Original Article

Prognostic value and clinicopathological correlation of the tumor regression grade in neoadjuvant chemotherapy for gastric adenocarcinoma: a retrospective cohort study

Yi Wang[1,2,3,4#^], Handong Xu[1,2,3,4#], Can Hu[1,2,3,4], Pengcheng Yu[1,2,3,4], Zhehan Bao[1,2,3,4], Yanqiang Zhang[2,3,4], Ruolan Zhang[1,2,3,4], Shengjie Zhang[2,3,4], Bing Li[5], Jean-Marie Aerts[6], Zhiyuan Xu[2,3,4], Xiangdong Cheng[2,3,4]

[1]The First Clinical Medical College of Zhejiang Chinese Medical University, Hangzhou, China; [2]Department of Gastric Surgery, The Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Institutes of Basic Medicine and Cancer (IBMC), Chinese Academy of Sciences, Hangzhou, China; [3]Diagnosis and Therapy Center of Upper Gastrointestinal Tumor in Zhejiang Province, Hangzhou, China; [4]International Cooperation Base for Cancer Molecular Diagnosis and Intelligent Screening of Zhejiang Province, Hangzhou, China; [5]Leuven Health Technology Centre China Centre, Hangzhou, China; [6]Department of Biosystems, Division Animal and Human Health Engineering, KU Leuven, Leuven, Belgium

Contributions: (I) Conception and design: Z Xu, X Cheng; (II) Administrative support: X Cheng; (III) Provision of study materials or patients: Y Wang, H Xu, C Hu; (IV) Collection and assembly of data: Y Wang, H Xu, C Hu, P Yu, Y Zhang, Z Bao, R Zhang; (V) Data analysis and interpretation: Y Wang, C Hu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Xiangdong Cheng; Zhiyuan Xu. The Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Institutes of Basic Medicine and Cancer (IBMC), Chinese Academy of Sciences, Hangzhou 310022, China.
Email: chengxd@zjcc.org.cn; xuzy@zjcc.org.cn.

Background: Neoadjuvant chemotherapy (NACT) and radical gastrectomy are the gold standard treatments for resectable advanced gastric cancer (GC). However, the prognostic value of the pathological tumor regression grade (TRG) of NACT remains controversial. This retrospective study aimed to investigate the correlation between the TRG after NACT and clinicopathological features as well as its prognostic value in advanced GC.

Methods: In total, 551 patients with GC who received NACT combined with surgical resection at the Zhejiang Cancer Hospital from April 2004 to December 2019 were included. The demographic characteristics, treatment response, tumor characteristics, treatment regimens, and survival data were reviewed from the medical records of all patients. The Chi-square test was used to analyze the correlation between TRG and clinicopathological factors. Kaplan-Meier univariate analysis and Cox regression multivariate analysis were used to determine the independent risk factors affecting the prognosis of GC patients.

Results: Among the 551 patients with advanced GC who accepted NACT treatment, 14 were determined to be in TRG 0, 98 in TRG 1, 257 in TRG 2, and 182 in TRG 3. Also, TRG was significantly correlated with the cT stage (P=0.015), ypT stage (P<0.001), ypN stage (P<0.001), ypTNM stage (P<0.001), vascular tumor thrombus (P<0.001), Borrmann classification (P=0.042), and lymph node ratio (LNR) (P<0.001). Furthermore, patients who had a good pathological response to NACT had a better prognosis, with a 3-year overall survival (OS) of 70.9% versus 48.8% in patients who had a poor pathological response. We also found that TRG (P=0.042, HR =1.65) was an independent prognostic factor affecting the OS of GC patients.

Conclusions: TRG plays a significant role in the prognostic value in neoadjuvant chemotherapy for gastric adenocarcinoma. Patients with higher cT stage, higher levels of pre-CA199 and pre-CA125 may have worse pathological response.

^ ORCID: 0000-0002-5714-5943.

