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RESEARCH ARTICLE

Comparison of the predictive value of pathological response at primary tumor and lymph node status after neoadjuvant chemotherapy in locally advanced gastric cancer

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Abstract

Background Preoperative chemotherapy has been increasingly used in locally advanced gastric cancer (LAGC). However, the prognostic factors are still insufficient. This study aimed to investigate the prognostic significance of pathological response of the primary tumor to neoadjuvant chemotherapy (NACT) and the lymph node status after NACT.

Methods Data from 160 patients with LAGC treated with NACT followed by gastrectomy and met the inclusion criteria between March 2016 and December 2019 were retrospectively reviewed. Pathological evaluation after NACT was based on the grade of pathological response of the primary tumor and the status of lymph node. Survival curves for overall survival (OS) and disease-free survival (DFS) were estimated using the Kaplan–Meier method, and the log-rank test was used to compare survival difference. Univariate and multivariate analyses for prognostic factors were based on the Cox regression.

Results Among 160 selected cases, 90 had pathological response (PR), while 70 had no pathological response (nPR) to NACT. Smaller tumor size was presented in PR group, which also had lower level of signet ring cell features, compared to nPR group (all $p < 0.05$). Based on the status of lymph nodes, nodal status (−) group showed smaller tumor size, lower depth of tumor invasion, better differentiated degree, lower level of signet ring cell features, lower rate of lymphatic and venous invasion and less advanced ypTNM stage (all $p < 0.05$). Survival was equivalent between PR and nPR group (all $p > 0.05$), while patients with no lymph node metastasis had better DFS than that with lymph node metastasis (HR 0.301, 95% CI 0.194–0.468, $p = 0.002$). Multivariable Cox regression analysis identified that lymph node status after NACT was an independent prognostic factor associated with survival (OS: hazard ratio 1.756, 95% CI 1.114–3.278, $p = 0.029$; DFS: hazard ratio 1.901, 95% CI 1.331–3.093, $p = 0.012$).

Conclusion Lymph node status is a potential independent prognostic factor for LAGC patients treated with NACT and may be more efficient than pathological response in primary tumor.

Keywords Gastric cancer · Lymph node · Neoadjuvant chemotherapy · Pathological response · Survival

Introduction

Gastric cancer is one of the most frequently diagnosed malignancies, accounting for the third leading cause of cancer-related death worldwide [1]. Neoadjuvant chemotherapy (NACT) followed by gastrectomy was aimed to downstage the primary tumor, reduce tumor size, eliminate micrometastases and facilitate R0 resection in locally advanced gastric cancer (LAGC) [2]. The MAGIC trial and FNCLCC/FFCD trial have demonstrated the potential benefit of NACT, compared with surgery alone [3, 4]. These results were further verified by the multicenter trial FLOT4, which promoted the recommended use of NACT as the standard mode for LAGC [5]. Thus, evaluation the survival benefit

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of the preoperative therapy on the prognosis of patients with LAGC has been increasingly necessary. The effect of NACT could be assessed through histopathological examination of the resected specimen by applying pathological tumor regression grading (TRG) systems [6]. There are several commonly adopted TRG systems with different cutoff values and different principles for LAGC, including the College of American Pathologists (CAP) system, which has superior inter-rater consistency [7].

Although TRG is widely adopted to evaluate the pathological response to NACT, its prognostic value is still controversial [8–11]. In some cases, TRG showed good pathological response to NACT, but patients still relapsed subsequently and had an unsatisfactory outcome [12, 13]. Despite one of the goals of NACT is eliminating the micrometastases which may have spread to the lymph nodes, TRG systems were mainly used to assess the primary tumor, it has not been elucidated whether the assessment of the status of lymph nodes resected after NACT would contribute to predicting the prognosis of LAGC patients [2, 9, 14]. Lymph node metastases has been reported to be the only independent predictor of survival after chemotherapy and surgery in patients with gastroesophageal cancer [15]. Nevertheless, it has not been well elaborated in gastric cancer after NACT. Also, whether the metastasis of lymph node after NACT might cover up the survival benefit of TRG when analyzed simultaneously is still unclear.

The present study aimed to investigate the predictive value of pathological response to NACT at primary tumor and lymph node status after NACT in the survival of LAGC patients.

