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ABOUT COVER

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ORIGINAL ARTICLE

Retrospective Study

Timing of surgery after neoadjuvant chemotherapy for gastric cancer: Impact on outcomes

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Author contributions: Liu Y and Zhang KC designed the study and wrote the manuscript; Xi HQ and Huang XH contributed to the patient material; Liu Y collected the clinical data; Gao YH and Liang WQ contributed to data analysis and validation; all authors have reviewed and approved the final manuscript.

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Abstract

AIM

To evaluate whether the neoadjuvant chemotherapy (NACT)-surgery interval time significantly impacts the pathological complete response (pCR) rate and long-term survival.

METHODS

One hundred and seventy-six patients with gastric cancer undergoing NACT and a planned gastrectomy at the Chinese PLA General Hospital were selected from January 2011 to January 2017. Univariate and multivariable analyses were used to investigate the impact of NACT-surgery interval time (< 4 wk, 4-6 wk, and > 6 wk) on pCR rate and overall survival (OS).

RESULTS

The NACT-surgery interval time and clinician T stage were independent predictors of pCR. The interval time > 6 wk was associated with a 74% higher odds of pCR as compared with an interval time of 4-6 wk (P = 0.044), while the odds ratio (OR) of clinical T_3 *vs* clinical T_4 stage for pCR was 2.90 (95%CI: 1.04-8.01, P = 0.041). In Cox regression analysis of long-term survival, post-neoadjuvant therapy pathological N (ypN) stage significantly impacted OS (N_0 *vs* N_3: HR = 0.16, 95%CI: 0.37-0.70, P = 0.015; N_1 *vs* N_3: HR = 0.14, 95%CI: 0.02-0.81, P = 0.029) and disease-free survival (DFS) (N_0 *vs* N_3: HR = 0.11, 95%CI: 0.24-0.52, P = 0.005; N_1 *vs* N_3: HR = 0.17, 95%CI: 0.02-0.71, P = 0.020). The surgical procedure also had a positive impact on OS and DFS. The hazard ratio of distal gastrectomy *vs* total gastrectomy was 0.12 (95%CI: 0.33-0.42, P = 0.001) for OS, and 0.13 (95%CI: 0.36-0.44, P = 0.001) for DFS.

CONCLUSION

The NACT-surgery interval time is associated with pCR but has no impact on survival, and an interval time > 6 wk has a relatively high odds of pCR.

Key words: Gastric cancer; Timing of surgery; Neo-adjuvant chemotherapy

Core tip: The impact of interval time between completion of neoadjuvant chemotherapy and surgery on pathological complete response (pCR) had been proved in colorectal cancer and esophageal cancer. However, no such research was found in gastric cancer. To evaluate whether the interval time impacts efficiency of neoadjuvant chemotherapy, 176 patients with gastric cancer were recruited. The interval time and clinical T stage were proved predictors of pCR. Post-neoadjuvant therapy pathological N stage and surgical procedure have a significant impact on the long-term survival. An interval time > 6 wk was associated with a higher odds of pCR.

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INTRODUCTION

Surgery is the only curative treatment for gastric cancer (GC). Although standard surgery has been performed in recent years, overall survival (OS) at 5 years for GC patients remains at 20%-30%[1]. Since more and more clinical trials have validated the survival benefit of preoperative chemotherapy[2-4], neoadjuvant chemotherapy (NACT) has been gradually accepted by clinicians.

Making patients experience significant tumor downstaging and even a pathologic complete response (pCR) is the most important goal of NACT. It has been proven that patients who have a pCR may achieve superior OS and fewer local or systemic recurrence than those with a partial or no response[5,6]. Therefore, every potential way has been explored to maximize the possibility of attaining a pCR. Since the Lyon R90-01 trial found that patients undergoing surgery at an interval of 6-8 wk after NACT showed improvement in clinical tumor response and pathologic downstaging compared with a 2-3-wk interval[7], a growing number of studies have proven that a longer interval is significantly related to increased pCR rates, increased tumor downstaging, and potential superior OS in rectal cancer[8-11]. However, in esophageal cancer, results are conflicting. Some studies found that a longer interval was associated with higher pCR rates that might improve the prognosis[12,13]; even intervals beyond 12 wk have been thought to be safe[14]. Yet, other studies failed to validate the connection between longer intervals and pCR rates, and found that longer intervals were disadvantageous to long-term OS[15,16]. To our knowledge, the optimal timing of performing surgery after NACT has never been studied in GC. An interval time of 4-6 wk was first practiced in some NACT clinical trials[17,18]. However, an interval of 4-6 wk has never been validated as being optimal. Thus, the aim of this study was to assess the link between NACT-surgery interval time and pCR rates and/or OS.

