Original Article

Impact of the time from the completion of neoadjuvant chemotherapy to surgery on the outcomes of patients with gastric cancer

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Background: Gastrectomy is usually recommended within 5 to 6 weeks after the completion of neoadjuvant chemotherapy (NCT). However, the optimal timing of surgery is not clearly defined.

Methods: This study retrospectively reviewed the clinical records of 229 patients with locally advanced gastric cancer (GC) who underwent curative gastrectomy after NCT between 2006 and 2016. The effect of the time to surgery (TTS), defined as ≤4, 5–6, and >6 weeks, on patient outcomes was examined. Descriptive statistics and Cox proportional hazards models were used.

Results: Seventy of 229 patients (30.6%) had surgery within 4 weeks after their last dose of NCT, 103 (45.0%) within 5–6 weeks, and 56 (24.5%) after 6 weeks. The median age was 56.0 [interquartile range (IQR), 47.0–63.0] years, and the median TTS was 34.0 (IQR, 26.0–42.0) days. The three groups did not significantly differ regarding most surgical and histopathological characteristics except for the NCT regimen (P=0.010), number of cycles of NCT (P=0.017) and pathological stage (P=0.015). The NCT regimen was the only independent factor associated with TTS >6 weeks (P=0.015). The 3-year progression-free survival (PFS) estimates were 41.9%, 42.8% and 61.7% in patients who underwent surgery in ≤4, 5–6, and >6 weeks after NCT, respectively (P=0.044). The 3-year overall survival (OS) estimates were 57.7%, 58.0% and 68.2% in the three groups, respectively (P=0.202). According to multivariable analysis, compared with the interval of ≤4 weeks, patients who underwent surgery at 5–6 or >6 weeks had equivalent PFS and OS.

Conclusions: The NCT-surgery interval time has no impact on patient outcomes.

Keywords: Gastric cancer (GC); Neoadjuvant chemotherapy (NCT); Time to surgery; Prognosis

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Introduction

Neoadjuvant chemotherapy (NCT) followed by curative resection has been increasingly adopted to prolong the survival of patients with locally advanced gastric cancer (GC) through the ability of NCT to reduce micrometastases, downstage the tumor, and improve tumor resectability (1-4). In the era of multimodal therapy, surgeons are frequently confronted with the challenge of scheduling surgery at an appropriate time after the completion of NCT. Patients with incomplete resolution of chemotherapy-related

toxicity, a worsened nutrition status or serious comorbidities are more likely to fare poorly after premature surgery (5,6). However, concomitant with surgery postponement is potentially impaired prognosis, psychological distress, and a worsened quality of life (7,8). In clinical practice, primary tumor resection is usually scheduled within a few weeks from the last dose of preoperative chemotherapy, but the optimal time interval between the end of NCT and definitive surgery has not yet been defined.

The time interval from the completion of NCT to definitive surgery is arbitrarily decided in most trials that have investigated the survival benefit of NCT (1,9). To the best of our knowledge, only one retrospective study has examined gastrectomy timing after NCT, suggesting that a longer NCT-surgery interval increased the odds of a pathologically complete response (pCR) but had no influence on survival (10).

Whereas preclinical models have confirmed biologically better outcomes with shorter intervals between surgical treatment and the initiation of adjuvant chemotherapy (11-13), no such biological evidence was in favor of a shorter interval between the completion of NCT and surgery. We hypothesized that a longer interval would not impair survival based on the ability of NCT to systemically eliminate micrometastases before surgery.

Methods

Study population

Patients with locally advanced GC (T3/T4, or N+) who underwent NCT followed by gastrectomy between 2006 and 2016 at a high-volume tertiary referral center were retrospectively reviewed. The exclusion criteria were as follows: (I) active synchronous tumors; (II) urgent symptoms; (III) received NCT outside of our institution; (IV) underwent radiotherapy in addition to chemotherapy; and (V) unevaluable TTS. Urgent symptoms referred to symptoms that warranted interventions, including bleeding, ileus, and gastric pyloric obstruction. The Institutional Review Board of the National Cancer Center/Cancer Hospital has reviewed and approved this study and has also agreed that individual patient consent was not required to report clinical outcomes alone. The outcomes of this study did not affect the management of the patients. The patients' personal data have been secured.