Materials and methods

Study subjects

From our prospectively maintained database, we reviewed all the patients who underwent gastrectomy with lymphadenectomy for gastric cancer between March 2016 and December 2019 at the department of general surgery of Peking Union Medical College Hospital. The inclusion criteria of our study were as follows: (1) age ranged from 20 to 80 years old; (2) histopathological evidence of gastric adenocarcinoma examined by endoscopic biopsy; (3) locally advanced gastric cancer (8th AJCC clinical stage: cT2-T4; N1-3; M0); (4) underwent neoadjuvant chemotherapy followed by radical gastrectomy with lymphadenectomy; (5) postoperative pathological evaluation was recorded. The exclusion criteria were as follows: (1) underwent radical gastrectomy directly without neoadjuvant chemotherapy; (2) underwent preoperative radiotherapy; (3) suffering from other malignant tumor or gastric remnant cancer; (4) early gastric cancer or late gastric cancer that lost the opportunity for radical surgery; (5) suboptimal lymphadenectomy (< D2 and/or removal of less than 15 lymph nodes); (6) incomplete information on diagnosis, therapy and evaluation. Finally, a total of 160 patients were eligible for analysis. This retrospective study was reviewed and approved by the Institutional Review Board of Peking Union Medical College Hospital. Written informed consent of each patient was obtained.

Preoperative evaluation

Preoperative staging was evaluated by contrast-enhanced computed tomography (CT) and endoscopic ultrasonography (EUS) completed with biopsy for histopathological diagnosis where appropriate, and expressed as cTNM according to the 8th edition AJCC Staging Manual. Indication for neoadjuvant chemotherapy was evaluated for each patient through a multidisciplinary tumor board, included surgeons, oncologists, radiotherapists, radiologists, pathologists and endoscopists.

Neoadjuvant/preoperative chemotherapy

Based on the guidelines of National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO), patients with cT2 or cT2 + gastric adenocarcinoma are recommended to receive preoperative chemotherapy regardless of the N stages [16, 17]. Several studies have been carried out to investigate the efficacy of preoperative chemotherapy for patients with LAGC. Among them, two large-scale RCT trials RESOLVE and RESONANCE suggested that the preoperative SOX regimen is beneficial in terms of R0 resectability and TRG [18, 19]. At present study, the preoperative S-1 plus oxaliplatin (SOX) regimen consists of 130 mg/m2 oxaliplatin on day 1 with orally 80 mg/m2 once a day on days 1–14. The perioperative treatment was repeated two to four times every three weeks according to the clinical stages. The interval between the last preoperative chemotherapy and surgical operation was around one month.

Pathological evaluation after neoadjuvant chemotherapy

Patients in our study had a final pathological result (ypTNM) after the comprehensive review of a team of upper gastrointestinal pathologists. The recommendations of College of American Pathologists (CAP) were adopted to assess the pathological response of gastrectomy specimens to neoadjuvant chemotherapy [20]. A four-category system was designated for grading tumor regression: CAP 0 represents complete response; CAP 1 represents single cancer cells or rare small groups of cancer cells were residual (near-complete response); CAP 2 represents residual cancer with

evident tumor regression (partial response); CAP 3 represents extensive residual cancer without evident tumor regression (poor or no response) (Fig. 1). At present study, patients were divided into two groups according to the grade of tumor regression. CAP 0, CAP 1 and CAP 2 were defined as pathological response (PR) whereas CAP 3 was defined as no pathological response (nPR). In addition, patients were also divided into nodal status (−) group and nodal status (+) group according to whether tumor cells infiltrate into lymph node after neoadjuvant chemotherapy. The pathological report was preliminarily written by one junior pathologist and then reviewed by another senior pathologist. Both of them were specialized in upper gastrointestinal diseases.

Follow-up

After resection, patients were required to visit the outpatient clinic at 3 weeks interval, then 3 months interval during the first postoperative year, and 6 months interval in the second and third postoperative year, and once a year thereafter. The dates and events of relapse and death were collected from telephone interviews and electrical medical records. The primary end point was overall survival (OS) and disease-free survival (DFS). OS was defined as the intervals from the date of surgery to death from any cause. DFS was determined as the interval from the date of surgery to either the first relapse or death from any cause.

Statistical analysis

Continuous variables were described as mean (standard deviation), categorical variables were described as frequency (percentage). Differences between groups were analyzed by Student's t test and χ^2 test or Fisher's exact test for continuous and categorical variables, respectively. Survival curves for OS and DFS were estimated using the Kaplan–Meier method, and the log-rank test was used to compare survival difference. The Cox regression analysis was adopted to assess the prognostic risk of demographic, clinical and pathological characteristics on OS and DFS, and the statistically significant factors from the univariate analysis (<0.05) were then taken into the final multivariable analysis. Statistical analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA) in conjunction with GraphPad Prism 8 (GraphPad Prism Software, Inc., San Diego, CA, USA), and p value <0.05 was considered statistically significant.