MATERIALS AND METHODS

Study patients

This was a retrospective study for which we recruited 216 patients with GC who underwent NACT at the Chinese PLA General Hospital from January 2011 to January 2017. The criteria for inclusion were: (1) GC was diagnosed using endoscopy and a biopsy; (2) Patients who underwent NACT and a planned gastrectomy; and (3) All clinical pathological information was available, including NACT relevant information, surgical parameters, imaging information, pathological diagnosis, perioperative therapy, and follow-up data. The exclusion criteria were: (1) Patients older than 75 years; and (2) Patients who ever received chemoradiotherapy. Finally, only 176 patients were included (Figure 1). Before NACT, endoscopic ultrasound (EUS) and contrast-enhanced computed tomography (CE-CT) had been performed to assess clinical stage and confirm that patients had $T_{2-4}N_{0-3}M_0$ GC, according to the Japanese classification of gastric carcinoma[19].

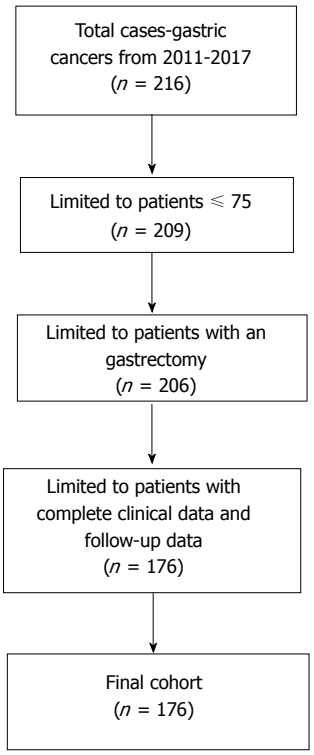

Figure 1 Flow diagram of patient inclusion.

NACT and surgery

Most patients (*n* = 167) received 2-4 cycles of a SOX regimen (S-1 80 mg/m^2 per day, PO, days 1-14, and oxaliplatin 130 mg/m^2 per day, Ⅳ, infusion on day 1), which is widely used in Asia[20]; the remaining patients (*n* = 9) received a XELOX regimen (capecitabine 1000 mg/m^2 per day, PO, days 1-14, and oxaliplatin 130 mg/m^2 per day, IV, infusion on day 1). After two cycles of chemotherapy, the curative effect was evaluated using EUS and CT according to RECIST1.1[21]. A gastrectomy was carried out immediately when imaging showed an observable increase in tumor size or tumor disappearance. If imaging indicated a decrease in tumor size, another one or two cycles of chemotherapy could be performed. The planned operations after NACT were conducted by experienced surgeons. Patients without evidence of metastasis underwent a gastrectomy with a D2 lymphadenectomy. For other patients, the type of operation was decided by a multidisciplinary team. The location of the primary tumor determined whether a proximal, distal, or total gastrectomy was selected.

Histopathology analysis and follow-up

The same pathologist microscopically analyzed all resected specimens. Patients with post-neoadjuvant therapy pathological (yp)T0N0M0 GC were defined as having a pCR and all others were defined as not having a pCR[11]. Clinical examinations and abdominal CT were performed every 6 mo for 3 years. Digestive endoscopy was performed at least once a year. In March 2017, we confirmed the survival status of patients and the median follow-up time was 42 mo (range, 2-74 mo). Follow-up data were completed for all recruited patients.

Primary and secondary objectives

The primary objective was to evaluate the impact of NACT-surgery interval time on pCR rate and the optimal timing of operation. The secondary objective was to determine the association between NACT-surgery interval time and 3-year OS or disease-free survival (DFS). For that purpose, of the 171 patients who were admitted from January 2011 to March 2014, 121 were selected.

