression coding system (Code 1: metastasis present without regression; Code 2: metastasis present with regression; Code 3: regression present without metastasis), codes were assigned only to cases showing either regression or metastatic involvement. Twenty-three patients with neither metastasis nor regression (no metastasis/no regression) were not included in the regression coding system.

Table 1. Demographic and clinicopathologic characteristics (n = 134).

Characteristic	All patients (n = 134)
Age (mean ± SD, years)	61.5 ± 9.8
Sex, n (%)	
– Male	99 (73.9)
– Female	35 (26.1)
Clinical T stage, n (%)	
– cT2	20 (14.9)
– cT3	79 (59.0)
– cT4a	35 (26.1)
Clinical N stage, n (%)	
– cN0	13 (9.7)
– cN1–2	73 (54.5)
– cN3	48 (35.8)
Received NACT, n (%)	134 (100.0)
Post-op mean LN count (range)	34 (2–87)
Median metastatic LN (range)	2 (0–85)
Lymph node regression, n (%)	
– Positive	69/117 (59.0)
– Negative	48/117 (41.0)
Post-NACT tumor size, n (%)	
– <4.5 cm	64 (48.1)
– 4.5–8 cm	49 (36.8)
– >8 cm	21 (15.1)
Histologic grade, n (%)	
– Grade 1 (well–moderate)	75 (56.0)
– Grade 2 (poor)	59 (44.0)
Lauren type, n (%)	
– Intestinal	86 (64.2)
– Diffuse	48 (35.8)
Vital status at last follow-up, n (%)	
– Alive	87 (65.4)
– Deceased	46 (34.6)
Recurrence, n (%)	
– Local recurrence	4 (3.0)
– Distant metastasis	30 (22.4)
– Total recurrence	34 (25.4)

Numbers may not add up to the total (n = 134) due to missing pathological or follow-up data in some cases. Specifically, LN regression data were unavailable for 10 patients.

LN, lymph node; NACT, neoadjuvant chemotherapy. There may be differences between the total number of patients (n = 134) and the sum of individual variables due to variable-specific missing data. Lymph nodes were histologically evaluated in 117 patients; however, regression codes were applied only to cases showing regression or metastasis (n = 94).

Table 2. Distribution of TRG subgroups and lymph node regression codes.

TRG system	Subgroup	n	%
Becker	Grade 1a (<10%)	16	11.9%
	Grade 1b (10–50%)	13	9.7%
	Grade 2 (50–90%)	37	27.6%
	Grade 3 (>90%)	68	50.7%
AJCC/CAP	Score 0 (CR)	16	11.9%
	Score 1 (minimal)	16	11.9%
	Score 2	59	44.0%
	Score 3	43	32.1%
JGCA	Score 0 (NR)	30	22.4%
	Score 1a (67–99%)	26	19.4%
	Score 1b (34–66%)	26	19.4%
	Score 2 (10–33%)	36	26.9%
	Score 3 (<10%)	16	11.9%
JGCA2017	Score 0 (CR)	30	22.4%
	Score 1a (<10%)	26	19.4%
	Score 1b (10–50%)	26	19.4%
	Score 2a (10–33%)	21	15.7%
	Score 2b (<10%)	15	11.2%
	Score 3 (NR)	16	11.9%
China	Grade 1 (marked)	31	23.1%
	Grade 2 (moderate)	56	41.8%
	Grade 3 (mild)	47	35.1%
Mandard	Grade 1 (CR)	15	11.3%
	Grade 2	13	9.7%
	Grade 3	29	21.8%
	Grade 4	43	32.4%
	Grade 5 (NR)	33	24.8%
LN code	Code 1 (Met + Reg –)	25	26.6%
	Code 2 (Met + Reg +)	51	54.3%
	Code 3 (Reg + Met –)	18	19.1%

Numbers may not add up to the total (n = 134) due to missing pathological or follow-up data in some cases.

TRG, tumor regression grade; AJCC, American Joint Committee on Cancer; CAP, College of American Pathologists; JGCA, Japanese Gastric Cancer Association; NR, no response; CR, complete response. Numbers may not add up to the total (n = 134), because 40 patients lacked variable-specific information (e.g., lymph node regression or follow-up), although they were otherwise eligible and included in the study. Percentages are calculated among patients with assignable LN regression codes (n = 94). Patients without metastasis and without regression were not coded and excluded from LN regression analyses.

Therefore, the number of evaluable cases for the regression coding system was 94. Among these evaluable patients (n = 94), 25 (26.6%) were Code 1, 51 (54.3%) were Code 2, and 18 (19.1%) were Code 3. Forty patients had missing LN regression data due to inadequate nodal sampling.

Post-neoadjuvant pathological tumor-node-metastasis (ypTNM), according to the AJCC 8th edition. In this classification, Stage IV denotes distant metastasis (M1) only, and pT4N3M0 cases are categorized within Stage III.

Distribution of TRG Systems

Distribution of TRG subgroups is shown in Table 2. Briefly: Becker: Grade 1a 16 (11.9%), 1b 13 (9.7%), 2 37 (27.6%), 3 68 (50.7%); AJCC/CAP: 0 16 (11.9%), 1 16 (11.9%), 2 59 (44.0%), 3 43 (32.1%); JGCA: Score 0 30

Table 3. Association between becker TRG and clinicopathologic variables.