Results

Baseline characteristics

We identified 160 patients with gastric adenocarcinoma that met the inclusion criteria. The mean age was 59.7 years (SD ± 12.6; range, 32–80 years) and 56.2% were male. Among the 160 patients, 27 patients were CAP 0, 32 patients

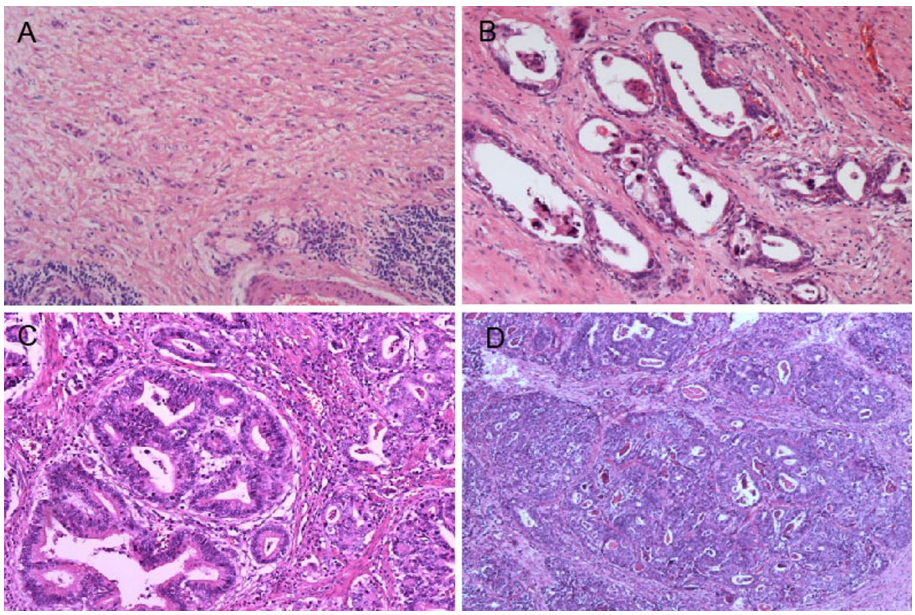

Fig. 1 Histological images of CAP grading. **A** for CAP 0: complete response to tumor treatment, acute and chronic inflammation of the stomach wall with fibrous tissue hyperplasia and no viable cancer cells can be found. **B** for CAP 1, almost complete response to tumor treatment and residual adenocarcinoma in the submucosa of the gastric wall with extensive fibrous tissue hyperplasia. **C** for CAP 2, partial response to tumor treatment and local gastric cancer cells invade the extramuscular fat tissue with fibrous tissue hyperplasia. **D** for CAP 3, no response to tumor treatment and local gastric cancer cells invade the muscle layer with no evident tumor regression

were CAP 1, 31 patients were CAP 2 and 70 patients were CAP 3. Based on the data above, 90 patients (56.2%; CAP 0, 1, 2) had pathological response while 70 patients (43.8%; CAP 3) had no pathological response. The mean number of harvested lymph nodes was 26.6 (SD ± 5.6; range, 17–45). The lymph node status of 96 patients (60.0%) was negative while that of 64 patients (40.0%) was positive.

Pathological analysis at primary site

Demographic, clinical and pathological characteristics stratified according to the grade of pathological response were shown in Table 1. PR group presented smaller tumors (3.7 vs. 5.5, $p = 0.009$) compared to nPR group. In regard to the signet ring cell features, 94.4% of patients in PR group had no signet ring cell features, significantly more than 75.7% in nPR group ($p = 0.001$). Patients with higher clinical T stage tended to have poorer pathological response ($p = 0.198$). There was no significant difference regarding age ($p = 0.587$), gender ($p = 0.904$), BMI ($p = 0.624$), cycle of NACT ($p = 0.517$), type of resection ($p = 0.504$), tumor location ($p = 0.349$), Lauren type ($p = 0.724$), histological grade ($p = 0.295$), the number of lymph nodes resected ($p = 0.469$), lymph node status ($p = 0.515$), lymphatic and venous invasion ($p = 0.747$; $p = 0.874$) between the two groups.