Chemotherapy and surgical treatment

Preoperative chemotherapy according to the SOX (S-1 80 mg/m^2 on days 1–14 and oxaliplatin 130 mg/m^2 on day 1) or XELOX regimen (capecitabine 1,000 mg/m^2 on days 1–14 and oxaliplatin 130 mg/m^2 on day 1) was performed with four 3-week cycles. Alternatively, paclitaxel (50 mg/m^2) was added to the SOX or XELOX regimen for patients with a good physical condition. Dosage reduction or withdrawal was applied in the case of severe adverse events during chemotherapy according to the clinician's decision. The antitumor effect was assessed according to Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) every two cycles (14). When tumor reduction was detected, the NCT was continued for another two cycles. Otherwise, gastrectomy or switching to other regimen was considered after obtaining informed consent and approval from patients. Surgery was usually performed within 5–6 weeks after the last dose of preoperative chemotherapy. Subtotal or total gastrectomy plus D2 lymphadenectomy was performed as required by the guidelines of the Japanese Gastric Cancer Association (15). Additional organ resection was indicated in the case of tumor involvement with adjacent organs, including resection of the spleen, colon, pancreas and liver, in addition to gastrectomy. Adjuvant chemotherapy was initiated 4 weeks after surgery using the same protocol as preoperatively. The adjuvant component was cancelled or postponed in the case of severe chemotherapy toxicity, postoperative complication, a worsened nutrition status, or other reasons.

Evaluation of clinicopathological variables

Patients were divided into three groups according to TTS: (I) ≤4 weeks; (II) 5–6 weeks; and (III) >6 weeks. The patient and clinicopathological characteristics, including age, gender, comorbidities, American Society of Anesthesiologists (ASA) risk score, clinical stage, NCT regimen and cycles, severe NCT toxicity, extent of gastrectomy, additional organ resection, operative duration, intraoperative blood loss, postoperative complications, length of postoperative hospital stay, examined lymph nodes, resection margin, differentiation, pT, pN, pStage, Mandard score, adjuvant chemotherapy and cycles were compared between the groups.

Postoperative therapy and follow up

After discharge, the patients were required to visit either the clinics of the medical oncologist at our center or that of a resident oncologist for postoperative therapy and follow up. All the patients were required to visit the clinics every 3 months during the first 2 postoperative years, every 6 months thereafter for 3 years, and yearly after 5 years. Recurrence and death were determined from hospital records or from telephone interviews.

Statistical analysis

To reduce the bias in the pretreatment waiting time, progression-free survival (PFS) and overall survival (OS) were defined as the time interval from the start of preoperative chemotherapy, rather than the date of diagnosis, to the date of the first documented recurrence or death, respectively. Categorical variables were analyzed using chi-squared or Fisher's exact test, and continuous data were analyzed using Student's t test or the Mann-Whitney U test. Survival was assessed by Kaplan-Meier estimates and was compared using the log-rank test. Cox regression models were applied to explore the association between TTS and survival outcomes after adjustment for potential confounders. All statistical tests were conducted using SPSS version 22.0 (SPSS, Inc., Chicago, IL, USA). Statistical significance was set at 2-sided P<0.05.

Results

The patient and clinical characteristics are summarized in *Table 1*. Seventy of two hundred twenty-nine patients (30.6%) had surgery within 4 weeks after their last dose of NCT, 103 (45.0%) within 5–6 weeks, and 56 (24.5%) after 6 weeks. The median age was 56.0 [interquartile range (IQR), 47.0–63.0] years, and the median TTS was 34.0 (IQR 26.0–42.0) days. One hundred twenty-eight patients (55.9%) received SOX/XELOX chemotherapy, and 101 (44.1%) received paclitaxel in addition to SOX/XELOX. One hundred thirty-one (57.2%) patients completed all the intended cycles of preoperative chemotherapy, 165 (72.0%) received adjuvant chemotherapy, and 86 of 165 (52.1%) completed all the intended cycles of postoperative chemotherapy. We analyzed the reasons for surgery delay among patients with TTS >6 weeks (*Table 2*). They were chemotherapy-related toxicity, severe postoperative complication, poor performance status and nutritional support requirement. Other reasons included patients' choice, economic reasons, and logistic reasons.