Variable	Grade 1a (n = 16)	Grade 1b (n = 13)	Grade 2 (n = 37)	Grade 3 (n = 68)	*p* value
Age ≥60, n (%)	10 (62.5)	8 (61.5)	23 (62.2)	44 (64.7)	0.980
Male sex, n (%)	12 (75.0)	10 (76.9)	28 (75.7)	49 (72.1)	0.930
cT3–4 vs cT2, n (%)	14 (87.5)	11 (84.6)	33 (89.2)	62 (91.2)	0.810
cN1–3 vs cN0, n (%)	13 (81.2)	12 (92.3)	31 (83.8)	68 (100.0)	0.120
Positive LN regression, n (%)	9 (60.0)	9 (81.8)	23 (74.2)	28 (46.7)	0.028
Lymphovascular invasion, n (%)	2 (12.5)	3 (23.1)	10 (27.0)	31 (45.6)	0.030
Tumor size <4.5 cm, n (%)	13 (81.3)	6 (46.2)	20 (54.1)	26 (38.2)	0.044
Tumor size 4.5–8 cm, n (%)	3 (18.8)	4 (30.8)	14 (37.8)	28 (41.2)	0.044
Tumor size >8 cm, n (%)	0 (0.0)	3 (23.1)	3 (8.1)	14 (20.6)	0.044

Table 4. AJCC/CAP TRG and clinicopathologic variables.

Variable	Score 0 (n = 16)	Score 1 (n = 16)	Score 2 (n = 59)	Score 3 (n = 43)	*p* value
Age ≥60, n (%)	11 (68.8)	10 (62.5)	36 (61.0)	28 (65.1)	0.950
Male sex, n (%)	13 (81.2)	12 (75.0)	47 (79.7)	27 (62.8)	0.250
cT3–4 vs cT2, n (%)	14 (87.5)	13 (81.2)	51 (86.4)	35 (81.4)	0.870
cN1–3 vs cN0, n (%)	12 (75.0)	14 (87.5)	49 (83.1)	35 (81.4)	0.620
Positive LN regression, n (%)	9 (60.0)	10 (76.9)	37 (72.5)	13 (34.2)	<0.001
Lymphovascular invasion, n (%)	2 (12.5)	3 (18.8)	15 (25.4)	26 (60.5)	0.001
Tumor size <4.5 cm, n (%)	13 (81.3)	6 (46.2)	20 (54.1)	26 (38.2)	0.001
Tumor size 4.5–8 cm, n (%)	3 (18.8)	4 (30.8)	14 (37.8)	28 (41.2)	0.001
Tumor size >8 cm, n (%)	0 (0.0)	3 (23.1)	3 (8.1)	14 (20.6)	0.001

Post-NACT tumor size showed a significant association with CAP TRG scores ($p = 0.001$).

(22.4%), 1a 26 (19.4%), 1b 26 (19.4%), 2 36 (26.9%), 3 16 (11.9%); JGCA2017: Score 0 30 (22.4%), 1a 26 (19.4%), 1b 26 (19.4%), 2a 21 (15.7%), 2b 15 (11.2%), 3 16 (11.9%); China: Grade 1 31 (23.1%), 2 56 (41.8%), 3 47 (35.1%); Mandard: Grade 1 15 (11.3%), 2 13 (9.7%), 3 29 (21.8%), 4 43 (32.4%), 5 33 (24.8%). Lymph node regression codes: Code 1, 25 (26.6%); Code 2, 51 (54.3%); Code 3, 18 (19.1%)

Association With Clinicopathologic Parameters

Relationships between each TRG system's subgroups and clinicopathologic variables appear in Tables 3,4. Key findings: higher TRG scores correlated with larger post-NACT tumor size ($p < 0.05$) and presence of lymph node metastasis ($p < 0.05$). JGCA2017 subgroups correlated with pre-treatment histologic grade ($p = 0.026$). AJCC/CAP and China TRG scores were lower in intestinal Lauren type compared to diffuse type ($p < 0.05$). Positive lymph node regression associated with lower TRG scores across all systems ($p < 0.05$). For Mandard, China, JGCA, and JGCA2017 systems, tumor size correlations are presented in **Supplementary Tables 1,2**.

Survival Analysis

Overall and Disease-Free Survival

At a median follow-up of 24 months, 46 patients (34.3%) died. The median overall survival (OS) was 18.7 months (95% CI 16.2–21.3), and the median disease-free survival (DFS) was 16.4 months (95% CI 14.1–18.7). Recurrence occurred in 34 patients (25.4%), including 4 cases of local recurrence and 30 cases of distant metastasis. Figs. 4,5 present the Kaplan–Meier curves for OS and DFS of the entire cohort after neoadjuvant chemotherapy. Survival outcomes according to pathological tumor-node-metastasis (TNM) stage are shown in **Supplementary Figs. 1,2**, demonstrating significantly shorter OS and DFS in patients with higher TNM stage ($p < 0.01$), consistent with the results in Tables 5,6. Pathologic N3 stage was associated with significantly worse DFS and a borderline worse OS. Based on Kaplan–Meier and log-rank analyses, lymph node metastasis was significantly associated with DFS but not with OS (Table 7).

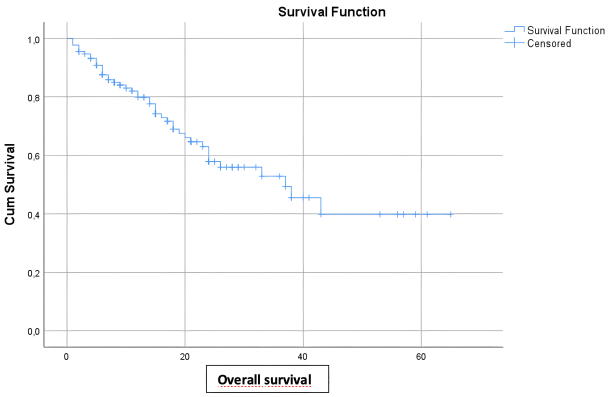

Fig. 4. Kaplan–Meier curves for overall survival according to LN metastasis. *p* values are derived from log-rank test.

