Which is the optimal management for locally advanced gastric cancer patients with TRG 0 and 1 after R0 resection?

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Background: Neoadjuvant chemotherapy (NAC) followed by surgery currently offers promise as a strategy for patients with locally advanced gastric cancer (GC). However, there is limited evidence to guide treatment for TRG 0 and 1 patients with locally advanced GC after R0 resection. This study set out to explore the optimal management for TRG 0 and 1 patients with locally advanced GC after R0 resection.

Methods: The retrospective data of 154 TRG 0 and 1 patients with locally advanced GC following R0 resection who were treated between January 2012 and December 2018 were collected and analyzed. The Kaplan-Meier method was used to estimate the survival rate. Multivariate analysis was performed using the Cox proportional hazards model.

Results: The median follow-up was 34.1 (range, 6.6–90.9) months. Six patients (3.9%) were lost during follow-up. Of the 27 patients who experienced relapse, 12 died, including 2 patients who died of non-neoplastic causes. The 5-year recurrence-free survival (RFS) and 5-year overall survival (OS) were 71.6% (95% CI: 68.5–79.6) and 82.9% (95% CI: 76.9–86.1) for the whole cohort, respectively. Univariate analysis revealed that patients with carcinoembryonic antigen (CEA) <5.0 ng/ml after NAC (77.7% *vs.* 20.1%, P<0.001), distal gastrectomy (91.7% *vs.* 67.5%, P=0.046) had higher 5-year RFS. Meanwhile, combined resection (55.6% *vs.* 73.1%, P=0.042), major complications (42.7% *vs.* 80.50%, P<0.001), and lymph node metastasis (ypN+) (52.0% *vs.* 83.7%, P<0.001) had lower 5-year RFS. The multivariate analysis showed that CEA level after NAC (HR =2.876, 95% CI: 1.051–7.872, P=0.040), major complications (HR =2.432, 95% CI: 1.062–5.567, P=0.035), and lymph node metastasis (ypN+) (HR =3.183, 95% CI: 1.242–8.161, P=0.016) were independent prognostic factors.

Conclusions: TRG 0 and 1 patients with local GC after R0 resection following NAC had a good prognosis, especially patients with CEA <5.0 ng/mL after NAC, and those without major complications or lymph node metastasis. Monotherapy or no chemotherapy may offer options for treating TRG 0 and 1 patients without adverse prognostic factors.

Keywords: Gastric cancer (GC); neoadjuvant chemotherapy (NAC); tumor regression grading; prognosis

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Introduction

Gastric cancer (GC) is one of the most common cancers in the world. In China, GC ranks as the second most common cancer, and occupies the same position in terms of cancer-related mortality (1). Owing to a lack of screening, locally advanced GC comprises more than 70% of GC diagnoses in China. Radical resection offers a promising treatment strategy for patients with resectable GC. However, the outcomes for locally advanced GC patients who receive surgery are not satisfactory because of distant lymph node or distant metastases, or recurrence (2). The discovery of new treatments is essential to improving the prognosis of GC.

Since it was reported in 1989, neoadjuvant chemotherapy (NAC) has attracted a high level of interest (3). At present, NAC followed by surgery is a helpful therapy for locally advanced GC. Many clinical investigations have shown that NAC can downstage the primary tumor, improve the R0 resection rate, treat potential micrometastases in advanced GC, and achieve a survival benefit (4-6). Nevertheless, many problems remain be solved in relation to NAC, including appropriate population choice, accurate preoperative staging, the choice of preoperative chemotherapy regimen, the efficacy criteria for preoperative chemotherapy, and the selection of a postoperative adjuvant chemotherapy regimen. After surgery, most patients who receive NAC receive post-operative chemotherapy, and to avoid ineffective and effective NAC, the regimen remains the same as it was before surgery.