Statistical analysis

We used the Chi-squared test or Fisher's exact test for binary and categorical variables, and ANOVA or *t*-tests for continuous variables, as appropriate. Patient and tumor characteristics were compared between the three groups at baseline and postsurgery. A bivariate analysis of patients, tumors and surgical characteristics, and pCR status was conducted. Tumor or treatment characteristics that achieved a *P*-value < 0.2 in univariate analysis were included in the multivariable analysis. Logistic regression was used to model the effects of optimal interval time on the odds of having a pCR, and factors independently associated with pCR were determined using a stepwise procedure. The Kaplan-Meier method was used to estimate survivor functions and the log-rank test was used for the comparison of survival curves. Multivariate analysis using Cox proportional hazards regression analysis with a stepwise procedure was performed to investigate independent factors of survival.

All the statistical analyses were performed using IBM SPSS Statistics version 22.0 software. The hazard ratio (HR) and 95% confidence interval (95%CI) were reported and used to assess the relationship between pCR rate and survival for each independent factor.

RESULTS

Among the 176 patients, 111 (63%) had an NACT-surgery interval time < 4 wk, 48 (27%) had an interval time of 4-6 wk, and 17 (9.7%) had an interval time > 6 wk. The median age was 57 years (range, 21-75 years) and the male to female ratio was 3.5/1. Characteristics of the study cohort are summarized in Table 1. Patient characteristics, tumor characteristics, and surgical procedure were compared among the three groups (< 4 wk, 4-6 wk, and > 6 wk). Age (*P* = 0.014), tumor differentiation (before NACT) (*P* = 0.000), clinical T stage (*P* = 0.006), and ypT stage (*P* = 0.045) were significantly different among the three groups. Forty (22.7%) patients had achieved a pCR; the pCR rate was 67.5% for those with a NACT-surgery interval time < 4 wk, 15% for those with a

Table 1 Demographic and tumor characteristics according to the neoadjuvant chemotherapy-surgery interval time and pathological complete response status *n* (%)

