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ORIGINAL ARTICLE

Is pathologic tumor regression grade after neo-adjuvant chemotherapy a promising prognostic indicator for patients with locally advanced gastric cancer? A cohort study evaluating tumor regression response

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Abstract

Background The MAGIC trial has shown perioperative chemotherapy does significantly improve overall survival of patients with gastric and esophagogastric junction carcinoma. The approach to evaluate the effectiveness of adjuvant chemotherapy is urgent in clinical practice.

Methods Totally, 264 patients with locally advanced gastric carcinoma (including esophagogastric junction carcinoma) treaded by perioperiate chemotherapy (SOX or XELOX) from May 2012 to December 2017 in our cancer center were included. Tumor response was evaluated by tumor regression grade (TRG, Mandard system) and Response Evaluation Criteria in Solid Tumor (RECIST v1.1). The clinical characteristics and the effect on survival were analyzed.

Result Univariate analysis showed TRG was correlated to tumor size, Lauren classification, grade of differentiation, histological type, postsurgical T category (ypT), postsurgical N category (ypN), vascular invasion or lymphatic invasion and so on. However, only Lauren classification and ypT were independent factors for TRG. On contrary to RECIST, TRG was founded to be a prognostic factor for DFS and OS on univariate analysis. Cox proportional hazards were established to evaluate the relationship among TRG, clinical-pathological factors and survival. On multivariate analysis, the chemotherapy cycle, Lauren classification, vascular invasion or lymphatic invasion, ypN and postsurgical pathologic stage were independent factors for OS and DFS, while TRG were negatively correlated to survival.

Conclusion TRG seems to be a promising prognostic indicator and it predicts the prognosis of patients with locally advanced gastric cancer after adjuvant chemotherapy more reasonably in comparisons to RECIST v1.1.

Keywords Gastric cancer · Adjuvant chemotherapy · Tumor regression grade · Evaluation · Predictor

Introduction

Thought with the improvement of surgical and medical therapeutic strategy in the treatment of gastric cancer (GC), Gastric cancer is the fourth most commonly diagnosed cancer and the second leading cause of cancer-related deaths

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worldwide [1, 2]. In China, locally advanced GC accounted for over 70% of diagnosing of gastric cancer, higher than that in Japan and Korea. Radical resection is the promising treatment strategy to cure resectable GC. However, over half of the patients presented with the poor outcome will subsequently relapse or die of GC after radical surgery, due to node, distance metastases or recurrence [3]. Previous studies have proved that perioperative chemotherapy combined with radical surgery more effectively prolongs patient survival for locally advanced GC than radical surgery, thus a multimodal treatment is urgent in practice [4]. The superiority of perioperative chemotherapy is to eliminate micrometastases, boost the odds of radical resection and increase the rate of completed adjuvant chemotherapy and down-stage [5, 6]. So to verify the effectiveness of adjuvant chemotherapy is crucial to the treatment of locally advanced GC. However, no certain approach to identify well-response of tumor regression after chemotherapy was available in gastric carcinoma until now. Several studied about pathologic tumor regression grade have been proposed to evaluate the relationship between TRG and prognosis, such as Mandard-TRG system, JGCA-TRG system, Becker-TRG system and so on [7–10]. Mandard et al. [7] firstly introduced the five-tiered TRG system in esophageal carcinoma, which has been used widely in digestive malignancy. The option criteria of pathological tumor regression grade for gastric cancer is a contentious issue. The purpose of this retrospective study is to verify the prognostic value of histopathological (Mandard-TRG) and radiological response (RECIST v1.1) to neo-adjuvant chemotherapy in the treatment of locally advanced gastric adenocarcinoma. Oncological outcomes were also assessed.

Methods

Patients

From May 2012 through December 2017, all patients with locally advanced gastric cancer (including esophagogastric junction carcinoma), undergoing neo-adjuvant chemotherapy combined with gastrectomy surgery in Cancer Hospital of China Medical University, Liaoning Cancer Hospital were prospectively enrolled in this study. The inclusion criteria included: (1) Histopathological examination diagnosis of gastric adenocarcinoma on well-established criteria; (2) Intraoperative exploration and postoperative TNM stage revealed no distant metastases and radical gastrectomy surgery was performed (R0, D2 or $D2^{+}$); (3) Locally advanced gastric carcinoma (clinical TNM stage: cT2 ~ T4 and cN1 ~ 3, II–III) and patients were proposed for the neo-adjuvant chemotherapy treatment; (4) 2–4 cycles of neo-adjuvant chemotherapy and several cycles of postoperative chemotherapy was underwent; (5) Age ranged from 20 to 75 years old. The study excluded cases for which: (1) Preoperative radiotherapy or immunotherapy was performed; (2) Suffering from other malignancies; (3) Gastric remnant carcinoma; (4) More than 1 lesion on the stomach; (5) Without complete follow-up data or accessible CT imaging to assess chemotherapy. A total of 264 patients received perioperative chemotherapy combined with radical surgery were prospectively collected in this study. All patients received a digestive endoscopy with biopsy, an echo-endoscopy (EUS) and a computed tomography (CT) of thorax, mediastinum and abdomen (including gastric enhanced and three-dimensional reconstruction CT scan, 256 layers). The clinical TNM stage was identified by CT scan combined with EUS according to the American Joint Committee on Cancer (AJCC) cancer staging Seven Edition TNM classification. This study was approved by the Ethics Committee of Liaoning Cancer Hospital.