Table 5. Univariate Cox regression for OS and DFS (reference group = JGCA2017 Score 2b, worst prognosis).

Variable	HR (95% CI) (OS)	*p* value (OS)	HR (95% CI) (DFS)	*p* value (DFS)
Age (per year)	1.02 (0.99–1.05)	0.305	0.99 (0.97–1.02)	0.539
cN3 vs cN1–2	1.31 (0.67–2.59)	0.433	1.64 (0.92–2.93)	0.094
T3–4 vs T0–2	2.17 (1.00–4.71)	0.051	2.96 (1.42–6.16)	0.004
pN positive vs negative	2.27 (1.09–4.73)	0.028	3.44 (1.68–7.04)	0.001
Lymph node regression (– = reference)	1.31 (0.72–2.38)	0.374	1.21 (0.71–2.04)	0.482
JGCA2017 Score 0 vs 2b	4.08 (1.47–11.34)	0.007	4.14 (1.81–9.49)	0.001
JGCA2017 Score 1a vs 2b	3.16 (1.06–9.43)	0.039	3.60 (1.52–8.53)	0.004
JGCA2017 Score 2a vs 2b	4.62 (1.60–13.30)	0.005	3.02 (1.21–7.52)	0.017
JGCA2017 Score 2b vs 2b	3.13 (0.95–10.26)	0.060	2.00 (0.69–5.78)	0.199
Becker 1b vs 3	1.08 (0.44–2.64)	0.866	0.67 (0.28–1.59)	0.362
Becker 2 vs 3	1.04 (0.54–2.01)	0.896	0.68 (0.37–1.24)	0.204
AJCC/CAP 1 vs 3	0.86 (0.37–1.99)	0.726	0.58 (0.26–1.30)	0.185
AJCC/CAP 2 vs 3	0.72 (0.38–1.38)	0.328	0.68 (0.39–1.19)	0.177
China 1 vs 3	0.48 (0.20–1.16)	0.102	0.28 (0.12–0.65)	0.003
China 2 vs 3	0.85 (0.45–1.61)	0.617	0.67 (0.38–1.15)	0.145
JGCA 0 vs 1b	2.32 (0.84–6.45)	0.106	2.26 (0.99–5.17)	0.054
JGCA 1a vs 1b	1.71 (0.57–5.10)	0.338	1.82 (0.77–4.33)	0.173
JGCA 2 vs 1b	2.25 (0.83–6.10)	0.112	1.39 (0.60–3.23)	0.441
Mandard (1–2/3–4 grouped) 1–2 vs 5	0.36 (0.14–0.92)	0.032	0.21 (0.09–0.53)	0.001
Mandard (1–2/3–4 grouped) 3–4 vs 5	0.65 (0.34–1.24)	0.190	0.57 (0.33–0.99)	0.047

HR, hazard ratio; OS, overall survival; DFS, disease-free survival. Reference group = JGCA2017 Score 2b (worst prognosis). LN regression was coded as + = 1, – = 0 (– = reference). HR <1 indicates better prognosis.

Table 6. Multivariate Cox regression analysis for OS and DFS.

Variable	HR (95% CI)	*p* value	HR (95% CI)	*p* value
JGCA2017 Score 0 vs 2b (OS)	0.25 (0.11–0.59)	0.002	0.30 (0.12–0.75)	0.009
JGCA2017 Score 1a vs 2b	0.33 (0.15–0.76)	0.009	0.35 (0.15–0.82)	0.018
JGCA2017 Score 1b vs 2b	0.60 (0.31–1.20)	0.150	0.65 (0.32–1.32)	0.220
JGCA2017 Score 2a vs 2b	0.80 (0.39–1.65)	0.540	0.85 (0.40–1.79)	0.670
JGCA2017 Score 2b	Reference		Reference	
cN3 vs cN1–2	2.05 (1.18–3.56)	0.010	1.90 (1.10–3.30)	0.020
Lymph node regression (– = reference)	0.42 (0.23–0.77)	0.005	0.50 (0.28–0.90)	0.018

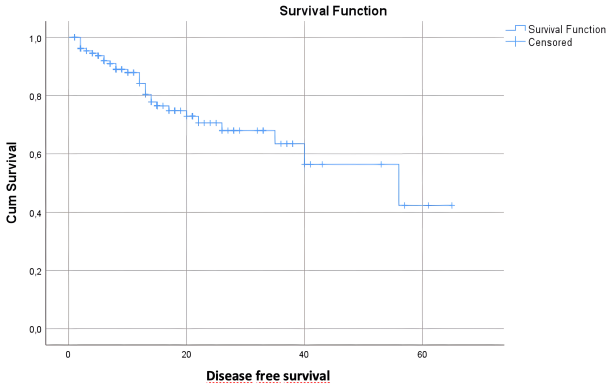

Fig. 5. Kaplan–Meier curves for disease-free survival according to LN metastasis. *p* values are derived from log-rank test.