Pathological analysis at lymph nodes

Based on the status of lymph nodes resected after NACT, patients were classified as nodal status (−) and nodal status (+), respectively. The characteristics stratified according to the status of lymph nodes were summarized in Table 2. Patients in nodal status (−) group presented smaller tumors (3.4 vs. 5.7, $p = 0.007$), lower depth of tumor invasion (ypT) ($p = 0.031$), better differentiated degree ($p = 0.04$) and less advanced ypTNM stage ($p < 0.001$), compared to nodal status (+) group. 94.7% of patients in nodal status (−) group had no signet ring cell features, significantly more than 73.4% in nodal status (+) group ($p < 0.001$). In addition, patients with no lymph node metastasis were more likely to have lymphatic and venous invasion ($p < 0.001$; $p = 0.017$). Age ($p = 0.607$), gender ($p = 0.871$), BMI ($p = 0.821$), clinical T stage ($p = 0.352$), cycle of NACT ($p = 0.063$), type of resection ($p = 0.402$), tumor location ($p = 0.560$), Lauren type ($p = 0.370$), the number of lymph nodes resected ($p = 0.667$) showed no significant difference between the two groups.

Survival analysis

The median follow-up for all patients was 39.1 months, no patient was lost during the follow-up. There was no significant difference in OS and DFS between PR and nPR group (OS: HR 0.807, 95% CI 0.423–1.163, $p = 0.154$; DFS: HR 0.686, 95% CI 0.441–1.066, $p = 0.080$) (Fig. 2A and B). Regarding the status of lymph node resected after NACT, patients with no lymph node metastasis had better DFS than that with lymph node metastasis (HR 0.301, 95% CI 0.194–0.468, $p = 0.002$). Whereas OS was not significantly different between the two groups (HR 0.657, 95% CI 0.403–1.071, $p = 0.093$) (Fig. 2C and D). The stratified analysis by the status of lymph node was further performed. For patients with pathological response, OS and DFS were better in patients with no lymph node metastasis than that with lymph node metastasis (OS: HR 0.346, 95% CI 0.173–0.693, $p = 0.004$; DFS: HR 0.312, 95% CI 0.148–0.659, $p = 0.001$). Similarly, for patients with no pathological response, the lymph node status showed remarkable prognostic significance in OS and DFS (OS: HR 0.439, 95% CI 0.192–1.001, $p = 0.019$; DFS: HR 0.320, 95% CI 0.177–0.579, $p < 0.001$) (Fig. 3A and B). However, when stratified analysis was performed by pathological response, whether patients had lymph node metastasis or not, survival curves showed that pathological response was not related to OS and DFS (all $p > 0.05$) (Fig. 3A and B).

Univariable Cox regression analysis of prognostic factors identified several potential predictors of OS and DFS (Table 3). Clinical T stage, pathological lymph node status and ypTNM stage were associated with OS and DFS. Additionally, pathological T stage significantly correlated with OS. Stepwise selection of variables and multivariable Cox regression analysis identified that pathological lymph node status (HR 1.756, 95% CI 1.114–3.278, $p = 0.029$) as being independent prognostic factors associated with OS, similar results were obtained regarding DFS (HR 1.901, 95% CI 1.331–3.093, $p = 0.012$).

Discussion

Although preoperative chemotherapy followed by radical surgery has been recommended to apply in LAGC by various treatment guidelines, the survival benefit is not commonly achieved in LAGC patients [21]. Tumors still grow back subsequently after the treatment, which emphasizes the necessity of identifying independent prognostic factors after NACT to carry out efficient postoperative treatment. The American Joint Committee on Cancer (AJCC) proposed a post-neoadjuvant therapy staging system for LAGC, however, this system is not always associated with the prognosis in multivariable analysis [22–24]. As a supplement, the TRG system, based on the amount of residual tumor, has been getting increasing attention [6, 25]. Actually, there have been more than five widely used TRG systems for LAGC worldwide according to two major principles: evaluating residual

Table 1 Clinical and pathological data of patients with advanced gastric cancer treated with NACT and gastrectomy grouped into pathological response (CAP 0, 1, 2) compared to no pathological response (CAP 3)