Treatment

Oxaliplatin combined with capecitabine or S-1 has been recommended as one of the standard perioperative chemotherapy regimens with Grade II recommendations for advanced gastric cancer in China [11–13]. Patients underwent a perioperative chemotherapy regimen of SOX or XELOX, divided into 2–4 preoperative and several postoperative cycles. The preoperative chemotherapy schedules comprised of Oxaliplatin (130 mg/m^2 intravenously in day 1), S-1 (The surface area: > 1.5 m^2 60 mg twice a day; 1.25–1.5 m^2 50 mg twice a day; < 1.25 m^2 40 mg twice a day, orally for 14 days) (SOX regimen) or Capecitabine (1000 mg/m^2 twice a day orally for 14 days) (XELOX regimen). The D2 or D2 plus lymphadenectomy, a radical gastrectomy surgery was regularly performed 2 weeks after 2–4 cycles neo-adjuvant chemotherapy. If the presence of peritoneal, hepatic metastasis or unresectable factors was suspected, additional surgical intervention is performed by diagnostic laparoscopy exploration. Once the involvement of unresectable factors was discovered after laparoscopy exploration, he or she would drop out of the study. Postoperative chemotherapy regimen was similar to preoperative chemotherapy regimen. The postoperative chemotherapy schedules were performed 1 month after the operation, consisting of Oxaliplatin (100 mg/m^2 intravenously in day 1), S-1 or Capecitabine (the same as preoperative chemotherapy in dose). Once severe adverse effect (level III–IV) associated with chemotherapy occurred, the dose adjustment was preceded by appropriately reducing dose (4–6 cycles) or changing to take S-1or Capecitabine alone for 1 year. Every cycle lasted 21 days.

Follow-up

A follow-up work included physical examination, laboratory detection of serum tumor marker (CEA, CA-199, CA-724, CA-125 and AFP), endoscopy and thorax, mediastinum and abdomen CT scan. Patients were evaluated every 3 months during the first 3 years, subsequently every 6 months for the following 2 years and once a year after 5 years. Once participants presented with discomfort symptoms during follow-up years, they should receive related examination immediately to evaluate whether recurrence or metastasis happened. The overall survival (OS) was defined as the time from the first day of neoadjuvant chemotherapy to the day when death took place or last follow-up day. The disease progression-free survival (DFS) was defined as the time from the first day after operation to the day when progression occurred or last follow-up day.

Response assessment

Two pathologists were blinded to the treatment arm and classified for pathologic response by reviewing hematoxylin and eosin-stained slides according to the Mandard tumor regression grading (TRG) system. If the maximum of residue was only areas of scar existed, the whole suspected lesion was submitted completely for histological examination. All of the slides were reviewed by two experienced pathologists. The criteria of TRG system grading pathologic response were as follows: TRG 1(complete regression or fibrosis with no evidence of tumor cells), TRG 2 (fibrosis and rare residual cancer cells), TRG 3 (fibrosis outgrowing residual cancer), TRG 4 (rare fibrosis and Residual cancer outgrowing fibrosis), and TRG 5 (tumor without evidence of regressive changes). When a disagreement between pathologists happened, a consensus was sought by three pathologists rereviewing and discussing the sides together. CT images (gastric enhanced and three-dimensional reconstruction, 256 layers) were reviewed by two experienced radiologists and graded for radiological response according to Response Evaluation Criteria in Solid Tumors (RESIST v1.1) system in a blind manner. In cases of disagreement between radiologists, three radiologists reevaluated CT images and reached a consensus diagnosis.

Clinicopathological features

Patients' clinicopathological features consist of tumor size, location (U, M, L), Lauren classification (intestinal, diffuse or mixed), grade of differentiation (well or moderate, poor), histological type (adenocarcinoma, signet ring or mucinous carcinoma), vascular invasion or lymphatic invasion, Borrmann type, pathologic TNM stage (postoperative category), extent of resection (total, distal or proximal) and so on.

Statistical analysis

All continuous values are presented as mean ± standard deviation. Categorical data were expressed as a percentage, and statistical analysis was conducted using the Chi-square test or Fisher's test to assess the effect of clinicopathological characteristics on TRG (Mandard) variance. Logistic regression was used to analyze independent factors associated with TRG. The multivariable Cox proportional hazard model and univariate analysis were used to analyze prognostic risk on OS and DFS. The Kaplan–Meier method was used to calculate survival curves for DFS and OS; Differences associated with tumor pathologic or radiological response between the curves were assessed using the log-rank test. Data was proceeded by SPSS 23.0 software. The P value was considered to be statistically significant at the 5% level and P value of < 0.05 in univariate analysis were taken into the multivariate analysis.

Results

Clinicopathological characteristics, tumor response and survival

A total of 264 patients with radical surgery and perioperative chemotherapy were finally included in the study. Patients' clinicopathological features were shown in Table 1. Most patients were male (73.9%), and their age ranging from 25 to 75 (median: 59 years old). Tumor size range from 1 to 18 cm (median: 3.0 cm) and a majority of tumors located in L area (65.2%), presented with intestinal type (59.5%), displayed poor differentiation (61.7%) and adenocarcinoma histological type (66.7%). A minority of patients showed vascular invasion or lymphatic invasion (33.7%), negative node (32.6%) and underwent total gastrectomy surgery (34.8%). 209 patients (78.9%) received preoperative chemotherapy and 99 patients (37.5%) underwent postoperative chemotherapy of SOX regimen. A reduction from the starting dose of at least one of the chemotherapeutic agents or changing to oral drug alone was necessary for 119 (45.1%) people. 158 patients (59.8%) were classified as stage III (postsurgical pathological stage). The results of tumor response (both pathological and radiological) for patients treated with neo-adjuvant chemotherapy were as follows: TRG1: 7.2% ($n = 19$); TRG2: 22.7% ($n = 60$); TRG3: 38.3% ($n = 101$); TRG4: 30.3% ($n = 80$); TRG5: 1.5% ($n = 4$); CR: 3.1% ($n = 8$); PR: 53.4% ($n = 141$); SD: 38.6% ($n = 102$) and PD: 4.9% ($n = 13$) (Table 2). Patients were followed for a