Histologic response to NAC is useful for assessing the sensitivity of the tumor to chemotherapy and predicting prognosis in patients. Several studies have proposed four tumor regression grade (TRG) systems, the criteria of which are shown in *Table 1*. In 1994, a five-layered TRG system for esophageal cancer was first proposed by Mandard *et al*. and has since been widely applied for malignancies of the digestive system (7). Because patients with TRG 1 and 2 demonstrate similar rates of survival, which are significantly better than patients with TGR 3, 4, and 5, in many studies, these 2 grades have been combined for survival analysis (8-11). In 1999, Ninomiya *et al*. conducted precise histological examinations of 18 gastric carcinoma patients who underwent gastrectomy after NAC and proposed new TRG criteria for GC, which are now usually referred to as the Japanese Gastric Cancer Association (JGCA) criteria (12). Becker *et al*. proposed a four-tiered grading system based on large number of GC patients and indicated tumor regression to be an independent prognostic factor of survival (13,14). At present, the most widely used TRG system for evaluating the efficacy of NAC in GC is the one proposed by Ryan *et al*. in 2005; this system was first applied to surgical specimens of rectal cancer and was later recommended by College of American Pathologists (CAP) as a pathological TRG system for GC (15). In most studies, GC patients who demonstrate histologic complete response or near complete response to NAC have been shown as having better survival (16-19). Whether these patients would benefit from a different regimen to the one administered preoperatively is still controversial.

In this study, according to CAP-TRG, we examined the relationship between clinical data and prognosis among TRG 0 and 1 patients with locally advanced gastric cancer who received NAC after R0 resection and explored the appropriate management of TRG 0 and 1 patients with locally advanced GC after R0 resection.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-3986).

Methods

Patient population

The retrospective clinical data of TRG 0 and 1 patients with locally advanced GC after R0 Resection who received treatment at The Affiliated Tumor Hospital of Zhengzhou University between January 2012 and December 2018 were included in the study. One hundred and fifty-four patients were enrolled in this study. Patients who met following criteria were included in the study: (I) aged 20–70 years old; (II) ECOG score of 0 or 1; (III) adenocarcinoma confirmed by biopsy specimen; (IV) computed tomography (CT) showed T3–4, N any, M0 or T any, N1–3, M0 before NAC; (V) D2 gastrectomy; (VI) R0 resection; (VII) no history of malignancy; (VIII) non-emergency surgery.

The protocol for the study project was approved by the Ethics Committee of The Affiliated Tumor Hospital of Zhengzhou University (No. 2020002), and it was conducted in accordance with the Declaration of Helsinki, as revised in 2013. Because of the retrospective nature of the research, the requirement for informed consent was waived.

Data on age, gender, serum CEA level, histology, macroscopic type, clinical stage, operation method (laparoscopy or open), operation type (total or distal gastrectomy), combined resection, lymph node metastasis (ypN), TRG, complications, NAC regimen and course,

Table 1 Criteria of four tumor regression grading systems

TRG system	Grade	Description
JGCA-TRG	0	No evidence of effect
	1a	Viable tumor cells occupy more than 2/3 of the tumorous area
	1b	Viable tumor cells remain in more than 1/3 but less than 2/3 of the tumorous area
	2	Viable tumor cells remain in less than 1/3 of the tumorous area
	3	No viable tumor cells remain
CAP-TRG	0	No viable cancer cells (complete response)
	1	Single cells or small groups of cancer cells (moderate response)
	2	Residual cancer outgrown by fibrosis (minimal response)
	3	Minimal or no tumor killed or extensive residual cancer (poor response)
Becker-TRG	1a	No residual tumor/tumor bed
	1b	<10% residual tumor/tumor bed
	2	10–50% residual tumor/tumor bed
	3	>50% residual tumor/tumor bed
Mandard-TRG	1	complete tumor regression
	2	scattered tumor cells within fibrosis
	3	tumor cells and fibrosis with predominance of fibrosis
	4	tumor cells and fibrosis with predominance of tumor cells
	5	no tumor regression

and adjuvant chemotherapy regimen and course were collected. The cut-off value for CEA was 5.0 ng/mL. The patients were categorized according to the Clavien-Dindo classification system (20). If a patient experienced two or more complications, the level of analysis was determined by the highest ranked complication. Complications of grades III–V were considered to be major complications.