	< 4 wk (*n* = 111)	4-6 wk (*n* = 48)	> 6 wk (*n* = 17)	*P* value	pCR (*n* = 40)	No pCR (*n* = 136)	*P* value
Age, yr, mean ± SD	55.5585 ± 10.8079	59.7916 ± 9.7891	61.5882 ± 9.5985	0.014	57.375 ± 9.862354	57.27206 ± 10.88013	0.908
Sex				0.974			0.174
Male	87 (78.38)	37 (77.08)	13 (76.47)		28 (70.00)	109 (80.15)	
Female	24 (21.62)	11 (22.92)	4 (23.53)		12 (3.00)	27 (19.85)	
Chemotherapy cycles				0.692			1.000
< 4	39 (35.14)	17 (35.42)	4 (23.53)		14 (35.00)	46 (33.82)	
⩾ 4	72 (64.86)	31 (64.58)	13 (76.47)		26 (65.00)	90 (66.18)	
ASA, yr, mean ± SD				0.083			0.467
1	8 (7.21)	1 (2.8)	2 (11.76)		4 (10.00)	7 (5.15)	
2	97 (87.39)	39 (81.25)	15 (88.24)		32 (80.00)	119 (87.50)	
3	6 (5.40)	8 (16.67)	0		4 (10.00)	10 (7.35)	
Histology (before NACT)				0.398			0.658
Tubular adenocarcinoma	90 (81.08)	40 (83.33)	15 (88.24)		34 (85.00)	111 (81.62)	
Mucinous	10 (9.01)	1 (2.08)	0 (0.00)		1 (2.50)	10 (7.35)	
Signet ring cell	9 (9.11)	4 (8.33)	1 (5.88)		3 (7.50)	11 (8.09)	
mixed type[1]	2 (1.80)	3 (6.25)	1 (5.88)		2 (5.00)	4 (2.94)	
Differentiation (before NACT)				0.000			0.032
Well	2 (1.80)	0 (0.00)	15 (88.24)		2 (5.00)	0 (0.00)	
Moderate	28 (25.23)	10 (20.83)	1 (5.88)		10 (25.00)	35 (25.74)	
Poor	81 (72.97)	38 (79.17)	1 (5.88)		28 (79.00)	101 (74.26)	
Clinical T stage				0.006			0.027
2	31 (27.93)	17 (35.42)	6 (35.29)		15 (37.50)	39 (28.68)	
3	24 (21.62)	19 (39.58)	8 (47.06)		16 (40.00)	35 (19.85)	
4	56 (50.45)	12 (25.00)	3 (17.65)		9 (22.50)	62 (51.47)	
Clinical N stage				0.170			0.012
Positive	89 (80.18)	33 (68.75)	11 (64.71)		24 (60.00)	109 (88.97)	
Negative	22 (19.82)	15 (31.25)	6 (35.29)		16 (40.00)	27 (11.03)	
Tumor location				0.650			0.044
Upper	45 (40.54)	23 (47.92)	6 (35.29)		10 (25.00)	64 (47.06)	
Middle	16 (14.41)	7 (14.58)	2 (11.76)		6 (15.00)	19 (13.97)	
Lower	45 (40.54)	14 (29.17)	7 (41.18)		22 (55.00)	44 (32.35)	
Diffuse type[2]	5 (4.51)	4 (8.33)	2 (11.76)		2 (5.00)	9 (6.62)	
Tumor diameter (before NACT)				0.134			0.069
⩽ 2 cm	15 (13.51)	8 (16.67)	2 (11.76)		7 (17.50)	18 (2.21)	
2-5 cm	50 (45.05)	21 (43.75)	13 (76.47)		24 (60.00)	60 (69.85)	
⩾ 5 cm	46 (41.44)	19 (39.58)	2 (11.76)		9 (12.50)	58 (27.94)	
Surgical procedure				0.363			0.002
Proximal gastrectomy	21 (18.92)	10 (20.83)	2 (11.76)		9 (22.50)	24 (17.65)	
Distal gastrectomy	32 (28.83)	10 (20.83)	8 (47.06)		19 (47.50)	31 (22.79)	
Total gastrectomy	58 (52.25)	28 (58.33)	7 (41.18)		12 (30.00)	81 (59.56)	
NACT-surgery interval time							0.043
< 4 wk					27 (67.50)	84 (61.76)	
4-6 wk					6 (15.00)	42 (30.88)	
> 6 wk					7 (17.50)	10 (7.35)	
ypT stage				0.045			
0	27 (24.32)	6 (12.50)	7 (41.18)				
1	7 (6.31)	9 (18.75)	3 (17.65)				
2	25 (22.52)	6 (12.50)	2 (11.76)				
3	38 (34.23)	15 (31.25)	4 (23.53)				
4	14 (12.61)	12 (25.00)	1 (5.88)				
ypN stage				0.187			
0	67 (60.30)	23 (47.92)	14 (82.35)				
1	7 (6.31)	7 (14.58)	2 (11.76)				
2	16 (14.41)	5 (10.42)	1 (5.88)				
3a	14 (12.61)	8 (16.67)	0				
3b	7 (6.31)	5 (10.42)	0				

[1]Mixed type: the tumor contains at least two kinds of cancer cell with different pathological classification, and the proportion of cancer cells in each type is similar; [2]Diffuse type: the region of tumor is beyond one part of the stomach (three parts of the stomach: cardiac and gastric fundus, gastric body, and pylorus and gastric antrum). pCR: Pathological complete response; NACT: Neoadjuvant chemotherapy.

NACT-surgery interval time of 4-6 wk, and 17.5% for those with a NACT-surgery interval time > 6 wk.