Table 1 Patient Clinicopathological characteristics

Characteristics	Value	Percentage (%)
Sex		
Male	195	73.9
Female	69	26.1
Age (y)		
≤60	159	60.2
>60	105	39.8
Tumor size (cm)		
≤5.0	203	76.9
>5.0	61	23.1
Location		
U	28	10.6
M	64	24.2
L	172	65.2
Lauren classification		
Intestinal	157	59.5
Diffuse or Mixed	107	40.5
Grade of differentiation		
Well-moderate	101	38.3
Poor	161	61.7
Histological type		
Adenocarcinoma	176	66.7
Signet-ring or mucinous carcinoma	88	33.3
Vascular invasion or lymphatic invasion		
Yes	89	33.7
No	175	66.3
Borrmann type		
I–II	102	38.6
III–IV	162	61.4
ypT category		
T0	19	7.2
T1–2	86	21.2
T3–4	159	7.6
ypN category		
N0	86	32.6
N1	30	11.4
N2	58	22
N3	90	34.1
Pathologic stage (ypTNM)		
I	57	21.6
II	49	18.6
III	158	59.8
Extent of resection		
Distal or proximal	172	65.2
Total	92	34.8
Preoperative adjuvant chemotherapy schedule		
SOX	209	78.9
XELOX	55	21.1
Postoperative adjuvant chemotherapy schedule		
SOX	99	37.5
XELOX	46	17.4
Dose reduce or single oral drug	119	45.1

Location, U/M/L, the upper/middle/lower third of stomach; ypT category, postsurgical T category after adjuvant chemotherapy; T0, no evidence of tumor cells; yp N, postsurgical N category after adjuvant chemotherapy

Table 2 Pathologic and Radiological response after neo-adjuvant chemotherapy and survival data

Characteristics	Value	Percentage (%)
Pathologic response		
TRG1	19	7.2
TRG2	60	22.7
TRG3	101	38.3
TRG4	80	30.3
TRG5	4	1.5
Radiological response		
CR	8	3.1
PR	141	53.4
SD	102	38.6
PD	13	4.9
Follow-up time (months)		
Median		40.0
Range		1.0–65.0
Outcome		
Metastasis or recurrence		139
Died of disease		124
3, 5-year DFS rate (%)		45.2/35.8
3, 5-year OS rate (%)		56.6/39.0

TRG tumor regression grade

median period of 40.0 months (range 1–65 months.). 3-, 5-years DFS and OS were 45.2, 35.8% and 56.6, 39.0%, respectively, in patients with locally advanced gastric carcinoma treated with perioperative chemotherapy (Table 2).

Clinicopathological characteristics associated with TRG

Pathologic response to chemotherapy (TRG) was associated with clinicopathologic variable, including, sex, tumor size, Lauren classification, grade of differentiation, histologic subtype, Borrmann type, vascular invasion or lymphatic invasion, ypT category and ypN category (all $P<0.05$, Table 3). Logistic regression analysis including variable above demonstrated that Lauren classification and ypT category was significantly related with TRG (RR: 0.334, 95%CI: 0.115–0.966, $P=0.043$; RR: 0.248, 95%CI: 0.096–0.641, $P=0.004$, Table 4).

Survival analysis

To discuss the relationship between TRG and survival data, survival data (3-years OS) was grouped and analyzed

Table 3 Clinicopathological variables associated with TRG

Characteristics	TRG			*P* value
	1–2	3	4–5	
Sex				0.017
Male	65	65	65	
Female	14	36	19	
Age (y)				0.096
≤60	40	63	56	
>60	39	38	28	
Tumor size (cm)				0.001
≤5.0	70	79	54	
>5.0	9	22	30	
Lauren classification				0.000
Intestinal	68	52	37	
Diffuse or Mixed	11	49	47	
Location				0.737
U	7	9	12	
M	20	26	18	
L	52	66	54	
Grade of differentiation				0.000
Well-moderate	44	34	23	
Poor	35	67	61	
Histological type				0.000
Adenocarcinoma	67	59	50	
Signet ring or mucinous carcinoma	12	42	34	
Borrmann type				0.000
I–II	46	30	26	
III–IV	33	71	58	
Vascular invasion or lymphatic invasion				0.002
Yes	65	61	49	
No	14	40	35	
ypT category				0.000
T0	19	0	0	
T1–2	30	18	8	
T3–4	30	83	76	
ypN category				0.005
N0	37	30	19	
N1	12	11	7	
N2	15	20	23	
N3	15	40	35	
Extent of resection				0.756
Total	53	63	56	
Distal or proximal	26	38	28	
Preoperative neoadjuvant chemotherapy schedule				0.536
SOX	64	80	65	
XELOX	15	21	19	

Location, U/M/L: the upper/middle/lower third of stomach; ypT category: postsurgical T category after adjuvant chemotherapy; T0: no evidence of tumor cells; yp N: postsurgical N category after adjuvant chemotherapy

Table 4 Independent factors associated with TRG

Characteristics	Relative risk	95% (CI)	*P* value
Sex	0.469	0.194–1.133	0.092
Tumor size	0.989	0.859–1.140	0.881
Lauren classification	0.334	0.115–0.966	**0.043**
Grade of differentiation	1.520	0.584–3.960	0.391
Histological type	0.673	0.280–1.616	0.375
Borrmann type	0.641	0.284–1.447	0.284
Vascular invasion or lymphatic invasion	0.875	0.361–2.120	0.767
ypT category			
T0	*	*	0.998
T1–2	0.248	0.096–0.641	**0.004**
T3–4			
ypN category			
N0	1.388	0.492–3.920	0.535
N1	0.833	0.244–2.840	0.770
N2	1.23	0.420–3.600	0.705
N3			

Statistically significant *P* values are given in bold ($P < 0.05$)

ypT category, postsurgical T category after adjuvant chemotherapy; T0, no evidence of tumor cells; yp N, postsurgical N category after adjuvant chemotherapy. TRG, tumor regression grade