Keywords: Tumor regression grade (TRG); neoadjuvant chemotherapy (NACT); gastric cancer (GC)

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Introduction

Gastric cancer (GC) is one of the most common malignant tumors worldwide and is a serious threat to people's life and health. According to the latest data, GC ranked fifth in terms of morbidity and fourth in terms of mortality (1), and the 5-year overall survival (OS) rate is only 35.1% (2,3). Although surgery is the main treatment for GC, surgical treatment alone cannot achieve satisfactory results in patients with advanced GC. Early clinical studies have confirmed that perioperative chemotherapy combined with surgical resection can improve the OS and disease-free survival (DFS) rates of patients compared with surgical resection alone (4,5). According to the 2021 Chinese Society of Clinical Oncology (CSCO) Clinical Guidelines for the diagnosis and treatment of GC, adjuvant chemotherapy is recommended for the treatment of patients with GC in the cT1-2N+M0 and cT3-4N0/+M0 stages before gastrectomy (6).

At present, computer tomography (CT), magnetic resonance imaging (MRI), positron emission tomography-CT (PET-CT), ultrasound contrast, and molecular biological detection are used to evaluate the efficacy of neoadjuvant chemotherapy (NACT). Although these methods have a certain application value in clinical practice and their role in prognostic value is unclear. The concept of TRG was first proposed by Mandard *et al.* (7). A previous study has confirmed that tumor regression grade (TRG) can be used to evaluate the response to neoadjuvant therapy for gastrointestinal tumors according to the morphological changes and regression degree of tumors after neoadjuvant therapy (8). The TRG is regarded as the most accurate indicator to evaluate the effectiveness of neoadjuvant therapy for cancer and has been widely applied and studied in the field of neoadjuvant therapy for colorectal cancer (9,10). In the field of GC, Blackham *et al.* analyzed 58 patients with surgical resection of GC after NACT in two medical institutions and found that TRG could not predict prognostic survival of patients (11). However, Lombardi *et al.* investigated the correlation between TRG and disease-free survival (DFS) and disease-specific survival (DSS) in 100 GC patients treated with NACT, and found that TRG was an independent prognostic factor (12). Hence, there is no unified standard for its application in neoadjuvant therapy for GC, and the prognostic value of GC remains controversial. The purpose of this study was to investigate the clinicopathological factors associated with TRG and the prognostic value of TRG in GC. We present the following article in accordance with the REMARK reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-537/rc).

Methods

Selection criteria and patients

This retrospective cohort study included GC patients admitted to the Zhejiang Cancer Hospital from April 2004 to December 2019 who received NACT combined with surgical resection. The inclusion criteria were as follows: (I) patients aged between 18 and 80 years; (II) patients who received NACT and surgical resection; (III) pathological diagnosis of gastric adenocarcinoma; and (IV) patients with complete TRG assessment, clinicopathological, and follow-up data. The exclusion criteria were as follows: (I) patients with a combination of other tumors or metastasis from other tumors; (II) those with residual GC; and (III) patients with severe liver or kidney insufficiency or other significant organ diseases. Finally, 551 patients were included in this study.

We reviewed the medical records of all patients and collected data including the demographic characteristics, treatment response, tumor characteristics, treatment regimens, and survival. This study was approved by the Ethics Committee of the Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital) (No. IRB-2020-300) and was performed in accordance with the Declaration of Helsinki (as revised in 2013). The informed consent of the patients was not required due to the retrospective nature of this study.

Clinicopathological characteristics

We collected the following data: age, gender, body mass

index (BMI), tumor location, surgical method, type of resection, cTNM [the eighth edition of the American Joint Committee on Cancer tumor node metastasis (AJCC-TNM 8th) system)], ypTNM (AJCC-TNM 8th), tumor grade of differentiation, vascular tumor thrombus, nerve invasion, lymph node ratio (LNR), Borrmann classification, tumor markers, and hematological indices. The chemotherapeutic regimens were divided into single-drug, two-drug, and three-drug regimen groups based on the number of drugs administered. At the same time, the included population was divided into the targeted drug group and the non-targeted drug group according to whether targeted drugs were used in combination with NACT. Finally, the chemotherapy cycles were recorded through the outpatient and inpatient medical record system. Survival information was obtained by telephone follow-up and medical records. The final follow-up assessment was conducted in September 2021. Most routine follow-up appointments included a physical examination, laboratory testing and an annual endoscopic examination. OS was defined as the duration from initial surgery to death or last follow-up.

TRG score assessment

The TRG score was assessed using the American Joint Committee on Cancer/College of American Pathologists (AJCC/CAP) criteria, which was included in the third edition of the National Comprehensive Cancer Network (NCCN) GC guidelines [2017] and was also routinely recommended by the CSCO. The four levels TRG score levels were defined as follows: (I) no residual cancer cell was defined as TRG 0; (II) single cells or small groups of cells was defined as TRG 1; (III) residual cancer with desmoplastic response was defined as TRG 2; and (IV) minimal evidence of tumor response was defined as TRG 3. Furthermore, the patients were divided into good responders (GR) and poor responders (PR) groups according to the TRG score.