Staging

The chests and abdomens of all of the patients were examined by CT scan. Clinical tumor stage was evaluated by two experienced roentgenologists, according to the eighth edition of the UICC staging system.

Chemotherapy regimen

The chemotherapy regimens were: (I) monotherapy: S-1and Capecitabine; (II) doublet chemotherapy: SOX, XELOX, and mFOLFOX6; and (III) triplet regimen: DOX, DCF, ECF, and FLOT. The chemotherapeutic dosage was adjusted according to the level of toxic reaction.

Surgery procedure

Between 3 and 4 weeks after NAC, all patients with no clear surgical contraindications were underwent radical gastrectomy with D2 lymphadenectomy according to the Japanese classification of gastric carcinoma (ver. 4) (21). After the gastrectomy, the specimen was removed through a small median abdominal incision under the xiphoid (about 6–8 cm), and reconstruction was performed in laparoscopy surgery. In open surgery, an incision approximately 20–25 cm in length was made from the xiphoid to the periumbilical area.

Pathological response

Pathological response was reevaluated by two pathologists in line with the tumor regression grading (TRG) system (15) as follows: TRG 0: no cancer cells, including lymph nodes (*Figure 1A*); TRG 1: single cells or small groups of cancer

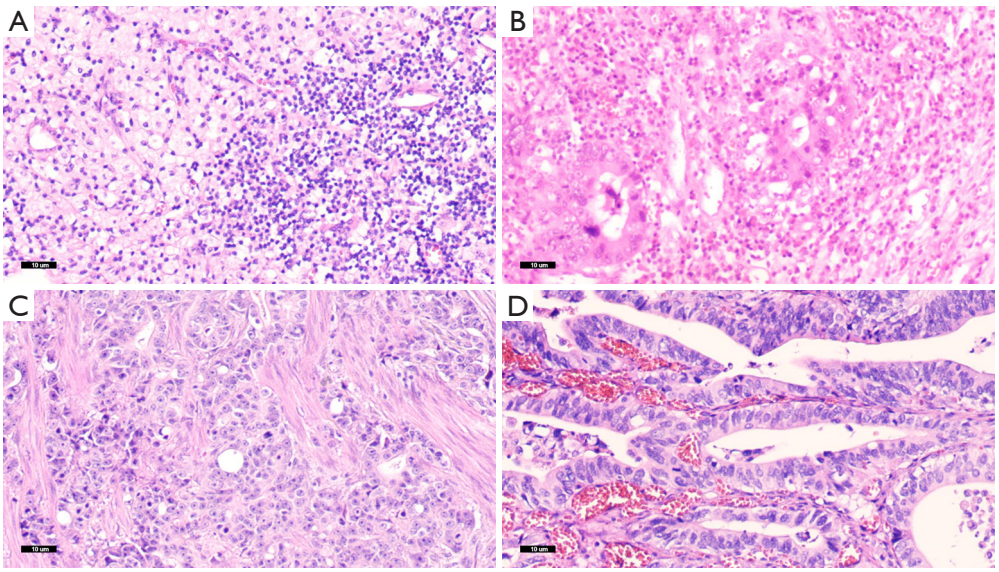

Figure 1 Images showing the different stages of the tumor regression grading system. (A) No cancer cells, lymphocytes, and histiocyte infiltration; (B) small groups of cancer cells, lymphocytes and histiocyte infiltration; (C) residual cancer outgrown by fibrosis; (D) minimal or no treatment effect. (H & E, original magnification ×100).

cells (*Figure 1B*); TRG 2: Residual cancer outgrown by fibrosis (*Figure 1C*), and TRG 3: minimum or no treatment effect and extensive residual cancer cells (*Figure 1D*).