*Too large to record

(Table 5). For patients with TRG1-2, TRG3, TRG4-5, 3-years OS rate was 77%, 49.4% and 48.3%, respectively ($HR_3 = 2.622$, 95%CI: 1.597–4.306, $HR_{4\text{-}5} = 2.587$; 95%CI: 1.554–4.306, $P = 0.001$), the results were shown in Table 5. Survival data for OS and was less favorable in patients with TRG3-5 in comparison to TRG1-2 as well ($P = 0.000$). But this difference was not significant in case of the data set was dichotomized into two groups: TRG3 versus TRG4-5 (HR = 1.020; 95%CI: 0.690–1.507, $P = 0.923$). The study included clinicopathologic characteristics, such as age, sex, tumor size, site of tumor, histologic subtype, vascular invasion or lymphatic invasion, etc. to conduct univariate analysis to analyze prognostic factors on OS and DFS (Tables 6, 7). Lauren classification, chemotherapy cycle, histological type, grade of differentiation, Borrmann type, tumor size, location, vascular invasion or lymphatic invasion, ypN category, ypT category, ypTNM stage and TRG were related with OS and DFS on univariate analysis (Tables 6, 7). Multivariable Cox proportional hazard model analysis including relative risk factor above showed Lauren classification, chemotherapy cycle, vascular invasion or lymphatic invasion, ypN category and ypTNM stage was significantly associated with OS and DFS (Lauren classification: $P = 0.029$ and $P = 0.045$; chemotherapy cycle: $P = 0.000$ and $P = 0.000$; vascular invasion or lymphatic invasion: $P = 0.015$ and $P = 0.021$; ypN category: $P = 0.007$ and $P = 0.001$;

yp TNM stage: $P = 0.035$ and $P = 0.025$, Table 6, 7). Pathological tumor regression grade (TRG) was significantly associated with survival on DFS ($P = 0.000$) and OS ($P = 0.000$) (Figs. 1, 2, 3). On the contrary radiological tumor regression response (RESCIT v1. 1) haven't shown significant differences in terms of survival on DFS and OS ($P = 0.219$; $P = 0.240$, Figs. 2, 3). Yet, TRG was not an independent risk factor associated with OS (HR: 1.445, 95%CI, 0.864–2.415, $P = 0.161$) and DFS (HR: 1.065, 95%CI, 0.629–1.803, $P = 0.816$). The results were shown in Table 6, 7.

Having established that TRG was one of prognostic significance for adequately staged patients treated by radical gastrectomy combined with perioperative chemotherapy, we sought to identify patient subgroups for whom the benefit was maximized and those for whom TRG was not of prognostic significance. Impact of TRG on OS for the patients with positive lymph nodes (postsurgical N category) was analyzed. Kaplan–Meier curve analysis found TRG was a prognostic variable for patients with positive lymph nodes (postsurgical N category ≥ N1) (Log rank, $P = 0.001$, Fig. 4b). However, the difference was not significant for patients with negative lymph nodes (Log rank, $P = 0.716$, Fig. 4a).

Table 5 Survival data by Mardard TRG in patients treated with chemotherapy plus surgery

Mardard TRG	3-year OS (%)	HR (95% CI)	*P* value
Mardard TRG (1 and 2 vs. 3 vs. 4 and 5)			0.001
1 and 2	77.0		
3	49.4	2.622 (1.597–4.306)	0.001
4 and 5	48.3	2.587 (1.554–4.306)	0.001
Mardard TRG (1 and 2 vs. 3, 4 and 5)			0.000
1 and 2	77.00		
3–5	49.20	2.606 (1.640–4.140)	0.000
Mardard TRG (3 vs. 4 and 5)			0.923
3	49.4		
4–5	48.3	1.020 (0.690–1.507)	0.923

Table 6 Prognostic variables associated with overall survival on univariate and multivariate analysis

Characteries	Univariate analysis			Multivariate analysis		
	β	HR (95%CI)	*P* value	β	HR (95%CI)	*P* value
Sex	0.164	1.178 (0.799–1.736)	0.408			
Age	−0.008	0.992 (0.972–1.013)	0.472			
Tumor size	0.133	1.142 (1.083–1.204)	0.000	0.065	1.067 (0.993–1.146)	0.678
Location			0.021			0.48
L	1.000					
M	0.119	1.127 (0.738–1.721)	0.581	0.272	0.762 (0.490–1.486)	0.228
U	0.719	2.053 (1.236–3.411)	0.005	0.064	0.938 (0.537–1.638)	0.822
Lauren classification	1.041	2.833 (1.975–4.063)	0.000	0.441	1.555 (1.047–2.308)	**0.029**
Grade of differentiation	0.833	2.301 (1.536–3.447)	0.000	0.158	1.171 (0.626–2.577)	0.621
Histological type	0.451	1.569 (1.090–2.259)	0.015	0.340	0.712 (0.454–1.116)	0.138
VIOLI	1.258	3.517 (2.461–5.025)	0.000	0.488	1.629 (1.099–2.418)	**0.015**
Borrmann type	0.782	2.187 (1.474–3.243)	0.000	0.017	1.017 (0.648–1.598)	0.940
ypT category						0.424
T0	1.000					
T1–2	0.416	1.516 (0.315–7.304)	0.604	0.530	0.589 (0.111–3.121)	0.534
T3–4	2.391	10.929 (2.682–44.537)	0.001	1.144	0.319 (0.048–2.096)	0.234
ypN category			0.000			**0.007**
N0	1.000					
N1	0.859	2.360 (1.046–5.323)	0.039	0.049	1.050 (0.415–2.659)	0.918
N2	1.509	4.524 (2.358–8.680)	0.000	0.273	1.314 (0.542–3.189)	0.546
N3	2.468	11.801 (6.558–21.234)	0.000	0.924	2.520 (1.057–6.005)	0.037
Pathologic stage (ypTNM)			0.000			**0.035**
I	1.000					
II	1.277	3.582 (1.098–11.703)	0.034	0.895	2.446 (0.727–8.230)	0.148
III	3.007	20.225 (7.356–55.605)	0.000	1.637	5.138 (1.454–18.158)	0.011
Extent of resection	0.361	1.435 (0.999–2.060)	0.054			
TRG	0.958	2.606 (1.640–4.140)	0.000	0.268	1.445 (0.864–2.415)	0.161
Chemotherapy schedule	−0.104	0.353 (0.241–0.518)	0.000	0.897	2.453 (1.554–3.871)	**0.000**