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics for windows, version 25.0 (IBM Corp, Armonk, NY, USA) and Graphpad Prism8 for windows, version 8.3.0 (GraphPad Software, San Diego, California, USA). Skewed data were expressed as median ± quartiles and count data were expressed as numerical values and percentages. Categorical variables were compared using the chi-square test or fisher's exact test. Survival curves were estimated using the Kaplan-Meier method. Multivariate analyses were performed using Cox regression analyses (the inclusion factors were both P<0.05 in the univariate Cox regression analysis results). The hazard ratios (HRs) and 95% confidence intervals (CIs) were also calculated. P<0.05 was considered to indicate a statistically significant difference.

Results

Clinicopathological characteristics and clinical results

As shown in *Table 1*, among the 551 included NACT advanced GC patients, the majority of the study population (56.4%) was aged over 60 years old, which comprised 413 (75.0%) males and 138 (25.0%) females were included. Analysis of the distribution of tumor sites revealed 165 cases (29.9%) of upper third GC, 106 cases (19.2%) of middle third GC, 255 cases (46.3%) of lower third GC, and only 25 cases (4.5%) of total GC. Among the 551 NACT advanced GC patients, 79.1% were classified as cTNM stages III–IV, and only 115 cases (20.9%) were classified as stage II. As for the ypTNM stage, more than half of the patients (55.4%) were stage III; 446 (80.9%) patients received less than four cycles of chemotherapy and 105 (19.1%) patients received more than four cycles of chemotherapy, the majority of which were double-drug regimens.

Correlation between the TRG and clinicopathological characteristics

According to the assessment results of TRG score (*Figure 1A*), 14 were determined to be in TRG 0, 98 in TRG 1, 257 in TRG 2, and 182 in TRG 3. A correlation between the TRG and clinicopathological characteristics was confirmed (*Table 2*). As shown in *Table 2*, cT stage (P=0.015), ypT stage (P<0.001), ypN stage (P<0.001), ypTNM stage (P<0.001), vascular tumor thrombus (P<0.001), Borrmann classification (P=0.042), and LNR (P<0.001) were correlated with the TRG. Furthermore, we also analyzed the correlation between the levels of tumor markers. As shown in *Table 3*, pre-CA199 (P=0.048), pre-CA125 (P=0.010), pos-CA199 (P<0.001), and pos-CA242 (P=0.042) were statistically correlated with the TRG. Moreover, the hematological indices were also analyzed (*Table 4*), and the results showed that the RBC (P=0.038), ALT (P=0.011) and AST (P=0.013) indices were statistically significant.

Table 1 Patient characteristics

Variable	N (%)
Age, year	
≥60	311 (56.4)
<60	240 (43.6)
Sex	
Male	413 (75.0)
Female	138 (25.0)
BMI (kg/m^2)	
<25	472 (85.7)
≥25	79 (14.3)
Surgery	
Open	495 (89.8)
Laparoscopy	56 (10.2)
Location	
Upper third	165 (29.9)
Middle third	106 (19.2)
Lower third	255 (46.3)
Total	25 (4.5)
Differentiated degree	
Poor/moderate-poor	387 (70.2)
Moderate/moderate-well/well	105 (19.1)
Unknown	59 (10.7)
Borrmann classification	
I	25 (4.5)
II	299 (54.3)
III	161 (29.2)
IV	66 (12.0)
cTNM stage	
II	115 (20.9)
III	365 (66.2)
IV	71 (12.9)
ypTNM stage	
I	57 (10.3)
II	150 (27.2)
III	305 (55.4)
IV	39 (7.1)
Vascular tumor emboli	
Positive	69 (12.5)
Negative	482 (87.5)
Nerve invasion	
Positive	85 (15.4)
Negative	466 (84.6)
Tumor size	
<5 cm	240 (43.6)
≥5 cm	189 (34.3)
Unknown	122 (22.1)
No. of cycles of preoperative chemotherapy	
<4	446 (80.9)
≥4	105 (19.1)
Chemotherapeutic regimens	
Single drug	14 (2.5)
Double drug	443 (80.4)
Three drug	94 (17.1)

BMI, body mass index; cTNM stage, clinical tumor node metastasis stage; ypTNM stage, post-neoadjuvant pathologic tumor node metastasis stage.