Follow-up

Overall survival (OS) was defined as the period from the initiation of NAC to death from any cause, and recurrence-free survival (RFS) was defined as the period from the initiation of NAC to recurrence or death from any cause. All of the patients were followed up every 3 to 6 months. Clinical examination and hematologic analysis were performed at each follow-up visit, including tumor marker assays for carcinoembryonic antigen (CEA), carbohydrate antigen 72-4 (CA72-4), and carbohydrate antigen 19-9 (CA19-9). Abdominal CT was performed every 6 months or when recurrence was clinically suspected. The cut-off date for overall survival was in June 2019, and the median follow-up was 34.1 (range, 6.6–90.9) months. Six patients (3.9%) were lost at follow-up.

Statistical analysis

For continuous variables, data presented as the mean ± SD and, for categorical variables, as proportions. For univariate analysis, differences in RFS between groups were evaluated by the log-rank test. A Cox proportional hazards model was used to perform multivariate analysis. Covariates with a P value <0.1 in the univariate analysis were included in the multivariate model. A P value <0.05 was considered to represent statistical significance. IBM SPSS Statistics, version 22 (IBM corporation, North Castle Drive, Armonk, NY, USA) was used to conduct all of the analyses.

Results

Patient characteristics

A total of 154 patients who underwent NAC combined with radical surgery for GC were ultimately included in this study. Their clinicopathological factors and treatment details are shown in *Table 2*. Most patients were male (78.6%), with ages ranging between 26 and 70 (median: 56 years old). The CEA level of 16 patients (10.4%) after NAC was positive. A majority of patients displayed differentiated histology (81.8%) and presented with Borrmann III/IV (58.4%). Before NAC, 40 (26.0%), 98 (63.6%), and 16 (10.4%) patients were classified as stage II, III and IV (clinical stage), respectively. A majority of patients received doublet chemotherapy (76.0%) as the regimen of NAC and their courses ranged from 2 to 6 cycles (median: 4). Open surgery, total gastrectomy, and combined resection were received by 110 (71.4%), 129

Table 2 The association between clinicopathological factors and treatments and recurrence-free survival

Variables	Univariate, N (%)	5 y-RFS	P value	Multivariate hazard ratio (95% CI)	P value
Age			0.959		
>60	53 (34.4)	69.6			
≤60	101 (65.6)	72.4			
Gender			0.931		
Male	121 (78.6)	70.7			
Female	33 (21.4)	73.9			
CEA level after NAC			0.000	2.876 (1.051–7.872)	0.040
Positive	16 (10.4)	20.1			
Negative	138 (89.6)	77.7			
Histology			0.921		
Differentiated	126 (81.8)	72.4			
Undifferentiated	28 (18.2)	67.3			
Macroscopic type			0.602		
Borrmann I/II	64 (41.6)	77.7			
Borrmann III/IV	90 (58.4)	67.3			
Clinical stage before NAC			0.302		
II	40 (26.0)	79.8			
III	98 (63.6)	65.9			
IV	16 (10.4)	83.3			
NAC regimen			0.944		
Doublet chemotherapy	117 (76.0)	73.3			
Triplet regimens	37 (24.0)	66.8			
NAC course			0.856		
>3	92 (59.7)	71.3			
≤3	62 (40.3)	71.0			
Operation method			0.114		
Open	110 (71.4)	77.7			
Laparoscopy	44 (28.6)	56.1			
Operation type			0.046	0.180 (0.024–1.370)	0.098
Distal gastrectomy	25 (16.2)	91.7			
Total gastrectomy	129 (83.8)	67.5			
Combined resection			0.042	1.436 (0.447–4.612)	0.543
Yes	12 (7.8)	55.6			
None	142 (92.2)	73.1			