Impact of NACT-surgery interval time on pCR

Table 1 also shows the bivariate association between

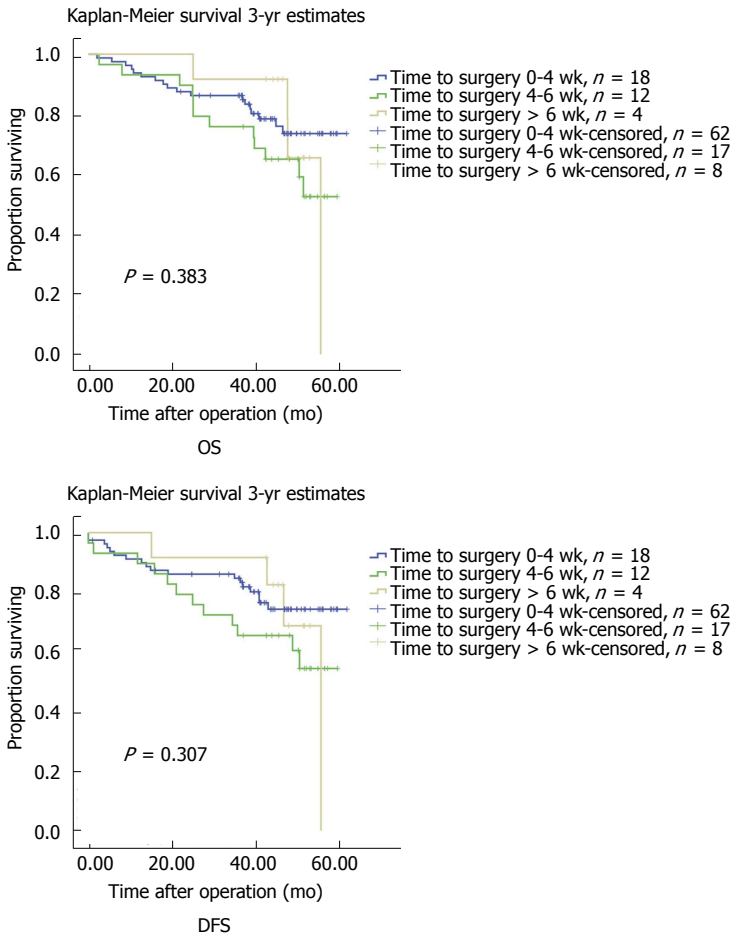

Figure 2 Overall survival and disease-free survival curves of the three groups. OS: Overall survival; DFS: Disease-free survival.

Table 2 Multivariate logistic analysis identifying independent predictors of pathological complete response

Factor	OR	95%CI	*P* value
Sex			
Male vs female	1.76	0.74-4.18	0.201
NACT-Surgery interval time			
< 4 wk *vs* > 6 wk	0.69	0.22-2.13	0.521
4-6 wk *vs* > 6 wk	0.26	0.07-0.96	0.044
Clinical T stage			
T2 *vs* T4	1.99	0.70-5.68	0.200
T3 *vs* T4	2.90	1.04-8.01	0.041
Clinical N stage			
Positive *vs* negative	2.12	0.90-4.97	0.086
Tumor diameter (before NACT)			
≤ 2 cm *vs* ≥ 5 cm	1.60	0.44-5.80	0.472
2-5 cm *vs* ≥ 5 cm	1.58	0.60-4.14	0.354

NACT: Neoadjuvant chemotherapy.

pCR and patient characteristics, tumor characteristics, and surgical procedure. NACT-surgery interval time (P = 0.043), tumor differentiation (before NACT) (P = 0.032), clinical T stage (P = 0.027), clinical N stage (P = 0.012), tumor location (P = 0.044), and surgical procedure (P = 0.002) were significantly different between patients with and without pCR.

Factors that have achieved a P-value < 0.2 in univariate analysis were selected for multivariate analysis, including gender, NACT-surgery and interval time, clinical T stage, clinical N stage, tumor diameter. The multivariate analysis (Table 2) showed that a NACT-surgery interval time of 4-6 wk was associated with a 74% lower change of having a pCR as compared with an NACT-surgery interval time > 6 wk (P = 0.044), while the OR of clinical T_3 *vs* clinical T_4 stage for pCR was 2.90 (95%CI: 1.04-8.01, P = 0.041).

Impact of NACT-surgery interval time on OS and DFS

Kaplan-Meier analyses for 3-year OS and DFS are presented in Figure 2. There was no significant difference among the three survival curves for both OS and DFS according to the log-rank test. The median OS was 41.5 mo (range, 20.0-61.8 mo) and median DFS was 39.5 mo (range, 0-61.8 mo).