Effect of the TRG on the prognosis of GC patients

The Kaplan-Meier method was used to plot the survival curves of the 551 GC patients included in this study (*Figure 1B*,*1C*), which revealed a statistically significant difference in the prognosis between the GR and PR groups (log-rank P<0.001). The GR group had a better prognosis, with a 3-year OS of 70.9% versus 48.8% in the PR group. Furthermore, we found that there was a significant difference in the 3-year OS between patients in TRG 1 and TRG 2 (69.8% *vs.* 51.8%, P=0.008), while patients in TRG 2 had a better 3-year OS than patients in TRG 3 (51.8% *vs.* 44.6%, P=0.044). However, there was no significant in the 3-year OS between patients in TRG 0 and in TRG 1 (77.9% *vs.* 69.8%, P=0.445).

Furthermore, univariate analysis (*Table 5*) showed that the cT stage (P<0.001), cN stage (P=0.001), cTNM stage (P=0.004), Borrmann classification (P<0.001), ypT stage (P<0.001), ypN stage (P<0.001), ypTNM stage (P<0.001),

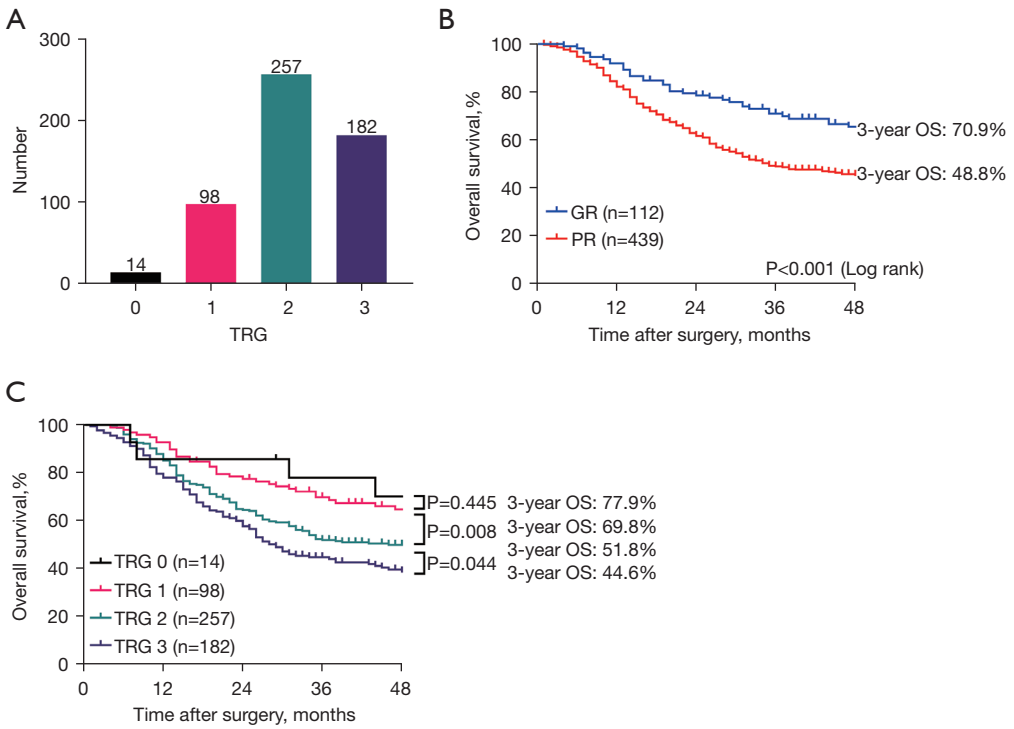

Figure 1 TRG distribution and Kaplan-Meier OS analyses of the TRG. (A) Distribution of the TRG (0–3) in 551 NACT gastric cancer patients; (B) the Kaplan-Meier OS analyses of GR and PR; (C) the Kaplan-Meier OS analyses of patients in different TRGs. TRG, tumor regression grade; OS, overall survival; GR, good responders; PR, poor responders; NACT, neoadjuvant chemotherapy.