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Univariate, N (%)	5 y-RFS	P value	Multivariate hazard ratio (95% CI)	P value
Major complications			0.000	2.432 (1.062–5.567)	0.035
Yes	31 (20.1)	42.7			
None	123 (79.9)	80.5			
Lymph node metastasis (ypN)			0.000	3.183(1.242–8.161)	0.016
N0	107 (69.5)	83.7			
N+	47 (30.5)	52.0			
Primary tumor			0.445		
PCR	84 (54.5)	65.7			
No PCR	70 (45.5)	77.9			
Adjuvant chemotherapy			0.144		
Yes	118 (76.6)	67.1			
None	36 (23.4)	88.0			
Adjuvant chemotherapy regimen			0.127		
None	36 (23.4)	88.0			
Monotherapy	42 (27.3)	72.2			
Doublet chemotherapy	57 (37.0)	56.6			
Triplet	19 (12.3)	87.4			

RFS, recurrence-free survival; CEA, carcinoembryonic antigen; NAC, neoadjuvant chemotherapy.

(83.8%) and 12 (7.8%) of the patients, respectively. Major complications were experienced by 31 patients (20.1%). After surgery, 107 patients (69.5%) had no lymph node metastasis (ypN0), and in 84 patients (54.5%) no cancer cells were discovered in the primary tumor. Adjuvant chemotherapy was administered to 118 patients (76.6%), 42 patients (27.3%) received oral drugs alone, 57 patients (37.0) received doublet chemotherapy, and 19 patients (12.3) received three-drug chemotherapy.

Factors associated with survival

After 34.1 (range, 6.6–90.9) months of follow-up, 27 patients had experienced relapse, 12 of whom died (including 2 patients who died of non-neoplastic causes). The 5-year RFS (*Figure 2A*) and 5-year OS (*Figure 2B*) were 71.6% (95% CI: 68.5–79.6) and 82.9% (95% CI: 76.9–86.1) for the entire cohort, respectively. The univariate analysis revealed that patients with CEA <5.0 ng/ml after NAC (77.7% *vs.* 20.1%, P<0.001), distal gastrectomy (91.7% *vs.* 67.5%, P=0.046) had higher 5-year RFS. Meanwhile, combined resection (55.6% *vs.* 73.1%, P=0.042), major complications (42.7% *vs.* 80.5%, P<0.001), and lymph node metastasis (ypN+) (52.0% *vs.* 83.7%, P<0.001) had lower 5-year RFS.

The covariates included in Cox proportional hazards model were CEA level after NAC, operation type, combined resection, major complications, and lymph node metastasis (ypN+). Based on the multivariate analysis, CEA level after NAC (HR =2.876, 95% CI: 1.051–7.872, P=0.040), major complications (HR =2.432, 95% CI: 1.062–5.567, P=0.035), and lymph node metastasis (ypN+) (HR =3.183, 95% CI: 1.242–8.161, P=0.016) are independent prognostic factors (*Table 2*).

The 5-year RFS rates for patients with CEA <5.0 ng/mL and CEA ≥5.0 ng/mL after NAC were 77.7% (95% CI: 74.0–81.4) and 20.1% (95% CI: 0–51.6), respectively (P=0.000) (*Figure 2C*). The 5-year OS rates for patients with CEA <5.0 ng/mL and CEA ≥5.0 ng/mL after NAC were 83.8% (95% CI: 74.4–93.2) and 79.8% (95% CI: 59.2–100), respectively (P=0.102) (*Figure 2D*). The 5-year RFS rates of patients with and without major complications were