Statistically significant *P* values are given in bold ($P < 0.05$)

Location, U/M/L, the upper/middle/lower third of stomach; ypT category, postsurgical T category after adjuvant chemotherapy; T0, no evidence of tumor cells; yp N, postsurgical N category after adjuvant chemotherapy; VIOLI, Vascular invasion or lymphatic invasion

Discussion

The study formulates clinicopathological characteristics associated with pathological tumor regression grade (TRG, Mandard) and reported the result of the prognostic impact of centrally analyzed tumor regression grade and other clinicopathological variables on survival in a retrospective cohort study for locally advanced gastric carcinoma patients treated with perioperative chemotherapy combined with surgery, representing the largest number cases associated with TRG (Mandard). It demonstrated that Lauren classification and postgurgical T category were significantly independent variable associated with TRG, which turned out to be a promising prognostic indicator for patients treated with perioperative chemotherapy combined with surgery. And it implied that Lauren classification was likely to be an important basis for postoperative chemotherapy regimen selection. However, TRG failed to be independent predictors of prognosis, so other predictive markers of survival require to be further studied.

Radical surgery combined with perioperative chemotherapy has been regarded as a promising treatment strategy for locally advanced resectable gastric cancer. MAGIC and FNLCLCC/FFCD trials demonstrated radical surgery combined with perioperative chemotherapy undertook a better survival than surgery alone (5-years OS: MAGIC, 36.3% vs. 23.0%, $P = 0.009$; FNLCLCC/FFCD, 38% vs. 24%, $P = 0.02$), prompting the application of this therapeutic pattern in the treatment of locally advanced gastric cancer [5, 14]. Similar results have been proved in several studies. CLASSIC trial reported when compared to radical surgery, radical gastrectomy combined with postoperative

Table 7 Prognostic variables associated with disease-free survival on univariate and multivariate analysis

Characteries	Univariate analysis			Multivariate analysis		
	β	HR (95%CI)	*P* value	*β*	HR (95%CI)	*P* value
Sex	0.148	1.160 (0.803–1.675)	0.429			
Age	−0.009	0.991 (0.972–1.010)	0.344			
Tumor size	0.750	2.117 (1.451–3.090)	0.000	0.410	1.507 (1.021–2.226)	**0.039**
Location			0.030			0.176
L	1.000					
M	0.162	1.176 (0.789–1.752)	0.426	0.067	1.069 (0.657–1.741)	0.788
U	0.856	2.353 (1.447–3.825)	0.001	0.523	1.687 (0.955–2.981)	0.072
Lauren classification	1.010	2.746 (1.958–3.852)	0.000	0.360	1.433 (1.002–2.071)	**0.045**
Grade of differentiation	0.887	2.428 (1.657–3.558)	0.000	0.212	1.237 (0.712–2.146)	0.450
Histological type	0.543	1.721 (1.223–2.421)	0.002	0.067	0.935 (0.603–1.450)	0.764
VIOLI	1.231	3.426 (2.445–4.800)	0.000	0.437	1.548 (1.069–2.241)	**0.021**
Borrmann type	0.846	2.330 (1.599–3.395)	0.000	0.134	1.143 (0.736–1.775)	0.551
ypT category (T0–2 vs. T3–4)	2.116	8.301 (4.412–15.618)	0.000	0.403	0.668 (0.201–2.220)	0.511
ypN category			0.000			**0.001**
N0	1.000					
N1	1.037	2.820 (1.355–5.871)	0.006	0.321	1.379 (0.600–3.170)	0.449
N2	1.594	4.923 (2.687–9.022)	0.000	0.404	1.498 (0.660–3.401)	0.334
N3	2.554	12.856 (7.397–22.343)	0.000	1.151	3.161 (1.397–7.153)	0.006
Pathologic stage (ypTNM)			0.000			**0.025**
I	1.000					
II	0.963	2.619 (0.943–7.272)	0.065	0.535	1.708 (0.593–4.923)	0.321
III	2.881	17.824 (7.702–41.249)	0.000	1.372	3.945 (1.361–11.433)	0.011
Extent of resection	0.446	1.562 (1.112–2.194)	0.010	0.275	0.759 (0.517–1.115)	0.160
TRG	0.858	2.358 (1.547–3.596)	0.000	0.063	1.065 (0.629–1.803)	0.816
Chemotherapy schedule	2.115	8.291 (5.398–12.734)	0.000	1.551	4.176 (2.917–7.624)	**0.000**

Statistically significant *P* values are given in bold ($P < 0.05$)

Location, U/M/L, the upper/middle/lower third of stomach; ypT category, postsurgical T category after adjuvant chemotherapy; T0, no evidence of tumor cells; yp N, postsurgical N category after adjuvant chemotherapy; VIOLI, Vascular invasion or lymphatic invasion

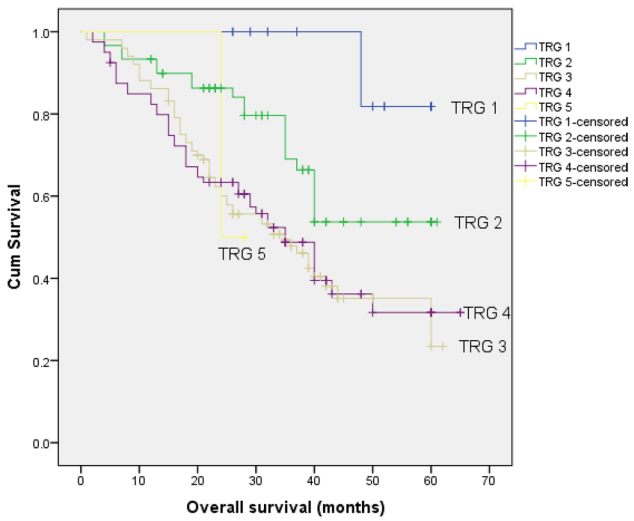

Fig. 1 Kaplan–Meier curves were employed to analyze survival data of OS associated with TRG in patients with locally advanced gastric cancer after perioperative chemotherapy

chemotherapy (XELOX) significantly increased patients' survival (3-years OS, 78% vs. 83%, $P < 0.05$) [15].Though lacking of comparisons to a nonchemotherapy control arm, our study results in terms of survival was in line with the MAGIC and FNLCLCC/FFCD trials showing a considerable 5-years OS (39.0%). In regard to chemotherapy treatment adherence and related adverse effect, our study showed majorities of patients (54.8%) completing all preoperative and postoperative chemotherapy without dose adjustment. While in the MAGIC trial, fewer than half of the patients completed all protocol chemotherapy [14]. The study depicted desired results in terms of perioperative chemotherapy regimen (SOX and XELOX) attributing to a good treatment adherence, acceptable related toxicity, and well treatment effectiveness.