Variable	Pathological response (CAP 0, 1, 2) $n=90$	No pathological response (CAP 3) $n=70$	p value[†]
Age (years)			
Mean (SD)	61.1 (12.7)	58.2 (9.2)	0.587[‡]
Gender			
Female	39 (43.3%)	31 (44.3%)	0.904
Male	51 (56.7%)	39 (55.7%)	
BMI			
Mean (SD)	22.8 (4.8)	23.4(5.2)	0.624[‡]
Pre-therapy tumor size (cm)			
Mean (SD)	3.7 (1.4)	5.5 (2.7)	*0.009*[‡]
Clinical T stage by EUS			
cT1/2	26 (28.9%)	14 (20.0%)	0.198
cT3/4	64 (71.1%)	56 (80.0%)	
No. of NACT cycles			
2	9 (10.0%)	7 (10.0%)	0.517
3	13 (14.4%)	6 (8.6%)	
4	68 (75.6%)	57 (81.4%)	
Type of resection			
Subtotal	34 (37.8%)	22 (31.4%)	0.504
Total	56 (62.2%)	48 (68.6%)	
Tumor location			
Upper third	30 (33.3%)	18 (25.7%)	0.349
Middle third	34 (37.8%)	33 (47.1%)	
Lower third	26 (28.9%)	19 (27.1%)	
Lauren type			
Intestinal	24 (26.7%)	21 (30.0%)	0.724
Diffuse/mixed	66 (73.3%)	49 (70.0%)	
Histological grade			
Well/moderately differentiated	29 (32.2%)	17 (24.3%)	0.295
Poorly differentiated	61 (67.8%)	53 (75.7%)	
Signet ring cell			
No	85 (94.4%)	53 (75.7%)	*0.001*
Yes	5 (5.6%)	17 (24.3%)	
No. of lymph nodes			
Mean (SD)	27 (11)	32(14)	0.469[‡]
Pathological N status			
ypN−	52 (57.8%)	44 (62.9%)	0.515
ypN+	38 (42.2%)	26 (37.1%)	
Lymphatic invasion			
No	39 (43.3%)	28 (40.0%)	0.747
Yes	51 (56.7%)	42 (60.0%)	
Venous invasion			
No	42 (46.7%)	34 (48.6%)	0.874
Yes	48 (53.3%)	36 (51.4%)	

[†]χ^2 test, except [‡]Student's t test

NACT neoadjuvant chemotherapy, *CAP* College of American Pathologists, *BMI* body mass index, *EUS* endoscopic ultrasonography, *yp* pathological status after neoadjuvant chemotherapy

p values < 0.05 are in italic

Table 2 Clinical and pathological data of patients with advanced gastric cancer treated with NACT and gastrectomy according to the nodal status after NACT

Variable	Nodal status (−) $n=96$	Nodal status (+) $n=64$	p value[†]
Age (years)			
Mean (SD)	60.3 (11.7)	58.9 (10.8)	0.607[‡]
Gender			
Female	43 (44.8%)	27 (42.2%)	0.871
Male	53 (55.2%)	37 (57.8%)	
BMI			0.821[‡]
Mean (SD)	23.3 (7.8)	23.1 (6.6)	
Pre-therapy tumor size (cm)			
Mean (SD)	3.4 (1.5)	5.7 (2.1)	*0.007*[‡]
Clinical T stage by EUS			
cT1/2	21 (21.9%)	19 (29.7%)	0.352
cT3/4	75 (78.1%)	45 (70.3%)	
No. of NACT cycles			
2	10 (10.4%)	6 (9.4%)	0.063[ψ]
3	16 (16.7%)	3 (4.7%)	
4	70 (72.9%)	55 (85.9%)	
Type of resection			
Subtotal	31 (32.3%)	25 (39.1%)	0.402
Total	65 (67.7%)	39 (60.9%)	
Tumor location			
Upper third	30 (31.3%)	18 (28.1%)	0.560
Middle third	42 (43.7%)	25 (39.1%)	
Lower third	24 (25.0%)	21 (32.8%)	
Lauren type			
Intestinal	30 (31.3%)	15 (23.4%)	0.370
Diffuse/mixed	66 (68.7%)	49 (76.6%)	
Histological grade			
Well/moderately differentiated	36 (37.5%)	10 (15.6%)	*0.04*
Poorly differentiated	60 (62.5%)	54 (84.4%)	
Signet ring cell			
No	91 (94.7%)	47 (73.4%)	*<0.001*
Yes	5 (5.2%)	17 (26.6%)	
Pathological T stage			
ypT0/1/2	27 (28.1%)	8 (12.5%)	*0.031*
ypT3/4	69 (71.9%)	56 (87.5%)	
No. of lymph nodes			
Mean (SD)	29 (14)	30 (11)	0.667[‡]
Lymphatic invasion			
No	54 (56.3%)	13 (20.3%)	*<0.001*
Yes	42 (43.7%)	51 (79.7%)	
Venous invasion			
No	53 (55.2%)	23 (35.9%)	*0.017*
Yes	43 (44.8%)	41 (64.1%)	
ypTNM			
0/I/II	60 (62.5%)	15 (23.4%)	*<0.001*
III/IV	36 (37.5%)	49 (76.6%)	