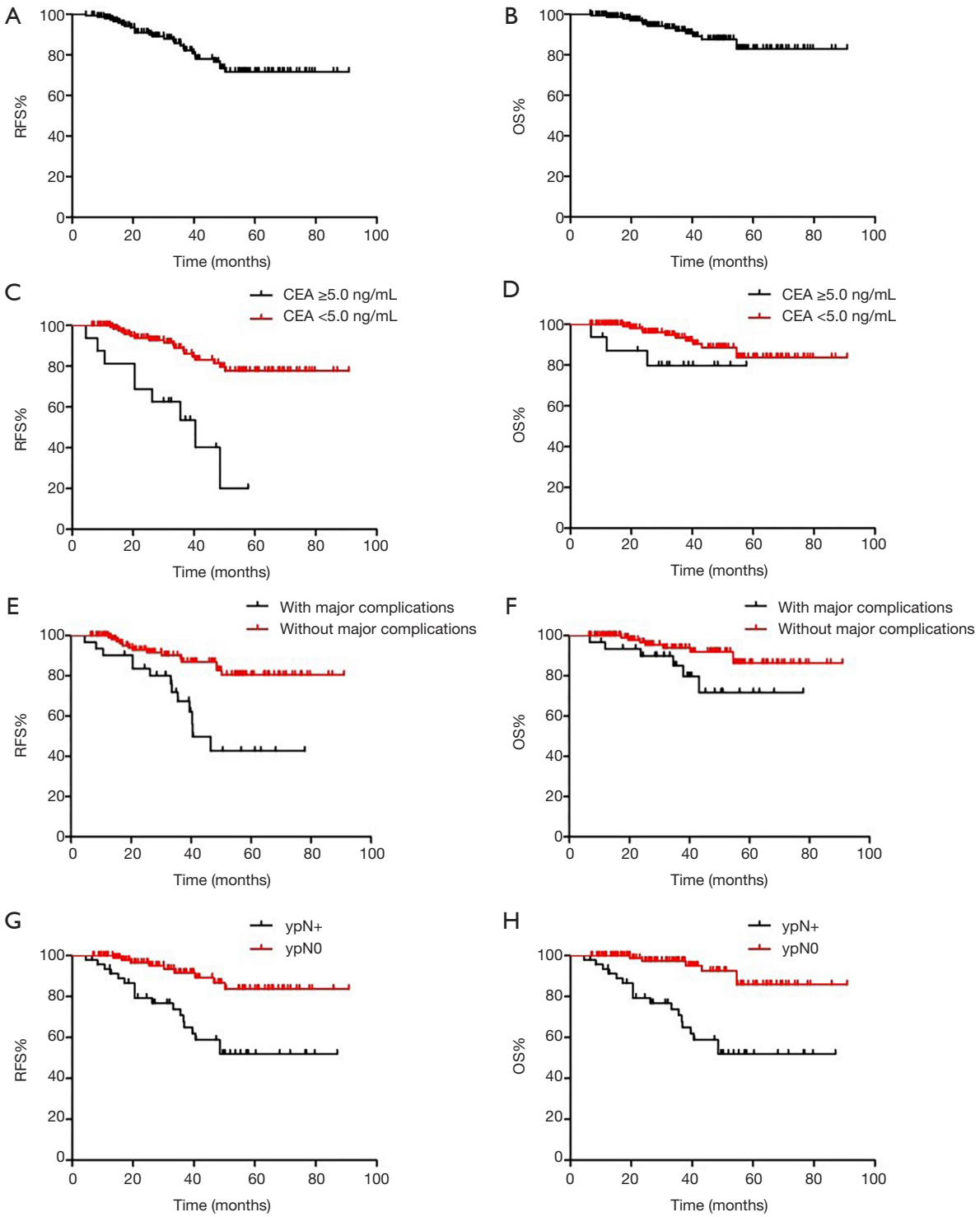

Figure 2 The prognostic value of clinicopathological factors. Kaplan-Meier survival curves for RFS (A) and OS (B) in the overall population. Kaplan-Meier curves for RFS (C) and OS (D) in patients based on CEA level after NAC. Kaplan-Meier curves for RFS (E) and OS (F) in patients based on major complications. Kaplan-Meier curves for RFS (G) and OS (H) in patients based on lymph node metastasis (ypN). RFS, recurrence-free survival; OS, overall survival; NAC, neoadjuvant chemotherapy.