Table 2 Correlation between the TRG and clinicopathological characteristics

Parameters	Number	GR (n=112), n (%)	PR (n=439), n (%)	χ^2	P value
Age (years)				1.525	0.217
<60	240	43 (17.9)	197 (82.1)		
≥60	311	69 (22.2)	242 (77.8)		
Gender				0.980	0.322
Male	413	88 (21.3)	325 (78.7)		
Female	138	24 (17.4)	114 (82.6)		
Tumor location				3.775	0.287
Upper third	165	35 (21.2)	130 (78.8)		
Middle third	106	26 (24.5)	80 (75.5)		
Lower third	255	49 (19.2)	206 (80.8)		
Total	25	2 (8.0)	23 (92.0)		
Surgical method				3.556	0.059
Open	495	106 (21.4)	389 (78.6)		
Laparoscopy	56	6 (10.7)	50 (89.3)		

Table 2 *(continued)*

Table 2 *(continued)*

Parameters	Number	GR (n=112), n (%)	PR (n=439), n (%)	χ^2	P value
Type of resection				0.244	0.885
PG	7	1 (14.3)	6 (85.7)		
DG	214	45 (21.0)	169 (79.0)		
TG	330	66 (20.0)	264 (80.0)		
Grade of differentiation				1.167	0.280
Poor/moderate-poor	387	57 (14.7)	330 (85.3)		
Moderate/moderate-well/well	105	20 (19.0)	85 (81.0)		
Unknown	59	35 (59.3)	24 (40.7)		
cT stage				10.022	0.015*
1	3	2 (66.7)	1 (33.3)		
2	74	23 (31.1)	51 (68.9)		
3	118	24 (20.3)	94 (79.7)		
4	356	63 (17.7)	293 (82.3)		
cN stage				3.201	0.362
0	43	8 (18.6)	35 (81.4)		
1	208	50 (24.0)	158 (76.0)		
2	172	33 (19.2)	139 (80.8)		
3	128	21 (16.4)	107 (83.6)		
cM stage				1.460	0.227
0	512	107 (20.9)	405 (79.1)		
1	39	5 (12.8)	34 (87.2)		
cTNM stage				5.965	0.051
II	115	32 (27.8)	83 (72.2)		
III	365	64 (17.5)	301 (82.5)		
IV	71	16 (22.5)	55 (77.5)		
ypT stage				43.656	<0.001*
1	48	23 (47.9)	25 (52.1)		
2	48	20 (41.7%)	28 (58.3)		
3	47	8 (17.0)	39 (83.0)		
4	408	61 (15.0)	347 (85.0)		
ypN stage				27.410	<0.001*
0	181	56 (30.9)	125 (69.1)		
1	118	22 (18.6)	96 (81.4)		
2	114	24 (21.2)	90 (78.9)		
3	138	10 (7.2)	128 (92.8)		

Table 2 *(continued)*

Table 2 *(continued)*

Parameters	Number	GR (n=112), n (%)	PR (n=439), n (%)	χ^2	P value
ypM stage				1.460	0.227
0	512	107 (20.9)	405 (79.1)		
1	39	5 (12.8)	34 (87.2)		
ypTNM stage				37.511	<0.001*
I	57	27 (47.4)	30 (52.6)		
II	150	38 (25.3)	112 (74.7)		
III	305	42 (13.8)	263 (86.2)		
IV	39	5 (12.8)	34 (87.2)		
Vascular tumor thrombus				12.436	<0.001*
No	482	109 (22.6)	373 (77.4)		
Yes	69	3 (4.3)	66 (95.7)		
Nerve invasion				3.385	0.066
No	466	101 (21.7)	365 (78.3)		
Yes	85	11 (12.9)	74 (87.1)		
Borrmann classification				8.207	0.042*
I	25	8 (32.0)	17 (68.0)		
II	299	69 (23.1)	230 (76.9)		
III	161	28 (17.4)	133 (82.6)		
IV	66	7 (10.6)	59 (89.4)		
LNR				20.347	<0.001*
<0.07	274	77 (28.1)	197 (79.1)		
≥0.07	277	35 (12.6)	242 (87.4)		
Chemotherapeutic regimens				0.566	0.753
Single drug	14	2 (14.3)	12 (85.7)		
Double drug	443	89 (20.1)	354 (79.9)		
Three drug	94	21 (22.3)	73 (77.7)		
Targeted drugs				0.000	1.000
Yes	544	111 (20.4)	433 (79.6)		
No	7	1 (14.3)	6 (85.7)		
Chemotherapy cycles				0.513	0.474
<4	446	88 (19.7)	358 (80.3)		
≥4	105	24 (22.9)	81 (77.1)		