Currently, for no unified standard for evaluating the effectiveness of perioperative chemotherapy are available, the identification of patients presented with better response to perioperative chemotherapy has become a crucial

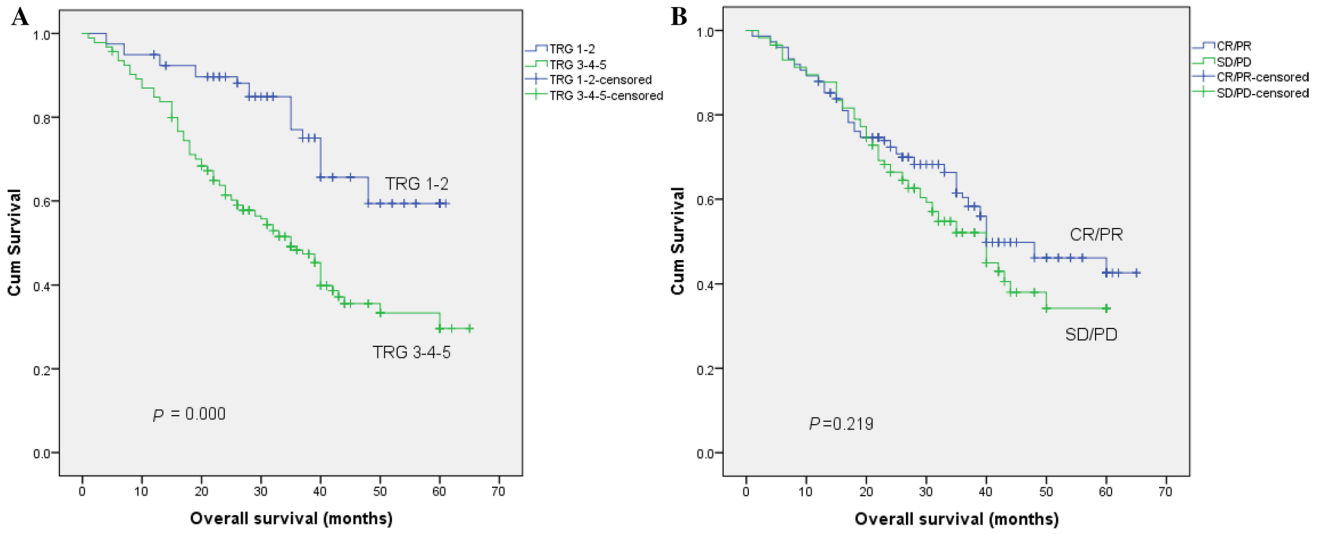

Fig. 2 Comparisons of overall survival by pathological and radiological tumor regression response in patients with locally advanced gastric cancer after perioperative chemotherapy. Kaplan–Meier survival analysis was employed to compare the difference between groups. A. Comparison of overall survival by pathological tumor regression response between TRG1-2 and TRG3-4-5, $P=0.000$. B. Comparison of overall survival by radiological tumor regression response between CR/PR and PD/CD, $P=0.219$

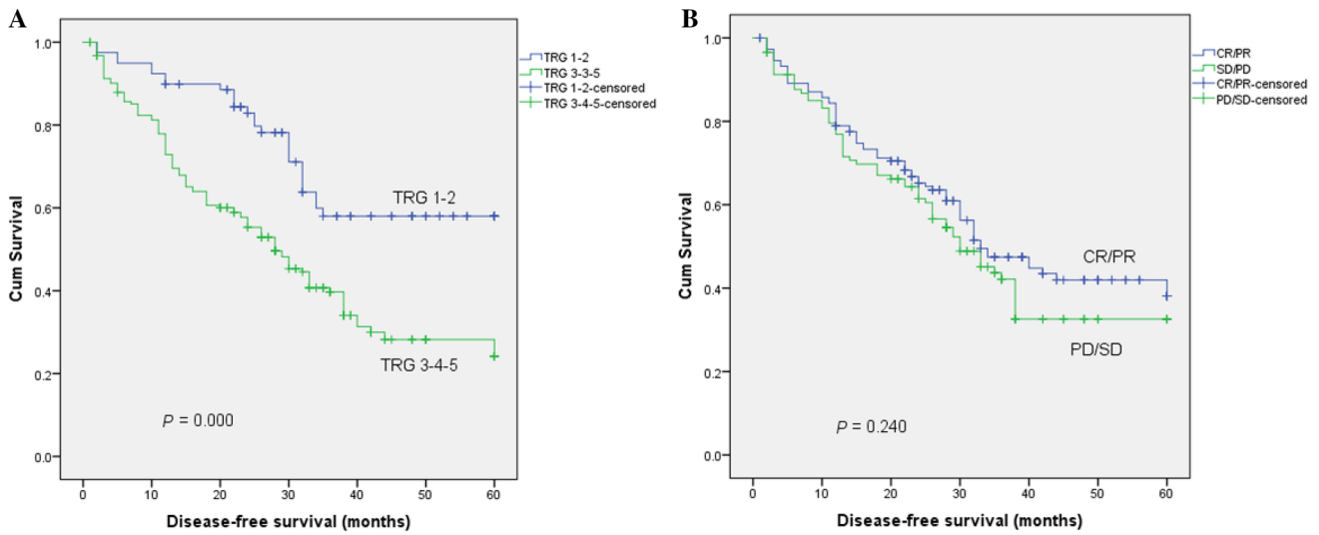

Fig. 3 Comparisons of disease-free survival by pathological and radiological tumor regression response in patients with locally advanced gastric cancer after perioperative chemotherapy. Kaplan-Meier survival analysis was employed to compare the difference between groups. A. Comparison of disease-free survival by pathological tumor regression response between TRG1-2 and TRG3-4-5, $P=0.000$. B. Comparison of disease-free survival by radiological tumor regression response between CR/PR and PD/CD, $P=0.240$