42.7% (95% CI: 20.0–65.4) and 80.5% (95% CI: 70.7–90.3), respectively (P=0.000) (*Figure 2E*). The 5-year OS rates of patients with and without major complications were 71.8% (95% CI: 50.8–92.8) and 86.4% (95% CI: 76.8–96.0), respectively (P=0.047) (*Figure 2F*). The 5-year RFS rates of ypN0 and ypN+ were 83.7% (95% CI: 73.1–94.3) and 52.0% (95% CI: 35.3–68.7), respectively (P=0.000) (*Figure 2G*), The 5-year OS rates of ypN0 and ypN+ were 85.9% (95% CI: 74.7–97.1) and 77.6% (95% CI: 63.7–91.5), respectively (P=0.044) (*Figure 2H*).

Discussion

At present, NAC is widely used in the standardized treatment of GC, using effective methods to accurately evaluate its efficacy is particularly important. TRG system is mainly to observe the degree of fibrosis of tumor tissues and the proportion of residual tumor cells. TRG system may reflect different efficacy of NAC, help formulate follow-up treatment regimen and predict prognosis. Many studies showed GC patients who demonstrate histologic complete response or near complete response to NAC have better survival (16-19). In this study, according to CAP-TRG, TRG 0 and 1 patients with local GC after R0 resection following NAC were found to have a good prognosis, which is similar to findings of previous studies (11,22). We also found CEA level after NAC, major complications, and lymph node metastasis (ypN+) to be independent prognostic factors. However, baseline characteristics and pre-surgical/surgical/post-surgical treatment do not guarantee recurrence-free long-term survival.

CEA is a serum tumor marker that has been used to diagnose and monitor of gastrointestinal malignancies for a long time, and its prognostic ability has been reported many times (23-25). In most previous reports, only preoperative or postoperative levels of CEA were evaluated. In our study, we found that CEA level after NAC has prognostic significance for the long-term survival of TRG 0 and 1 patients with locally advanced GC after R0 resection. A clinical evaluation by Sun and Zhang suggested that high preoperative serum levels of CEA are associated with a higher risk of death, and may predict clinical disease progression after NAC (26); however, the mechanisms of this have not been clarified. This is perhaps due to the association serum CEA concentration has with factors such as tumor differentiation, degree of vascular invasion, and location of CEA expression within cancer cells (27,28).

Previous data has suggested that long-term survival following curative gastrectomy is conversely affected by postoperative intra-abdominal infectious complications (29). Hayashi *et al*. demonstrated that postoperative infectious complications increase disease recurrence in GC patients (30). In this study, we found that major complications are poor prognostic factors. This outcome can be attributed to several factors. Firstly, the adaptive immune system can protect the host against cancer cells while inflammatory cytokines such as interleukin 1, 6, and 8 (IL-1/6/8) and tumor necrosis factor alpha (TNF-α) may hinder this process (31). Secondly, inflammation promotes the proliferation and survival of malignant cells (32). Thirdly, anastomotic leakage causes the deposition and implantation of viable exfoliated tumor cells in the enterocoelia, which may increase the local recurrence rate (33). Furthermore, complications always postpone the adjuvant chemotherapy.

Xu *et al*. discovered that ypN was significantly associated with survival, while postsurgical T category failed to be an independent factor of OS and DFS in patients after perioperative chemotherapy (8). In previous studies, gastric patients with residual cancer cells in the lymph nodes and no cancer cells in the primary tumor after NAC have shown worse survival than patients with no cancer cells in the primary tumor and lymph nodes (2). In this study, lymph node metastasis (ypN+) was another independent factor of poor prognosis, and can be considered as one of the most important prognostic variables for GC. The response of the primary tumor and lymph nodes to NAC was not identical. Pathological tumor response assesses the effects of chemotherapy by focusing attention on the fibrosis primary lesion but affording insufficient attention on the changes of lymph node.