*, P<0.05. TRG, tumor regression grade; GR, good responders; PR, poor responders; PG, proximal gastrectomy; DG, distal gastrectomy; TG, total gastrectomy; LNR, lymph node ratio; cT stage, clinical tumor stage; cN stage, clinical node stage; cM stage, clinical metastasis stage; cTNM stage, clinical tumor node metastasis stage; ypT stage, post-neoadjuvant pathologic tumor stage; ypN stage, post-neoadjuvant pathologic node stage; ypM stage, post-neoadjuvant pathologic metastasis stage; ypTNM stage, post-neoadjuvant pathologic tumor node metastasis stage.

Table 3 Correlation between the TRG and tumor markers

Tumor markers	Number	GR (n=112), n (%)	PR (n=439), n (%)	χ^2	P value
Pre-CA199 (U/mL)				3.901	0.048*
≤37	402	90 (22.4)	312 (77.6)		
>37	149	22 (14.8)	127 (85.2)		
Pre-CA125 (U/mL)				6.700	0.010*
≤35	502	109 (21.7)	393 (78.3)		
>35	49	3 (6.1)	46 (93.9)		
Pre-CA242 (U/mL)				1.575	0.210
≤20	477	101 (21.2)	376 (78.8)		
>20	74	11 (14.9)	63 (85.1)		
Pre-CA724 (U/mL)				0.032	0.858
≤6.9	370	76 (20.5)	294 (79.5)		
>6.9	181	36 (19.9)	145 (80.1)		
Pos-CA199 (U/mL)				13.398	<0.001*
≤37	451	105 (23.3)	346 (76.7)		
>37	100	7 (7.0)	93 (93.0)		
Pos-CA125 (U/mL)				3.656	0.056
≤35	514	109 (21.2)	405 (78.8)		
>35	37	3 (8.1)	34 (91.9)		
Pos-CA242 (U/mL)				4.137	0.042*
≤20	512	109 (21.3)	403 (78.7)		
>20	39	3 (7.7)	36 (92.3)		
Pos-CA724 (U/mL)				3.249	0.071
≤6.9	433	95 (21.9)	338 (78.1)		
>6.9	118	17 (14.4)	101 (85.6)		

*, P<0.05. TRG, tumor regression grade; GR, good responders; PR, poor responders; pre, before neoadjuvant chemotherapy; pos, after neoadjuvant chemotherapy; CA199, carbohydrate antigen 199; CA125, carbohydrate antigen 125; CA242, carbohydrate antigen 242; CA724, carbohydrate antigen 724.

tumor size (P<0.001), tumor grade of differentiation (P<0.001), vascular tumor thrombus (P<0.001), nerve invasion (P=0.002), TRG group (P<0.001), as well as the levels of pre-CA199 (P=0.002), pre-CA125 (P=0.033), and pre-CA242 (P=0.014) were prognostic factors for GC. Subsequently, the factors with an index of P<0.05 by using univariate Cox regression analysis were subjected to multivariate Cox regression analysis. Furthermore, the multivariate analysis (*Table 5*) revealed that cTNM stage (P=0.005, HR 1.69, 95% CI: 1.17–2.44), ypN stage (P=0.020, HR 1.89, 95% CI: 1.11–3.22), tumor grade of differentiation (P=0.014, HR 0.61, 95% CI: 0.41–0.90), and the TRG (P=0.042, HR 1.65, 95% CI: 1.02–2.67) were independent factors affecting the prognosis of GC patients.