Survival by TRG Systems

Median OS and DFS values according to the JGCA2017 subgroups are summarized in Table 8. Survival comparisons using the Becker, AJCC/CAP, JGCA, and JGCA2017 TRG systems demonstrated statistically significant differences in OS and/or DFS (Becker: OS $p = 0.078$, DFS $p = 0.021$; AJCC/CAP: OS $p = 0.048$, DFS $p = 0.035$; JGCA: OS $p = 0.031$, DFS $p = 0.031$; JGCA2017: OS $p = 0.043$, DFS $p = 0.015$). These comparisons indicate that patients achieving Score 0 or 1a, representing complete or near-complete regression, experienced a clinically meaningful survival advantage compared with those with Score 2b (worst prognosis). This finding suggests that near-complete regression constitutes a critical prognostic threshold in gastric cancer. Detailed survival analyses for the Mandard and Chinese TRG systems, which did not retain independent prognostic significance in multivariable models, are presented in **Supplementary Tables 3,4**.

Univariable and Multivariable Cox Regression

Univariable analyses included age (continuous), cT, clinical N, pathologic N, lymph node regression, and all TRG systems (JGCA2017, Becker, AJCC/CAP, Mandard [grouped 1–2 and 3–4 vs 5], China, JGCA). Variables that reached

Table 7. Overall and disease-free survival by selected clinicopathologic variables.

Variable	n	Median OS (months) [95% CI]	*p* value	Median DFS (months) [95% CI]	*p* (log-rank) value
Sex—female	35	37 (29–45)	0.620	34 (24–44)	0.180
Sex—male	99	38 (31–46)		48 (41–56)	
Pathologic TNM stage—I (pT0–1 N0)	19	26 (18–34)	0.163	26 (18–34)	0.028
Pathologic TNM stage—II (pT2–3 N0–1)	42	17 (13–21)		16 (12–20)	
Pathologic TNM stage—III (pT3–4 N1–2, pT4N3)	39	16 (13–19)		14 (12–17)	
Pathologic TNM stage—IV (M1)	34	16 (11–21)		12 (8–16)	
Pathologic N stage—N0 (pN0)	39	22 (16–28)	0.188	22 (16–28)	0.039
Pathologic N stage—N1–3	95	16 (13–19)		14 (12–17)	
LN metastasis—absent	39	22 (16–28)	0.188	22 (16–28)	0.039
LN metastasis—present	95	16 (13–19)		14 (12–17)	
Pathologic T stage—pT0–2 vs pT3–4	36	22 (16–28)	0.251	22 (16–28)	0.072
Pathologic T stage—pT3–4 vs pT0–2	98	16 (13–19)		14 (12–17)	

OS, overall survival; DFS, disease-free survival; TNM, tumor-node-metastasis. *p* values are derived from the Kaplan–Meier method with log-rank test.

Table 8. Survival differences by TRG system (example: JGCA2017).

JGCA2017 subgroup	n	Median OS (months) [95% CI]	*p* value	Median DFS (months) [95% CI]	*p* value
Score 0	30	30 (21–39)	0.043†	28 (20–36)	0.015†
Score 1a	26	34 (26–42)		32 (23–41)	
Score 1b	26	33 (24–42)		31 (22–40)	
Score 2a	21	24 (17–31)		23 (16–30)	
Score 2b	15	21 (13–29)		20 (12–28)	
Score 3	16	15 (5–25)		15 (5–25)	

†Pairwise comparisons vs Score 3 (log-rank test):

Score 0 vs 3: OS $p = 0.005$; DFS $p = 0.015$.

Score 1a vs 3: OS $p = 0.019$; DFS $p = 0.009$.

Score 2a vs 3: OS $p = 0.002$; DFS $p = 0.004$.

Score 2b vs 3: OS $p = 0.015$; DFS $p = 0.301$.

the $p < 0.10$ threshold included pathologic T, pathologic N, clinical N (for DFS), lymph node regression, and selected categories of the JGCA2017 and Mandard TRG systems (Table 5). Age did not reach the threshold. Multivariable analysis for OS (Table 6) showed JGCA2017 Score 0 vs 2b (worst prognosis) HR 0.25 (95% CI 0.11–0.59; $p = 0.002$), Score 1a vs 2b (worst prognosis) HR 0.33 (95% CI 0.15–0.76; $p = 0.009$), cN3 vs cN1–2 HR 2.05 (95% CI 1.18–3.56; $p = 0.010$), lymph node regression (+ vs –) HR 0.42 (95% CI 0.23–0.77; $p = 0.005$). For DFS (Table 6), JGCA2017 Score 0 vs 2b (worst prognosis) HR 0.30 (95% CI 0.12–0.75; $p = 0.009$), cN3 vs cN1–2 HR 1.90 (95% CI 1.10–3.30; $p = 0.020$), and lymph node regression (+ vs –) HR 0.50 (95% CI 0.28–0.90; $p = 0.018$). These findings indicate that patients with Score 0 or 1a have a markedly reduced risk of recurrence compared to those with Score 2b (worst prognosis), confirming that near-complete regression is associated with significant clinical benefit.

Lymph Node Regression and Survival

Lymph node regression code analysis showed no significant difference in OS among the different groups (Fig. 6, Table 9). In contrast, DFS differed significantly between the lymph node regression groups (Fig. 7, Table 10). Pairwise log-rank comparisons demonstrated statistically significant differences between Code 1 and Code 2 ($p = 0.048$), Code 2 and Code 3 ($p = 0.020$), and Code 1 and Code 3 ($p = 0.004$). The median DFS was longest in the Code 3 group and shortest in the Code 2 group.