Recurrence was experienced by 29.5% of patients. As shown in Table 3, NACT-surgery interval time was not found to be independently associated with OS or DFS. Independent factors associated with OS were ypN stage (N_0 *vs* N_3: HR = 0.16, 95%CI: 0.37-0.70, P

Table 3 Multivariable analysis identifying independent predictors of overall survival and disease-free survival

Independent predictor	3-yr estimate (overall survival)			3-yr estimate (disease-free survival)		
	HR	95%CI	*P* value	HR	95%CI	*P* value
NACT-Surgery interval time						
< 4 wk *vs* > 6 wk	0.49	0.11-2.129	0.340	0.43	0.10-1.85	0.258
4-6 wk *vs* > 6 wk	0.99	0.24-4.06	0.985	0.93	0.23-3.80	0.922
Age						
⩽ 60 *vs* > 60	0.90	0.34-2.37	0.833	0.84	0.32-2.19	0.720
Sex						
Female *vs* male	1.27	0.40-4.04	0.688	1.24	0.39-3.99	0.716
Histology (before NACT)						
Tubular adenocarcinoma *vs* mixed type	2.56	0.24-26.94	0.433	2.25	0.22-22.56	0.491
Mucinous *vs* mixed type	3.79	0.21-70.55	0.372	3.12	0.18-53.99	0.435
Signet ring cell *vs* mixed type	5.71	0.40-81.22	0.199	4.99	0.37-66.54	0.224
Differentiation (before NACT)						
Well and moderate *vs* poor	2.49	0.99-6.24	0.052	2.45	0.98-6.11	0.054
Clinical T stage						
T2 *vs* T4	1.51	0.42-5.39	0.524	1.67	0.48-5.84	0.422
T3 *vs* T4	0.99	0.31-3.16	0.980	0.98	0.31-3.11	0.968
Clinical N stage						
Positive *vs* negative	0.45	0.13-1.62	0.221	0.49	0.14-1.74	0.270
Tumor diameter (before NACT)						
⩽ 2 cm *vs* ⩾ 5 cm	3.16	0.61-16.45	0.171	2.88	0.57-14.65	0.202
2-5 cm *vs* ⩾ 5 cm	1.91	0.72-5.10	0.196	1.74	0.65-4.65	0.267
Tumor location						
Upper *vs* diffuse type	1.04	0.15-7.33	0.973	0.99	0.14-6.98	0.989
Middle *vs* diffuse type	1.11	0.16-7.78	0.915	1.16	0.17-8.05	0.879
Lower *vs* diffuse type	4.41	0.78-25.18	0.095	3.94	0.69-22.50	0.123
Surgical procedure						
Proximal gastrectomy *vs* total gastrectomy	0.69	0.17-2.73	0.593	0.79	0.20-3.07	0.729
Distal gastrectomy *vs* total gastrectomy	0.12	0.33-0.42	0.001	0.13	0.36-0.44	0.001
ypT stage						
T0 *vs* T4	1.04	0.15-7.20	0.968	1.27	0.18-9.08	0.811
T1 *vs* T4	0.57	0.09-4.14	0.601	0.588	0.86-4.04	0.589
T2 *vs* T4	1.15	0.24-5.53	0.858	1.29	0.26-6.46	0.756
T3 *vs* T4	0.60	0.15-2.09	0.387	0.59	0.16-2.18	0.425
ypN stage						
N0 *vs* N3	0.16	0.37-0.70	0.015	0.11	024-0.52	0.005
N1 *vs* N3	0.14	0.02-0.81	0.029	0.17	0.02-0.71	0.020
N2 *vs* N3	0.47	0.11-1.98	0.302	0.40	0.09-1.67	0.208

NACT: Neoadjuvant chemotherapy.

= 0.015; N_1 *vs* N_3: HR = 0.14, 95%CI: 0.02-0.81, *P* = 0.029) and surgical procedure (distal gastrectomy *vs* total gastrectomy: HR = 0.12, 95%CI: 0.33-0.42, *P* = 0.001). For DFS, independent factors were also ypN stage and surgical procedure.

DISCUSSION

The impact of the NACT-surgery interval on pCR and survival has been proven in rectal cancer and esophageal cancer[8,14]. However, the optimal NACT-surgery interval time and its association with survival, to the best of our knowledge, have never been investigated in GC. Similar to what was found in rectal cancer, the results of the present study suggest that a NACT-surgery interval time > 6 wk had a positive impact on pCR compared with either 4-6 wk or < 4 wk. However, the NACT-surgery interval time did not have an impact on either OS or DFS.