Discussion

GC is one of the most common malignant tumors worldwide. Early diagnosis of GC is difficult and the overall prognosis is poor (13). For locally advanced gastrointestinal

Table 4 Correlation between the TRG and hematological indices

Hematological indices	TRG	M (P25, P75)	Wilcoxon rank sum test	
			Z value	P value
WBC (10^9/L)	GR	5.50 (4.30, 7.00)	0.174	0.862
	PR	5.50 (4.20, 7.60)		
RBC (10^{12}/L)	GR	3.83 (3.47, 4.14)	2.074	0.038*
	PR	3.67 (3.27, 4.07)		
Hb (g/dL)	GR	9.90 (8.60, 11.48)	0.376	0.707
	PR	9.60 (8.60, 11.20)		
PLT (10^9/L)	GR	151.50 (110.50, 199.25)	0.389	0.698
	PR	151.00 (112.00, 247.00)		
ALT (U/L)	GR	28.50 (17.25, 38.00)	2.534	0.011*
	PR	22.00 (16.00, 34.00)		
AST (U/L)	GR	31.00 (25.00, 47.75)	2.495	0.013*
	PR	28.00 (22.00, 38.00)		
ALB (g/L)	GR	39.60 (35.90, 42.20)	0.229	0.819
	PR	39.80 (35.80, 42.50)		

*, P<0.05. TRG, tumor regression grade; GR, good responders; PR, poor responders; WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin.

tumors, preoperative treatment is recommended as the standard treatment (14). Compared with surgery alone, perioperative chemotherapy combined with surgical resection significantly improves the progression-free survival (PFS) and OS of patients with resectable GC (4). At present, the TRG is regarded as the most accurate index to evaluate the efficacy of neoadjuvant therapy (15), and the importance of TRG in the prognosis of colorectal cancer has been confirmed. As a good variable for predicting prognosis, TRG can provide a reference for individualized prognostic evaluation as well as assessment of the potential therapeutic effect in colorectal cancer patients (10,16). However, the risk factors and prognostic value of TRG in GC remain controversial.

At present, numerous studies have explored the clinicopathological factors affecting the pathological response to NACT in GC. A previous retrospective study by Xu *et al.* (17), which included 304 patients with advanced GC who received preoperative chemotherapy, found that CA199, CA724, differentiation degree, and maximum lymph node diameter were related to pathological reactions following chemotherapy. Ikoma *et al.* (18) analyzed 356 patients with non-metastatic gastric adenocarcinoma who had received preoperative chemotherapy and found that high pathological response was associated with higher ypT and ypN stages as well as ypM1 and R1 resection. However, no pre-treatment factors were found to be associated with pathological response, except for signet ring tissue type and tumor site. Moreover, Xu *et al.* (19) analyzed the correlation between the TRG and clinical information, pathological data, and serum tumor markers in 264 patients with advanced GC who received NACT with the SOX (comprised of oxaliplatin and S-1) or XELOX (comprised of oxaliplatin and capecitabine) regimens. Their results showed that only Lauren type and ypT stage were independent factors affecting the TRG. In this study, we explored the influencing factors of the TRG in 551 patients with advanced GC in our center and found that the cT stage (P<0.001), ypT stage (P<0.001), vascular tumor thrombus (P=0.013), pre-CA125 (P=0.024), and pos-CA199 (P=0.031) were independent influencing factors of the TRG. We also confirmed that the ypT stage was an independent factor affecting the TRG in different types of studies because the TRG is partly based on pathological assessment. However, the assessed value of preoperative factors and hematological indicators on the influencing factors of the TRG varied

Table 5 Prognostic factors in the univariate and multivariate analyses for GC patients who received neoadjuvant therapy

Parameters	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Gender	0.89	0.69–1.15	0.373	–	–	–
Age	0.93	0.74–1.17	0.543	–	–	–
cT stage (cT_{1+2} *vs.* cT_{3+4})	2.35	1.53–3.59	<0.001*	0.89	0.36–2.21	0.795
cN stage (cN_0 *vs.* cN_+)	2.73	1.50–4.99	0.001*	1.49	0.77–2.87	0.234
cTNM stage (II *vs.* III/IV)	1.58	1.16–2.16	0.004*	1.69	1.17–2.44	0.005*
Borrmann classification (I/II *vs.* III/IV)	1.60	1.27–2.02	<0.001*	1.12	0.85–1.47	0.431
Surgical method	0.90	0.60–1.35	0.619	–	–	–
ypT stage (ypT_{1+2} *vs.* ypT_{3+4})	2.49	1.68–3.68	<0.001*	1.24	0.50–3.07	0.636
ypN stage (ypN_0 *vs.* ypN_+)	3.50	2.57–4.76	<0.001*	1.89	1.11–3.22	0.020*
ypTNM (I/II *vs.* III/IV)	3.51	2.63–4.69	<0.001*	1.60	0.91–2.82	0.102
Tumor size	1.61	1.25–2.07	<0.001*	1.32	0.99–1.75	0.056
Grade of differentiation	0.40	0.28–0.58	<0.001*	0.61	0.41–0.90	0.014*
Vascular tumor thrombus	1.74	1.28–2.37	<0.001*	1.09	0.72–1.65	0.676
Nerve invasion	1.58	1.18–2.10	0.002*	0.93	0.64–1.35	0.690
TRG group	1.88	1.35–2.61	<0.001*	1.65	1.02–2.67	0.042*
Pre-CA199	1.48	1.16–1.90	0.002*	1.31	0.92–1.86	0.142
Pre-CA125	1.51	1.03–2.20	0.033*	1.49	0.97–2.30	0.068
Pre-CA242	1.47	1.08–2.01	0.014*	0.93	0.60–1.44	0.734
Pre-CA724	1.25	0.98–1.59	0.069	–	–	–