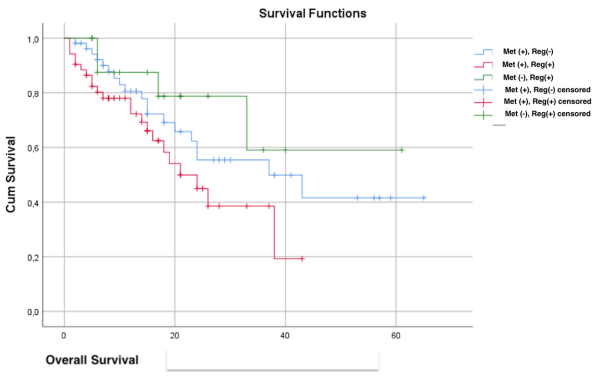

Fig. 6. Overall survival curve stratified by lymph node regression code.

Discussion

This multicenter, retrospective analysis is, to our knowledge, the first to directly compare six histological TRG

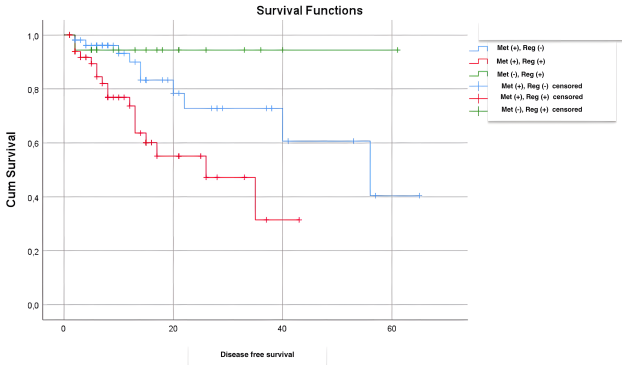

Fig. 7. Disease-free survival curve stratified by lymph node regression code.

Table 9. Lymph node regression code and OS.

LN code	n	Median OS (months) (95% CI)	Log-rank *p* value
Code 1	24	20.0 (13.5–27.0)	Reference
Code 2	51	14.0 (10.9–16.6)	0.77
Code 3	18	19.6 (12.6–26.5)	0.29

Pairwise log-rank (OS): Code 1 vs 2 $p = 0.77$; Code 2 vs 3 $p = 0.35$; Code 1 vs 3 $p = 0.29$.

Table 10. Lymph node regression code and DFS.

LN code	n	Median DFS (months) (95% CI)	Log-rank *p* value
Code 1	24	16.5 (10.4–22.6)	Reference
Code 2	51	12.3 (9.5–15.1)	0.3
Code 3	18	19.1 (12.0–26.2)	0.2

Pairwise log-rank (DFS): Code 1 vs 2 $p = 0.30$; Code 2 vs 3 $p = 0.012$; Code 1 vs 3 $p = 0.20$.

systems—including the Japanese Gastric Cancer Association 2017 classification—with lymph node regression codes in a large cohort of gastric adenocarcinoma patients treated with NACT followed by surgery. By integrating primary tumor and nodal response, our work addresses an underexplored question in prognostic stratification following NACT—previous studies have evaluated individual systems in isolation [8,9].

Our principal finding is that the JGCA2017 system, with its granular subdivision of treatment effect into Score 0, 1a, 1b, 2, and 3, demonstrated the strongest independent association with overall and disease-free survival. Specifically, patients categorized as Score 0 or 1a (complete or "near-complete" tumor regression) had significantly longer survival compared to Score 2b (worst prognosis). For instance, the JGCA2017 six-tier system has been highlighted in recent comparative studies investigating the predictive accuracies of various TRG systems in locally advanced gastric cancer [4], underscoring its potential for more precise evaluation of treatment response [2]. Methodologically, the JGCA2017's well-defined criteria—clear cutoffs for residual tumor and scar tissue—likely explain its superior prognostic performance. Moreover, the use of JGCA2017 may enhance reproducibility, supporting its robustness in routine pathological practice [8,10]. Beyond statistical significance, several features may explain why the JGCA2017 system provided stronger prognostic performance than alternative TRG classifications. Its percentage-based, six-tier design retains prognostic detail within partial responders rather than collapsing them into broad categories, thereby minimizing misclassification when residual tumor burden varies. The system's explicit cutoffs separating vital tumor from therapy-induced scar tissue mirror the biological evolution of gastric tumor beds under chemotherapy, enhancing validity and interpretability. In our cohort, JGCA2017 categories also aligned with established indicators of aggressive disease—larger residual tumor size, nodal involvement, higher histologic grade, and diffuse Lauren type—supporting that the system reflects underlying tumor biology rather than statistical noise. Taken together, these attributes suggest that JGCA2017 is reproducible in daily pathology practice and clinically actionable for risk-adapted adjuvant strategies.

When placed in the context of existing literature, our results corroborate previous observations regarding the value of detailed TRG assessment and extend findings to a multicenter European cohort [8]. Other classifications, such as AJCC/CAP and China classifications, showed prognostic relevance in univariate analyses but did not remain independent in multivariate models [7,11]. This underscores the importance of subclassification within partial response categories and highlights JGCA2017 as the most robust system in our study. Tumor regression grade is a descriptive measurement defined as a histological response to neoadjuvant therapy. While several TRG systems demonstrated prognostic value in univariate or Kaplan–Meier analyses [2,10,12], only JGCA2017 retained independent prognostic significance in multivariate Cox regression. Our work therefore emphasizes that not all TRG classifications are equally reliable, and the discussion has been limited to statistically supported findings. While earlier investigations have indicated the importance of primary tumor regression for prognosis [4], the precise prognostic effect of regression changes in lymph nodes has previously been less transparent [13,14]. Our work contributes significantly by elucidating this aspect.