[†]χ^2 test, except [‡]Student's t test and ψ Fisher's exact test

NACT neoadjuvant chemotherapy, *BMI* body mass index, *EUS* endoscopic ultrasonography, *yp* pathological status after neoadjuvant chemotherapy

p values < 0.05 are in italic

tumor in relation to fibrotic changes and estimating residual tumor in relation the previous tumors site [7]. As TRG systems only assess the primary lesion, the prognostic value of pathological response in LAGC is still controversial. Becker et al. found that TRG was an independent prognostic factor in 480 patients with LAGC undergoing NACT combined with gastrectomy, while Ikoma et al. investigated 356 LAGC patients receiving radical surgery following preoperative therapy, and found that pathological response correlated with OS but not as an independent prognostic factor [25, 26].

Since the difference of TRG systems, to allow better consistency and reproducibility, we assessed the pathological response based on the recommendations of College of American Pathologists and defined group of pathological response and no pathological response. We found that PR group presented smaller tumor, lower depth of tumor invasion, less advanced ypTNM stage and lower level of signet ring cell features, which were consistent with previous studies [9, 27, 28]. Nevertheless, no difference was seen regarding lymph node status. Although the elimination of micrometastases which might spread to the perigastric lymph nodes is one of the main goals of NACT and the effect of NACT on lymph nodal status in LAGC patients has been verified to reduce the total lymph node count and metastasis, the evaluation of pathological response used for prognostic estimation centered on the primary tumor [29, 30].

In clinical practice, we found that even some patients had good pathological response in primary tumor after NACT, they still had a unsatisfactory prognosis if the lymph node status metastases exists. Whereas for some patients who had poor pathological response in primary tumor but negative lymph node status after NACT, the prognosis was good. It inspired us to think whether the lymph node status is more efficient than pathological response in primary tumor after NACT for predicting the outcomes of patients, and whether positive lymph node metastases covered up the efficacy of pathological response in primary tumor after NACT to some extent. At present study, we also classified the patients as nodal status (−) and nodal status (+) based on the status of lymph nodes. As expect, nodal status (−) group showed smaller tumor size, lower depth of tumor invasion and signet ring cell features, better differentiated degree, lower rate of lymphatic and venous invasion and less advanced ypTNM stage. It was worth noting that the grade of pathological response at the tumor site was not significantly associated with lymph node status, 42.2% of patients with pathological response still had lymph node metastasis. A cohort study found that 62.8% of LAGC patients with good pathological response to preoperative chemotherapy had lymph node metastasis [31]. Zhu et al. reported that lymph node status correlated with the grade of pathological response in primary tumor, but only 1 of 3 had good tumor regression in primary tumor among these patients who had no lymph node