*, P<0.05. TRG, tumor regression grade; pre, before neoadjuvant chemotherapy; cT stage, clinical tumor stage; cN stage, clinical node stage; cTNM stage, clinical tumor node metastasis stage; ypT stage, post-neoadjuvant pathologic tumor stage; ypN stage, post-neoadjuvant pathologic node stage; ypTNM stage, post-neoadjuvant pathologic tumor node metastasis stage; CA199, carbohydrate antigen 199; CA125, carbohydrate antigen 125; CA242, carbohydrate antigen 242; CA724, carbohydrate antigen 724.

among different types of studies. At the same time, there are few studies on hematological indicators to predict the TRG; using multi-dimensional clinical data to establish a TRG prediction model may be a potential method, although more studies are needed for further confirmation.

We further explored the effect of the TRG on the prognosis of NACT GC patients. Univariate analysis via the Kaplan-Meier method found that the GR group had a significantly better prognosis than the PR group (P<0.001), indicating that the higher the TRG grade, the worse the prognosis. Furthermore, multivariate analysis by Cox regression showed that the TRG was an independent risk factor affecting the prognosis of patients. This result was consistent with the findings of Lombardi *et al.* (12), whose study included 100 GC patients who received NACT and showed that the TRG could be an independent prognostic factor by exploring the correlation between the TRG and DFS and DSS. Also, a previous meta-analysis involving 17 studies suggested that pathological response was significantly related to the improvement of OS in patients with gastroesophageal junction tumors, and proposed that the TRG should be considered a strong prognostic factor to guide postoperative treatment and follow-up (20). At present, the role of the TRG in predicting prognosis is controversial and inconclusive. Stark *et al.* (21) reviewed 247 patients with gastric adenocarcinoma who received chemotherapy or chemoradiotherapy combined with surgical resection and found that the TRG was not associated with recurrence-free survival (RFS), local recurrence (LR), or distant recurrence (DR) by using

the percentage of surviving tumor cells in the specimen to represent the TRG. Furthermore, Blackham *et al.* conducted a TRG study on 58 GC patients from two institutional databases and also found that TRG was not an independent factor affecting the survival prognosis of patients (11). Thus, the current value of the TRG in prognosis remains controversial, and more studies are needed to confirm its significance.

In this study, we found that a higher cT stage, higher ypT stage, presence of vascular tumor thrombus, and abnormality of pre-CA125, pre-CA199, pos-242, and pos-CA199 were associated with higher TRG grades, and higher TRG grades predicted worse prognosis. Also, the TRG was confirmed as an independent risk factor. However, there are still some deficiencies in this study that should be noted. Firstly, the included patients had received various chemotherapy regimens and underwent different chemotherapy cycles, and thus, the pathological response to chemotherapy would be affected by the differences in regimen and cycle. Secondly, the included patients were followed up for a long time, and only the OS was collected as a prognostic indicator, without the DFS and metastasis rate. Thirdly, there were some deviations in the preoperative evaluation of the clinical TNM stage due to the image quality and other factors.

Conclusions

TRG plays a significant role in the prognostic value in neoadjuvant chemotherapy for gastric adenocarcinoma. Patients with higher cT stage, higher levels of pre-CA199 and pre-CA125 may have worse pathological response.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the ethics committee of the Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital) (No. IRB-2020-300) and was performed in accordance with the Declaration of Helsinki (as revised in 2013). The informed consent of the patients was not required due to the retrospective nature of this study.

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