However, tumor regression grade alone may not fully capture treatment response, as lymph node status remains a major prognostic determinant. In our analysis, distinct survival patterns were observed among the three lymph node regression codes. Patients classified as Code 3 (regression without residual metastasis, n = 18) achieved the most favorable median DFS of 19 months (95% CI 12–26). This finding likely reflects complete nodal eradication following neoadjuvant chemotherapy, which may serve as a surrogate marker of chemosensitivity and systemic disease control. In contrast, Code 2 (metastasis with regression, n = 51) was associated with the poorest median DFS of 12.3 months (95% CI 9.5–15.1). Code 1 (metastasis without regression,

n = 24) demonstrated relatively longer DFS, with a median of 16.5 months (95% CI 10.4–22.6), whereas Code 3 showed the most favorable outcomes, suggesting that even partial nodal regression may confer prognostic relevance. These results highlight the potential value of incorporating nodal regression into postoperative risk stratification beyond conventional TRG systems. Importantly, LN regression remained an independent prognostic factor in multivariate analysis, further supporting its clinical utility alongside JGCA2017.

Although differences in overall survival (OS) between lymph node regression codes did not reach statistical significance, the median OS values are presented descriptively. The median OS was 20.0 months (95% CI 13.5–27.0) in Code 1, 14.0 months (95% CI 10.9–16.6) in Code 2, and 19.6 months (95% CI 12.6–26.5) in Code 3. While these results were not statistically significant, the pattern suggests that nodal regression may still provide prognostic information, particularly when interpreted together with DFS outcomes, where significant differences were observed.

Beyond primary tumor assessment, our three-tier lymph node regression code (0: no regression with metastasis; 1: regression with metastasis; 2: regression without metastasis) provided additional prognostic discrimination. The presence of lymph node metastases is a well-established negative prognostic factor in upper gastrointestinal carcinomas [13], and tumor regression can be observed in the primary tumor and within lymph node metastases after neoadjuvant therapy [15]. These regressive changes, such as nodular and hyaline fibrosis, foamy histiocytes, or acellular mucin, are histological indicators of treatment response [13]. Patients in Code 2 exhibited markedly longer disease-free survival compared to Codes 1 and 0. This suggests that nodal fibrosis, even with residual microscopic disease, is associated with a more favorable outlook. Our study found that positive lymph node regression was associated with lower TRG scores in the Becker and AJCC/CAP systems ($p < 0.05$). This approach in gastric cancer highlights the importance of nodal response in predicting prognosis [16,17]. Indeed, study has shown that the fibrosis ratio in metastatic lymph nodes can serve as a prognostic indicator and may improve existing lymph node staging in advanced gastric cancer [15]. Our findings align with studies demonstrating that lymph node response correlates with survival in gastric cancer patients after neoadjuvant chemotherapy [14,18], highlighting its importance as a predictor of outcomes.

In addition to survival outcomes, our study also revealed important associations between TRG systems and several clinicopathologic parameters that may carry biological implications. Higher TRG scores were consistently associated with larger residual tumor size following NACT and with the presence of lymph node metastasis, suggesting that insufficient tumor regression is a marker of aggressive disease biology. We also observed that higher histologic grade was associated with poorer TRG categories, supporting the concept that tumors with intrinsically aggressive histology are less likely to respond favorably to chemotherapy [2,13,17,19]. Similarly, differences according to Lauren type indicate that intestinal-type tumors may be more chemosensitive than diffuse-type tumors, which aligns with the recognized resistance of diffuse gastric cancers [20–23]. Moreover, the association between adverse TRG scores and the presence of lymphovascular invasion emphasizes that weaker regression is often coupled with enhanced invasive and metastatic potential, in line with evidence that lymphovascular invasion (LVI) is a poor prognostic factor in gastric cancer [24–26]. Taken together, these correlations suggest that TRG systems, particularly JGCA2017, reflect histological regression after therapy and provide insight into the underlying tumor biology, chemosensitivity, and aggressiveness.

Despite these strengths, our study has limitations. Its retrospective design introduces potential selection bias, and NACT regimens varied across centers, potentially affecting response uniformity. Follow-up duration, while adequate for initial prognostic evaluation, remains relatively short for long-term outcomes. The sample size, although reasonable, may be underpowered for subgroup analyses of less frequent histological subtypes (e.g., diffuse Lauren type). The relatively small number of events raises the possibility of model overfitting despite efforts to collapse categories and restrict variables. Moreover, multiple pairwise comparisons were performed across different TRG systems and lymph node regression groups without formal adjustment for multiplicity. As such, inflation of type I error cannot be excluded, and the survival analyses should be regarded as exploratory, with p values interpreted with caution. Finally, although limited data on NACT regimens were available in a few patients (e.g., FLOT, FOLFOX, ECF/ECX), the numbers were too small to allow meaningful subgroup analyses; therefore, all patients were analyzed collectively as having received NACT. External validation in larger, independent cohorts will be necessary to confirm these observations.

Clinically, our findings support the adoption of JGCA2017 and the three-tier lymph node code in routine pathology reports. For patients achieving Score 0/1a and Code 2, de-escalation of adjuvant therapy and less intensive surveillance protocols could be considered, whereas those in higher-score or lower-code categories may benefit from intensified follow-up or enrollment in clinical trials evaluating novel adjuvant strategies. Identifying patients who respond well to preoperative therapy through TRG assessment can provide crucial insights for prognostication and guide further clinical decisions.