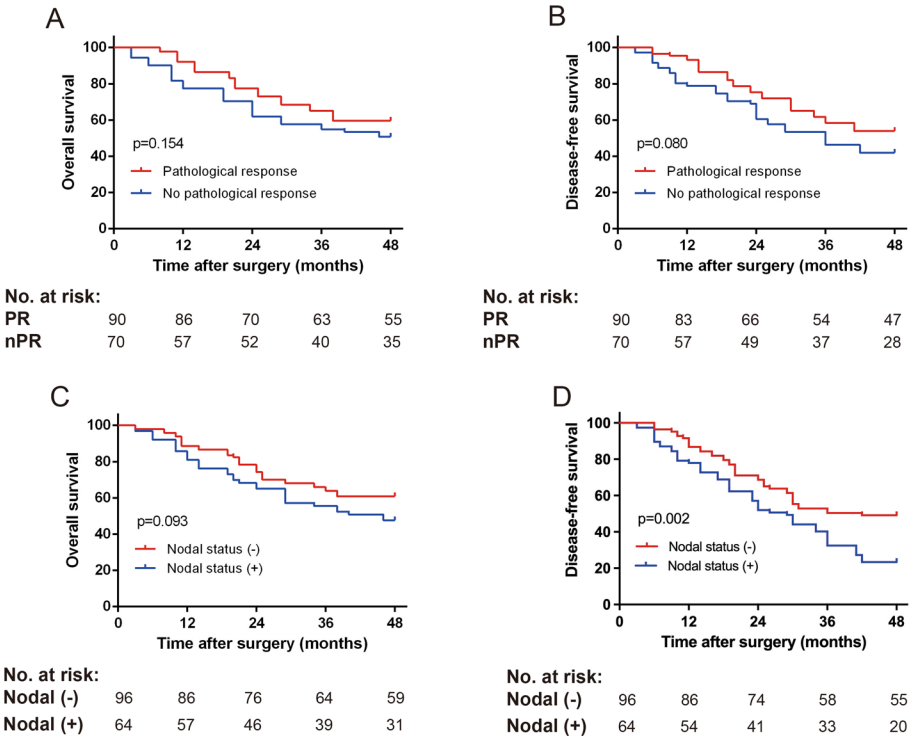

Fig. 2 Overall survival and disease-free survival of gastric cancer patients according to the pathological response and nodal status. **A** and **B** Survival analysis for patients between PR group and nPR group. **C** and **D** Survival analysis for patients between nodal status (−) group and nodal status (+) group

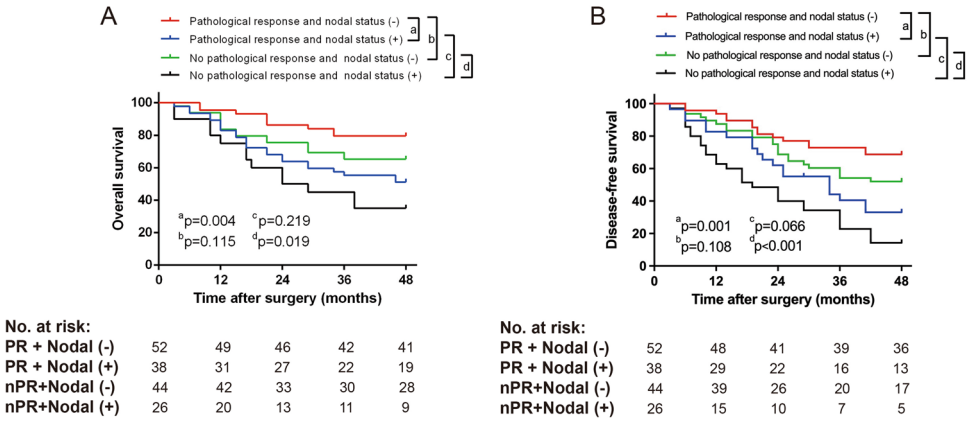

Fig. 3 Overall survival and disease-free survival of gastric cancer patients based on the combination of nodal status and grade of pathological response. **A** for OS. **B** for DFS

metastasis [32]. The correlation between primary tumor response and lymph node status needs further investigation.

One of the main goals focused on preoperative chemotherapy still refers to elucidate the correlation between the improvement in prognosis and the response to treatment. However, we found that survival was equivalent between PR and nPR group. The lymph node metastasis and tumor recurrence remain common even in patients with good pathological response highlighted this. In contrast, although the OS was not significantly different, a better DFS was presented in patients of nodal status (−) group compared to nodal status (+) group. Furthermore, the stratified analysis by the status of lymph node showed that among patients with pathological response, OS and DFS were better in patients with no lymph node metastasis than that with lymph node metastasis. And it was the same among patients with no pathological response. Surprisingly, pathological response at primary tumor did not improve the prognosis of patients even adjusted for the nodal status. As the univariable and multivariable analysis demonstrated, pathological nodal status was an independent prognostic factor related to survival. This was consistent with several previous studies, where nodal status has been established as an independent predictor of survival [9]. Therefore, nodal status after preoperative treatment might serve as a reliable surrogate predictor for survival in the course of evaluating the therapy's impact and exploring the most promising regimen for NACT. Maybe it could even combine with TRG systems to enhance the prognostic value.