The TNM system is well known as an effective predictor of the prognosis of GC patients. Although pre-operative TNM staging by CT scans and post-operative staging by pathology are not in perfect agreement, clinical TNM staging is crucial for planning appropriate treatment and predicting the survival of GC patients without preoperative treatment (34,35). In our study, no correlation was found between the baseline characteristics and RFS. Kurokawa *et al*. reported that histological response validated the response assessment criteria for overall survival in NAC for GC, better than RECIST or TNM (36). Cho *et al*. reported 22 patients who achieved pCR after NAC had a good prognosis (22), with an overall survival rate at 5 years of 85%; however 19 of the subjects had either stage III or IV disease based on the 7th TNM edition, 2 were positive

for peritoneal cytology, and 12 did not receive adjuvant chemotherapy. In our study, there was no correlation discovered between RFS and pre-surgical, surgical, or post-surgical treatments. As such, we can gather that tumor load or treatment are not predictive of long-term survival in TRG 0 and 1 patients after NAC. The biology of GC with TRG 0 and 1 with NAC is likely to be distinct from non-TRG 0 and 1 tumors, and this is reflected in the prognosis.

The non-operative management (NOM) strategy was first put forward by Habr-Gama *et al*. (37), who found that rectal cancer patients achieved clinical complete response to neoadjuvant chemoradiotherapy and total mesorectal excision is no longer required. NOM may preserve sphincter function and avoid surgery-related complications, and is a new norm in the treatment of rectal cancer. As far as we know, no similar reports on GC exist. Several problems impelled us to carry out similar clinical research on GC. Firstly, GC patients achieving pCR after NAC is uncommon in clinical practice, the pCR rate were respectively 13.0%, 10.0% and 16.0% by using the ECF(-like) (38), DCF (39), and FLOT (6) regimen (6). Next, clinical response seems to correlate poorly with pathology in preoperative staging of gastric adenocarcinoma after NAC, Thirdly, pathological response has a higher validity than radiography (36).

Previous studies have revealed brain metastasis from GC occurs in less than 1% of clinical cases (40,41). Fields *et al*. reported the incidence of brain metastasis in pCR patients to be 8%, and one-third of the metastases experienced by pCR patients were brain metastases (42). Due to blood-brain barrier, penetration of chemotherapeutic agents into central nervous system (CNS) is diminished (43). As a result, TRG 0 and 1 patients may have increased risk of brain recurrence, and CNS symptoms in these patients should be acknowledged.

Since heterogeneity exists in GC cells, the identification of predictive biomarkers may make a better prognosis in patients more likely. A new molecular classification was proposed, which divided GC into four subtypes: MSI tumors, EBV-infected tumors, genomically stable tumors, and chromosomally unstable tumors (44). EBV-infected tumors are associated with better prognosis (45). Several studies have demonstrated the expression of LGR5, FZD7 to represent a worse prognosis in GC (46,47).

Nevertheless, there is a possibility that the results were influenced by several factors. Firstly, the inherent limitations of this study's retrospective nature may have introduced selection bias, although we applied up inclusion criteria to take this into account. Secondly, the relatively small number of patients and the low incidence of TRG 0 and 1 may have limited the power of the study. Finally, the variety in chemotherapy regimens is another potential limitation.

Conclusions

In conclusion, TRG 0 and 1 patients with locally advanced GC after R0 resection following NAC had a good prognosis. The surgical procedure and perioperative care should be approached with caution to avoid causing complications. Monotherapy or no chemotherapy may serve as treatment options for TRG 0 and 1 patients while avoiding adverse prognostic factors. Further research on the predictive and prognostic factors for TRG 0 and 1 patients, such as the role of definition of EBV, early 18-FDG-PET assessment, MMR, and microsatellite status could help with management-related decision-making.

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Footnote

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Data Sharing Statement: Available at http://dx.doi.org/10.21037/atm-20-3986

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-3986). The authors have no conflicts of interest to declare.

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. The protocol for the research project was approved by the Ethics Committee of The Affiliated Tumor Hospital of Zhengzhou University (No. 2020002) and conformed to the provisions of the Declaration of Helsinki, as revised in 2013. Because of the retrospective nature of the research, the requirement for informed consent was waived.

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