Prospective validation and standardization of these systems are warranted. Further research into ancillary biomarkers, such as tumor-infiltrating lymphocytes and stromal-lymphocyte infiltration, could further refine prognostic assessment and treatment selection in conjunction with TRG, particularly in human epidermal growth factor receptor 2-positive and triple-negative breast cancers. These investi-

gations, alongside established TRG systems, could refine predictive models for patient response and prognosis, leading to more personalized treatment strategies for gastric cancer.

Conclusions

In conclusion, our study underscores the prognostic value of histological tumor regression grading systems and lymph node regression in locally advanced gastric adenocarcinoma after neoadjuvant chemotherapy. Among the systems analyzed, the JGCA2017 subgroups—especially Scores 0 and 1a—emerged as strong independent predictors of overall and disease-free survival in multivariate analyses. Positive lymph node regression was also identified as an independent protective factor. The integration of JGCA2017 for primary tumor regression with a three-tier code for lymph node regression provides a practical framework for stratifying patients, enabling more precise prognostication and potentially guiding personalized treatment strategies. As this was an exploratory analysis without formal multiplicity correction, the results should be interpreted with some caution. Nevertheless, they highlight clinically meaningful patterns that merit prospective validation and international standardization to consolidate their role in routine practice.

Availability of Data and Materials

The data analyzed are available from the corresponding author upon reasonable request.

Author Contributions

ÖG, SB, HK: conceptualization, methodology, investigation, supervision, writing—original draft, writing—review & editing. EP: data curation, methodology, investigation, validation. TBÖ: conceptualization, visualization, writing—review & editing. PA, EY, SY: data curation, formal analysis, investigation. NYE: data curation, formal analysis, investigation, validation, visualization. ÖÖ: writing—review & editing, data curation, project administration, resources, supervision, visualization. All authors have been involved in revising the manuscript critically for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

The ethical approval for this study was obtained from the Ethics Committee of Basaksehir Cam and Sakura City Hospital, University of Health Sciences, Istanbul, Turkey (Approval No: 2024-15). The study was conducted in accordance with the Declaration of Helsinki. Due to the anonymization of all patient data, the requirement for informed consent was waived. No personal identifying information was included in the study.

Acknowledgment

The preliminary version of this study was presented at the 31st National Pathology Congress (26–30 October 2022, Selçuk, İzmir, Turkey) and was awarded the first prize in the poster presentation category.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.62713/aic.4201.

References

[1] Pu K, Feng Y, Tang Q, Yang G, Xu C. Review of dietary patterns and gastric cancer risk: epidemiology and biological evidence. Frontiers in Oncology. 2024; 14: 1333623. https://doi.org/10.3389/fonc.2024.1333623.

[2] Xie JW, Lu J, Xu BB, Zheng CH, Li P, Wang JB, *et al*. Prognostic Value of Tumor Regression Grading in Patients Treated With Neoadjuvant Chemotherapy Plus Surgery for Gastric Cancer. Frontiers in Oncology. 2021; 11: 587856. https://doi.org/10.3389/fonc.2021.587856.

[3] Iwamoto T, Kajiwara Y, Zhu Y, Iha S. Biomarkers of neoadjuvant/adjuvant chemotherapy for breast cancer. Chinese Clinical Oncology. 2020; 9: 27. https://doi.org/10.21037/cco.2020.01.06.

[4] Zhu YL, Sun YK, Xue XM, Yue JY, Yang L, Xue LY. Unnecessity of lymph node regression evaluation for predicting gastric adenocarcinoma outcome after neoadjuvant chemotherapy. World Journal of Gastrointestinal Oncology. 2019; 11: 48–58. https://doi.org/10.4251/wjgo.v11.i1.48.

[5] Becker K, Mueller JD, Schulmacher C, Ott K, Fink U, Busch R, *et al*. Histomorphology and grading of regression in gastric carcinoma treated with neoadjuvant chemotherapy. Cancer. 2003; 98: 1521–1530. https://doi.org/10.1002/cncr.11660.

[6] Mandard AM, Dalibard F, Mandard JC, Marnay J, Henry-Amar M, Petiot JF, *et al*. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. Cancer. 1994; 73: 2680–2686. https://doi.org/10.1002/1097-0142(19940601)73:11<2680::aid-cncr2820731105>3.0.co;2-c.

[7] Chen HY, Feng LL, Li M, Ju HQ, Ding Y, Lan M, *et al*. College of American Pathologists Tumor Regression Grading System for Long-Term Outcome in Patients with Locally Advanced Rectal Cancer. The Oncologist. 2021; 26: e780–e793. https://doi.org/10.1002/onco.13707.

[8] Liu ZN, Wang YK, Zhang L, Jia YN, Fei S, Ying XJ, *et al*. Comparison of tumor regression grading systems for locally advanced gastric adenocarcinoma after neoadjuvant chemotherapy. World Journal of Gastrointestinal Oncology. 2021; 13: 2161–2179. https://doi.org/10.4251/wjgo.v13.i12.2161.

[9] Lütken C, Sheikh K, Willemoe GL, Achiam MP, Hasselby JP. Clinical assessment of tumor regression grade systems in gastroesophageal adenocarcinoma following neoadjuvant chemotherapy. Pathology, Research and Practice. 2021; 224: 153538. https://doi.org/10.1016/j.prp.2021.153538.