To determine the cutoff level, we plotted a curve of cumulative proportion of pCR by interval weeks (Figure 3). The curve shows that the slope is highest when the interval time is < 4 wk, and 4 and 6 wk are points of inflection. Meanwhile, the NACT-surgery interval time is commonly 4-6 wk, which is what clinicians in China have adopted. Thus, to prove whether a NACT-surgery interval time of 4-6 wk is optimal, after taking all factors into consideration, we divided the population into three groups by the cutoff levels of 4 and 6 weeks.

The impact of NACT-surgery interval time on pCR is the primary objective that we wanted to address. We defined pCR as T0N0M0, and partial response (PR) was not included in this study. This is because PR, which is confirmed using imaging according to RECIST[21], is more subjective and hence, more difficult to confirm than CR. In Table 1, age and tumor differentiation (before NACT) were significantly different among the three groups. The average age is highest in the > 6 wk group and lowest in the < 4 wk group. The result suggests that older patients may need a longer recovery

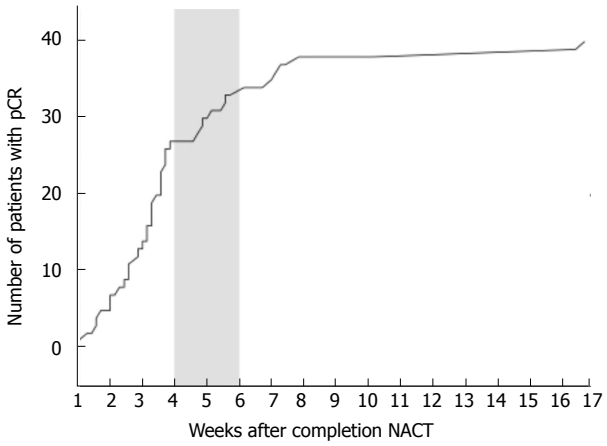

Figure 3 Cumulative frequency of pathological complete remission by neoadjuvant chemotherapy to surgery interval time. NACT: Neoadjuvant chemotherapy.

period from NACT. In the subsequent univariate and multivariable analyses, age was shown to have no impact on pCR and long-term outcomes. With respect to tumor differentiation, previous studies showed that the more differentiated a tumor, the higher the pathology response rate when patients were treated with a XELOX regimen[22,23]. However, results from our univariate analysis contradict these previous findings. The NACT-surgery interval time, tumor differentiation (before NACT), clinical T stage, clinical N stage, tumor location, and surgical procedure were significantly different between the pCR group and the no-pCR group. We had not included surgical procedure into univariate analysis, for the reason that the pCR status had been determined before surgery. The subsequent multivariable analysis proved that NACT-surgery interval time and cT stage was independent factors associated with having a pCR. Compared with clinical T_4 stage, patients with lower clinical T_2 or T_3 stage were more likely to achieve a pCR, although there was no significant difference between clinical T_2 and T_3 stages. This result is consistent with a previous study[24], which showed that lower T and N stages were linked with higher likelihood of pCR. Patients with a NACT-surgery interval time of 4-6 wk had a lower odds of having a pCR than those with an interval time > 6 wk (P = 0.044). Although a NACT-surgery interval time < 4 wk was associated with a 49% lower chance of having a pCR as compared with an interval time > 6 wk, the result was not statistically significant (P = 0.521). From these outcomes and the associations among them, we can conclude that the NACT-surgery interval time > 6 wk was the optimal interval time and had a positive impact on pCR as compared with the other groups.

This result is consistent with those from previous rectal and esophageal cancer studies[25-28], and it may be a common rule in gastrointestinal malignancies. Although many studies have shown that there is a positive impact from delaying the NACT-surgery interval time on pCR rate and short-term outcomes, the underlying mechanism has never been discussed. We speculate that it may be the result of multiple factors, including the ongoing effect of radiochemotherapy, changes in the tumor microenvironment, and recovery of immunity from chemotherapy. Additional basic medical studies may be needed to explain it.