Our present analysis contains certain limitations. Due to its retrospective nature and relatively limited number of

Table 3 Result of univariable and multivariable Cox regression analysis of factors associated with survival

Variable	OS	*p* value	DFS	*p* value
Univariable analysis	HR (95% CI)		HR (95% CI)	
Age (years)	1.016 (0.998–1.035)	0.082	0.995 (0.978–1.013)	0.593
Gender				
Female vs. male	1.011 (0.632–1.616)	0.965	0.974 (0.633–1.498)	0.905
BMI	1.029 (0.955–1.110)	0.450	0.966 (0.903–1.033)	0.309
Pre-therapy tumor size (cm)	1.389 (1.167–1.846)	0.302	1.173 (0.905–1.467)	0.278
Clinical T stage by EUS				
cT3/4 vs. cT2	1.717 (1.015–2.905)	*0.044*	1.629 (1.349–2.683)	*0.051*
No. of NACT cycles		0.129		0.276
2	ref		ref	
3	0.610 (0.306–1.216)	0.160	0.615 (0.336–1.128)	0.116
4	1.064 (0.576–1.963)	0.843	0.810 (0.466–1.407)	0.455
Type of resection				
Subtotal vs. total	1.331 (0.787–2.251)	0.286	0.725 (0.468–1.125)	0.152
Lauren type				
Intestinal vs. diffuse/mixed	1.248 (0.750–2.079)	0.394	0.662 (0.428–1.025)	0.064
Histological grade				
Poorly vs				
Well/moderately differentiated	1.173 (0.717–1.918)	0.526	0.719 (0.467–1.106)	0.133
Signet ring cell				
Yes vs. no	1.561 (0.923–2.641)	0.097	1.354 (0.820–2.235)	0.237
Pathological T stage				
ypT3/4 vs. ypT0/1/2	1.783 (1.147–4.153)	*0.036*	1.295 (0.983–2.922)	0.097
No. of lymph nodes	0.993 (0.951–1.037)	0.757	1.028 (0.990–1.068)	0.149
Pathological N status				
ypN + vs. ypN−	1.967 (1.230–3.146)	*0.005*	1.647 (1.076–2.522)	*0.022*
Lymphatic invasion				
Yes vs. no	1.338 (0.818–2.189)	0.245	1.104 (0.712–1.712)	0.659
Venous invasion				
Yes vs. no	1.137 (0.708–1.826)	0.594	1.176 (0.758–1.823)	0.470
ypTNM				
III/IV vs. 0/I/II	2.178 (1.315–3.606)	*0.012*	1.641 (1.051–2.562)	*0.029*
Multivariable analysis	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Clinical T statge by EUS				
cT3/4 vs. cT1/2	2.124 (0.823–6.736)	0.124	1.142 (0.633–1.904)	0.763
Pathological T stage				
ypT3/4 vs. ypT0/1/2	1.171 (0.506–2.331)	0.882	1.305 (0.712–2.351)	0.309
Pathological N status				
ypN + vs. ypN−	1.756 (1.114–3.278)	*0.029*	1.901 (1.331–3.093)	*0.012*

OS overall survival, *DFS* disease-free survival, *HR* hazard ratio, *CI* confidence interval, *BMI* body mass index, *EUS* endoscopic ultrasonography, *yp* pathological status after neoadjuvant chemotherapy

p values < 0.05 are in italic

patients at a single institution, potential selection bias and excessive hazard ratios in the stratified analysis might exist. We did not assess the effect of NACT schemes in survival and only SOX regimen was involved in our study, adopting other schemes might have different effect on the results. In addition, the follow-up period is not long enough, which might hide the significance of pathological response in survival to a certain extent. Furthermore, several different TRG systems divide the grades of pathological response in three up to five groups, we separated our cohort into only two groups based on the pathological analysis at primary site and nodal status, future investigation identifying multiple

survival comparison based on the grades of pathological assessment using a larger sample is needed.

In conclusion, Lymph node status after NACT can serve as a potential independent prognostic factor for LAGC patients treated with NACT followed by surgery, and may be more efficient than pathological response in primary tumor to some extent. The combined application of nodal status and grade of pathological response could contribute to the clinical evaluation of NACT, as well as the prognosis of LAGC patients.

Authors contribution Su PF, Jiang L, Yu JC conceived and designed the analysis; Su PF, Jiang L, Zhang YJ, Yu T collected the data; Su PF, Kang WM, Liu YQ, Yu JC performed the analysis; Su PF wrote the paper: all authors reviewed and revised the manuscript.

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Data availability The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest Conflict of interest relevant to this article was not reported.

Ethical approval Clinical samples were gathered with written informed consent of patients according to a protocol reviewed and approved by the Institutional Review Board of Peking Union Medical College Hospital (IRB number: JS-2587).

Informed consent Informed consent was obtained from all individual participants included in the study.

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