[10] Lefevre A, Lefevre M, Bonnet S, Soularue E, Colle R, Ferraz JM, *et al*. Prognostic value of tumor regression grade (TRG) in patients with

gastric/gastroesophageal junction cancer treated by peri-operative chemotherapy and surgery: A single-center experience (Institut Mutualiste Montsouris, Paris, France). Journal of Clinical Oncology. 2025; 43: 486. https://doi.org/10.1200/jco.2025.43.4_suppl.486.

[11] Zhu Y, Sun Y, Hu S, Jiang Y, Yue J, Xue X, *et al*. Comparison of five tumor regression grading systems for gastric adenocarcinoma after neoadjuvant chemotherapy: a retrospective study of 192 cases from National Cancer Center in China. BMC Gastroenterology. 2017; 17: 41. https://doi.org/10.1186/s12876-017-0598-5.

[12] Lombardi PM, Mazzola M, Achilli P, Aquilano MC, De Martini P, Curaba A, *et al*. Prognostic value of pathological tumor regression grade in locally advanced gastric cancer: New perspectives from a single-center experience. Journal of Surgical Oncology. 2021; 123: 923–931. https://doi.org/10.1002/jso.26391.

[13] Reim D, Novotny A, Friess H, Slotta-Huspenina J, Weichert W, Ott K, *et al*. Significance of tumour regression in lymph node metastases of gastric and gastro-oesophageal junction adenocarcinomas. The Journal of Pathology. Clinical Research. 2020; 6: 263–272. https://doi.org/10.1002/cjp2.169.

[14] Pereira MA, Ramos MF, Dias AR, Cardili L, Ribeiro RR, Charruf AZ, *et al*. Lymph node regression after neoadjuvant chemotherapy: a predictor of survival in gastric cancer. Journal of Surgical Oncology. 2020; 121: 795–803. https://doi.org/10.1002/jso.25785.

[15] Lee SR, Kim HO, Son BH, Shin JH, Yoo CH. Prognostic significance of the metastatic lymph node ratio in patients with gastric cancer. World Journal of Surgery. 2012; 36: 1096–1101. https://doi.org/10.1007/s00268-012-1520-5.

[16] Hagi T, Makino T, Yamasaki M, Yamashita K, Tanaka K, Saito T, *et al*. Pathological Regression of Lymph Nodes Better Predicts Long-term Survival in Esophageal Cancer Patients Undergoing Neoadjuvant Chemotherapy Followed by Surgery. Annals of Surgery. 2022; 275: 1121–1129. https://doi.org/10.1097/SLA.0000000000004238.

[17] Jiang L, Ma Z, Ye X, Kang W, Yu J. Clinicopathological factors affecting the effect of neoadjuvant chemotherapy in patients with gastric cancer. World Journal of Surgical Oncology. 2021; 19: 44. https://doi.org/10.1186/s12957-021-02157-x.

[18] Sejben A, Kószó R, Kahán Z, Cserni G, Zombori T. Examination of tumor regression grading systems in breast cancer patients who received neoadjuvant therapy. Pathology & Oncology Research. 2020; 26: 2747–2754. https://doi.org/10.1007/s12253-020-00867-3.

[19] Kwong MLM, Denham L, Selleck MJ, Kim C, Kunihira K, Kubba R, *et al*. Response to Neoadjuvant Treatment Is Influenced by Grade in Gastric Cancer. The American Surgeon. 2019; 85: 1419–1422.

[20] Jiménez Fonseca P, Carmona-Bayonas A, Hernández R, Custodio A, Cano JM, Lacalle A, *et al*. Lauren subtypes of advanced gastric cancer influence survival and response to chemotherapy: real-world data from the AGAMENON National Cancer Registry. British Journal of Cancer. 2017; 117: 775–782. https://doi.org/10.1038/bjc.2017.245.

[21] Pattison S, Mitchell C, Lade S, Leong T, Busuttil RA, Boussioutas A. Early relapses after adjuvant chemotherapy suggests primary chemoresistance in diffuse gastric cancer. PLoS ONE. 2017; 12: e0183891. https://doi.org/10.1371/journal.pone.0183891.

[22] Zurlo IV, Basso M, Strippoli A, Calegari MA, Orlandi A, Cassano A, *et al*. Treatment of Locally Advanced Gastric Cancer (LAGC): Back to Lauren's Classification in Pan-Cancer Analysis Era? Cancers. 2020; 12: 1749. https://doi.org/10.3390/cancers12071749.

[23] Schirren R, Novotny A, Oesterlin C, Slotta-Huspenina J, Friess H, Reim D. Significance of Lauren Classification in Patients Undergoing Neoadjuvant/Perioperative Chemotherapy for Locally Advanced Gastric or Gastroesophageal Junction Cancers-Analysis from a Large Single Center Cohort in Germany. Cancers. 2021; 13: 290. https://doi.org/10.3390/cancers13020290.

[24] Fujikawa H, Koumori K, Watanabe H, Kano K, Shimoda Y, Aoyama T, *et al*. The Clinical Significance of Lymphovascular Invasion in Gastric Cancer. In Vivo. 2020; 34: 1533–1539. https://doi.org/10.21873/invivo.11942.

[25] Alangari AI, Kim S, Lee HH, Song KY, Seo H. Prognostic impact of lymphovascular invasion in node-negative gastric cancer: a retrospective cohort study. World Journal of Surgical Oncology. 2024; 22: 340. https://doi.org/10.1186/s12957-024-03629-6.

[26] Pande K, Rauniyar SK, Pudasaini S. Assessment of lymphovascular invasion in gastric carcinoma; do they always indicate lymph node metastasis? Journal of Pathology of Nepal. 2018; 8: 1251–1256. https://doi.org/10.3126/jpn.v8i1.19445.