The association between NACT-surgery interval time and long-term outcomes was also investigated. The survival curves of the three groups intersected at certain points and the log-rank test did not find any statistical significance among the curves (Figure 2). For both OS and DFS, Cox regression analysis showed that the NACT-surgery interval time and pCR (reflected by ypT_0 status) had no impact on survival. This result is contrary to our expectation because pCR is deemed to have a positive impact on survival. Meredith *et al*[29] and Abdul-Jalil *et al*[30] both reported that pCR was an independent factor for OS and DFS. We thought that the small sample size may be the limitation. Regarding the NACT-surgery interval time, many previous studies in esophageal cancer proved that the interval time did not have any effect on survival[13,15,31], while some studies in rectal cancer reached an opposite conclusion[26,28]. Our result is consistent with studies in esophageal cancer. Our finding that ypN stage had a significant impact on OS and DFS aligns with those from previous studies[32,33]. The surgical procedure was found to be also an independent factor that can influence OS and DFS. Patients on whom a distal gastrectomy was performed had a significant difference in survival compared with patients on whom a total gastrectomy was performed. The reason for this result may be that patients who undergo a distal gastrectomy have a greater chance of having a pCR, and also, may be the difference of surgical method itself.

There were some limitations to our study. Its retrospective nature may induce some bias. Our relatively short follow-up time for survival (3-year estimates) and the absence of information regarding diseases not treated at the PLA General Hospital after the operation may have impacted our results. Also, our single institute research cannot avoid sampling bias and may not be representative. The small sample size was the biggest limitation, and the number of patients with interval time > 6 wk was not sufficient to explore more timing groups or the maximum interval time (such as 6-8 wk, 8-12 wk, and > 12 wk). A future multi-center randomized control trial with a larger sample size may be needed to validate our results.

To conclude, the NACT-surgery interval time > 6 wk can increase the chance of a pCR, but the NACT-surgery interval time does not have an impact on long-term survival.

ARTICLE HIGHLIGHTS

Research background

The impact of the interval time from the completion of neoadjuvant

chemotherapy (NACT) to surgery on pathological complete response (pCR) and survival has been proved in rectal cancer and esophageal cancer. However, the optimal NACT-surgery interval time and its association with survival, to the best of our knowledge, have never been investigated in gastric cancer. This study can provide evidence for the timing of surgery and patients with neoadjuvant chemotherapy may benefit from it.

Research motivation

To investigate whether the interval time between NACT and surgery have an impact on pCR was our main topic. The investigation lays a foundation for the further RCT research.

Research objectives

There were two objectives in this study. The primary objective was to evaluate the impact of NACT-surgery interval time on pCR rate and the optimal timing of operation. The secondary objective was to determine the association between NACT-surgery interval time and 3-year OS or disease-free survival (DFS). If the impacts are existent, more studies will focus on the investigation of optimal interval time and this evidence will bring a change in treatment plan for GC patients with neoadjuvant chemotherapy.

Research methods

This is a retrospective study, in which we realized our objectives through data analysis using bivariate analysis, logistic regression analysis, and Cox proportion hazards regression. These methods are routinely used in studies and have high stability.

Research results

The impact of the NACT-surgery interval time on pCR has been proved and the interval time > 6 wk can increase the chance of a pCR. Clinical T stage also have an impact on pCR. The independent predictors of long-term survival are ypN stage and surgical procedure. These findings for the first time proved the impact of the NACT-surgery interval time on pCR in gastric cancer and give a reference for the optimal interval time. The further investigations of accurate optimal interval time are needed.

Research conclusions

The authors for the first time investigated and found the impact of the NACT-surgery interval time on pCR, and the optimal interval time may be > 6 wk. This result is consistent with those from previous rectal and esophageal cancer studies, and we speculate that it may be the result of multiple factors, including the ongoing effect of radiochemotherapy, changes in the tumor microenvironment, and recovery of immunity from chemotherapy. Additional basic medical studies may be needed to explain it.

Research perspectives

Further studies, either retrospective or prospective, are needed to investigate more interval time groups with a large sample size. Also, it is meaningful to investigate the mechanism of this finding through basic medical studies.

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