issue and many authors have proposed different methods (pathological tumor regression, radiological tumor regression, serum tumor marker and molecular biomarker) for the evaluation of tumor regression after chemotherapy [16–19]. Indeed, clinical outcome is the ultimate goal to evaluate the effectiveness of perioperative chemotherapy. But the clinical outcome requires long-term follow-up, and it is necessary to continuously evaluate the phased effectiveness during the whole treatment course, which contributes to provide guidance for the following treatment. Evaluation of tumor regression after neo-adjuvant chemotherapy may be beneficial to make choices of post-operative chemotherapy regimen. Many kinds of pathological tumor regression have been introduced to evaluate the effectiveness of neo-adjuvant chemotherapy, such as Mandard system, Becker system, and Dwork system and so on. In the year of 1994, Mandard et al. [7] first proposed the five-tiered system to assess tumor regression in

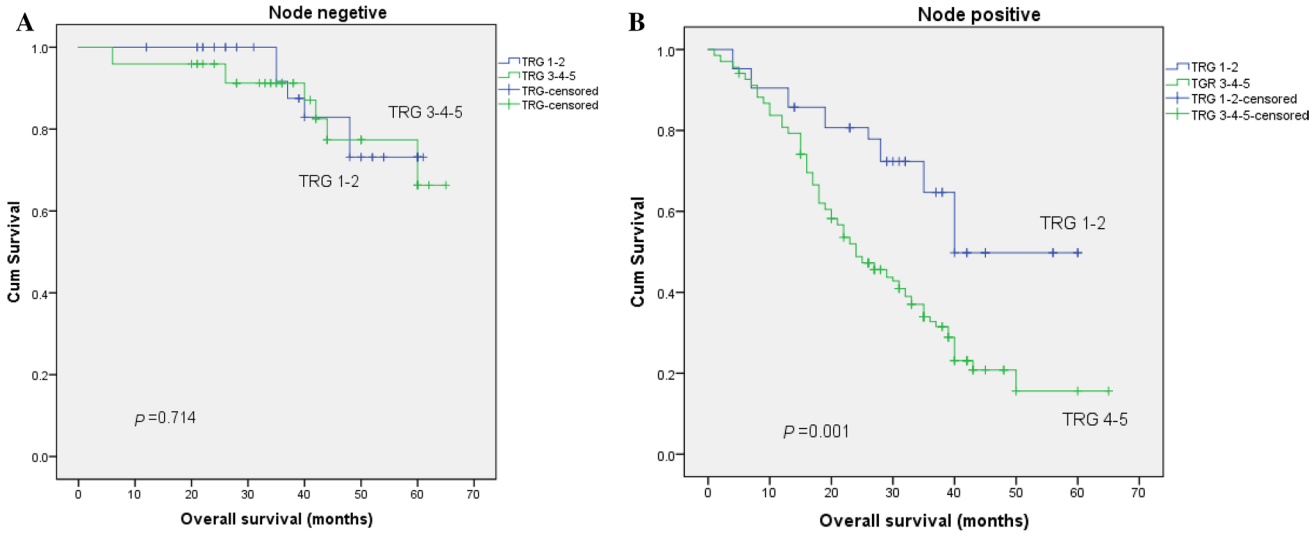

Fig. 4 Comparisons of overall survival by pathological tumor regression response in patients with negative and positive lymph nodes. A. Comparison of overall survival by pathological tumor regression response in patients between TRG1-2 and TRG3-4-5, $P=0.714$. B. Comparison of overall survival by pathological tumor regression response in patients between TRG1-2 and TRG3-4-5, $P=0.001$

esophageal squamous cell carcinoma after preoperative chemotherapy (Oxaliplatin) combined with radiological chemotherapy and then it was widely used in rectum carcinoma as well. However, the effect of TRG (Mandard) applied to locally advanced gastric cancer need to be verified. Zhu et al. demonstrated TRG corrected tightly with clinicopathological characteristics (ypT, ypN, vascular invasion or lymphatic invasion, histological type, etc.) and survival in locally advanced gastric adenocarcinoma [20]. But Smyth EC et al. conducted a randomized trial showing pathologic response to chemotherapy was not significantly associated with any clinicopathological variable, including age, sex, site of tumor, or histologic subtype [3]. Our study result revealed TRG was correlated to tumor size, Lauren classification, grade of differentiation, histological type, postsurgical T category (ypT), postsurgical N category (ypN), vascular invasion or lymphatic invasion and so on. However, only Lauren classification and ypT were independent factors for TRG. The reason for why the discrepancy produced was reasonably related to different TRG classifications methods. Smyth EC's study included clinicopathological variable of age, sex, location and histology and the tumor regression grade was classified into nearly response (TRG1-2) and scarce response (TRG3-5), which differs from our investigation with a three-tiered system (TRG1-2, TRG3, TRG4-5). While Zhu et al. proposed the five-tiered system (TRG1, 2, 3, 4, 5) to analyze associated clinicopathologic variable. Additionally, in our series, Lauren classification significantly related with TRG (a promising indicator of adjuvant chemotherapy assessment), which indicated Lauren classification seems to be an important biomarker to identify better response to preoperative chemotherapy so that providing guidance on how to choose appropriate neo-adjuvant chemotherapy protocol.

The prognostic value of pathological and radiological tumor regression was also discussed in this study. Tomasello et al. reported a meta-analysis of 17 published studies about neo-adjuvant chemotherapy for gastric and esophageal cancer that pathological tumor regression was not significantly associated with survival (HR = 0.6, $P=0.07$) [21]. But Smyth EC et al. deemed good tumor regression (TRG 1 or 2) is associated with improved OS in chemotherapy-treated patients in univariate analysis (HR = 1.94, 95%CI, 1.11–3.39, $P=0$ 0.02). Consistent with Elizabeth's study, our study result showed TRG was found to be a prognostic factor for DFS and OS. Furthermore, subset analysis of lymph node status suggested the predictor of survival appears limited to patients with positive lymph node (postsurgical category), supporting the concept that patients with positive nodes (postsurgical category) maximumly benefit from perioperative chemotherapy. In Mandard-TRG system, the category of nearly complete response is separated. But in our investigation, tumor regression was graded as two groups (TRG1-2 and TRG3-5). Because statistical analysis showed survival data in patients with TGR3 was not significantly different from those with TRG4-5 (HR = 1.020, 95%CI, 0.690–1.507, $P=0.923$).

As the Response Evaluation Criteria in Solid Tumors (RECIST v1.1) was widely applicated in neo-adjuvant therapy assessment, it was considered as the gold standard in the evaluation of tumor regression response for some solid malignances [16]. And even if previous studies reported radiological tumor regression was associated with survival

after neo-adjuvant chemotherapy in gastric cancer [22, 23]. On contrary to previous trial, no significant difference had been founded associated with clinical outcome in our study, though patients with radiological response of CP/PR received a better survival than those with PD/SD ($P = 0.219$; $P = 0.240$, Log-rank test). Its application of neo-adjuvant chemotherapy assessment in gastric cancer should be cautious. The inflammation and edema of tumor tissue after chemotherapy may distort the layers of the stomach, affecting the judgments of the infiltration depth and the boundary between tumor tissue and normal tissue after chemotherapy [24]. On the other hand, radiological tumor regression assessment requires the presence of a measureable lesion, which may not suitable for some lesion originating from digestive tract [16, 25]. Especially, poor stomach filling on CT images, presenting with immeasurable lesion, often leads to an underestimation of tumor size. Last but not least, radiological tumor regression evaluation of CT can hardly distinguish fibrosis, induced by chemotherapy from vital tumor tissue, which sometime leads to an error in evaluating the residual tumor size [26]. Indeed, Japanese JGOG0507-A trial compared the validity of response assessment criteria in neo-adjuvant chemotherapy for gastric cancer, showing it more reasonably evaluates the effectiveness of preoperative chemotherapy in pathological tumor response than RESCIT system [27]. And it highlighted that pathological tumor response was an appropriate surrogate endpoint of survival.

Interactions of various factors promote the occurrence and development of gastric cancer, presenting with complicated biological behavior, high heterogeneity and undesired prognosis. The grade of differentiation of gastric cancer reflects its malignant potential, histological subtype represents its biological characteristics and Lauren classification stands for its histological pathomorpaologic features. The prognostic value of grade of differentiation, histological subtype and Lauren classification has been proved by previous studies [28]. It reached a consensus that no prognostic marker is currently available beyond pathological TNM stage for patients with gastric cancer who received neo-adjuvant treatment [3]. Lymph node metastases, invasion depth and vascular invasion or lymphatic invasion are independent risk factors to predict prognosis in patients with gastric cancer [29]. Our study demonstrates that histological type, Lauren classification, vascular invasion or lymphatic invasion, ypN, postsurgical pathologic stage were significantly associated with survival, which was coincident with previous ones. Unfortunately, TRG and postsurgical T category failed to be independent factors for OS and DFS in patients after perioperative chemotherapy. Probably because pathological tumor response evaluated the effect of chemotherapy concentrating attention on the fibrosis primary lesion and never attached attention on the changes of lymph node after chemotherapy. As we all known, lymph node status was considered as one of the most important prognostic variables for gastric cancer. Ikoma et al. reported that the ypT category does not impact overall survival in node negative gastric cancer [30]. From this point, our study was in line with Ikoma's study, showing postsurgical T category was not independent factors for survival in patients after perioperative chemotherapy. Otherwise, we sought to identify patient subgroups for whom the benefit was maximized. It is discovered TRG was a prognostic variable for patients with positive lymph nodes (postsurgical N category). In conclusion, TRG was significantly associated with survival, but not an independent risk factor. Considering the survival benefit provided by preoperative chemotherapy, predictive markers identify patient subgroups for whom the benefit was maximized should be further studied.

Our study has some limitations, mainly for its retrospective design and small number of participants. The small number of participants may have produced selection bias, leading to possible false-positive or -negative results. We choose TRG-Mandard system for its operablility and it has been verified for patients with esophageal squamous cell carcinoma after adjuvant chemotherapy. The option criteria of pathological tumor regression grade for gastric cancer is a contentious issue. Firstly, without quantifying indicators, TRG-Mandard system was used to assess the effectiveness of chemotherapy based on the estimation proportion of fibrosis and residual cancer. Secondly, pathologists often choose several blocks rather than all tumor tissue for evaluation. While gastric cancer presented with high heterogeneity of response to chemotherapy, if underlying cancer demonstrates no response to chemotherapy, the assessment will lead to a biased assessment. Thirdly, TRG-Mandard system identifies residual cancer by reviewing hematoxylin and eosin-stained slides, which easily includes unvital tumor cell leading to an error in the effectiveness evaluation.

In a word, TRG seems to be a promising prognostic indicator and it predicts the prognosis of patients with locally advanced gastric cancer after neo-adjuvant chemotherapy more reasonable when compared to RECIST v1.1.

Author contribution Xing Xu searched and reviewed the literature, designed the research and wrote the paper. Guoliang Zheng designed the research and provided the clinical data. Yan Zhao performed statistical analysis. Tao Zhang reviewed the literature and interpreted the paper. Zhichao Zheng participated in reviewing the literature, designing the research, revising and writing the paper.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest

Ethical approval This study was approved by the Ethics Committee of Liao Ning Cancer Hospital.

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