The three groups did not significantly differ in terms of age, gender, comorbidities, ASA risk score, clinical stage, tumor location, clinical response and treatment-related toxicity except for the NCT regimen (P=0.010) and number of cycles of NCT (P=0.017). Multivariate analysis showed that the NCT regimen was the only independent factor associated with TTS >6 weeks (*Table 3*). The 3 groups did not differ significantly regarding most surgical and histopathological characteristics except for the pathological stage (P=0.015) (*Table 4*).

The median follow-up time for the 229 patients was 28.3 (IQR, 15.7–51.4) months. The median PFS was 31.0 [95% confidence interval (CI), 16.3–45.6] months, and the median OS was 68.6 (95% CI, not reached) months. The median time to death after the diagnosis of recurrence was 7.0 (IQR, 2.3–14.3) months. For the whole cohort, the 3-year PFS and OS rates were 49.9% and 61.5%, respectively. The 3-year PFS estimates were 41.9%, 42.8% and 61.7% in patients who underwent surgery in ≤4, 5–6, and >6 weeks after NCT, respectively (P=0.044). The 3-year OS estimates were 57.7%, 58.0% and 68.2% in the three groups, respectively (P=0.202). *Figure 1A,B* demonstrated Kaplan–Meier estimates of PFS and OS according to TTS.

In multivariable analysis, the extent of gastrectomy (total), tumor differentiation (poor/undifferentiated), pathological (T) stage (T3/T4), pN stage (N+), resection margin (R1), and adjuvant therapy (none/incomplete) were independently associated with poor OS (*Table 5*). The extent of gastrectomy (total), tumor differentiation (poor/undifferentiated), pN stage (N+), and resection margin (R1) were independently associated with poor PFS (*Table 6*).

Discussion

The present study found that the NCT regimen is the only independent factor associated with prolonged TTS (>6 weeks). TTS had no impact on the histopathological response or survival outcomes of patients with locally advanced GC who underwent preoperative chemotherapy.

The time interval to surgery is an important question frequently asked by patients but is also a question without a definite conclusion. Seminal trials whose results led to the introduction of preoperative chemotherapy into GC usually scheduled surgery within 4 and 6 weeks after the last dose of chemotherapy (1,3,9). However, no clinical trial has defined

Table 1 Patient and clinical characteristics by the interval from the completion of neoadjuvant therapy to surgery

Characteristic	Total patients (n=229)	Time to surgery ≤4 weeks (n=70)	Time to surgery 5–6 weeks (n=103)	Time to surgery >6 weeks (n=56)	P value
Time to surgery (day), median (IQR)	34.0 (26.0–42.0)	23.5 (18.8–25.0)	35.0 (31.0–39.0)	53.5 (46.3–60.8)	<0.001
Age (years), median (IQR)	56.0 (47.0–63.0)	58.0 (48.8–64.0)	55.0 (44.0–62.0)	57.0 (50.0–64.0)	0.196
Gender					0.188
Male	157	49	75	33	
Female	72	21	28	23	
Comorbidity					0.436
No	158	48	70	40	
1	53	14	28	11	
≥2	18	8	5	5	
ASA risk score					0.456
1–2	207	62	92	53	
3–4	22	8	11	3	
Clinical stage					0.133
IIIA	44	10	22	12	
IIIB	95	26	43	26	
IIIC	90	34	38	18	
NCT regimen					0.010
SOX/XELOX	128	42	47	39	
Paclitaxel plus SOX/XELOX	101	28	56	17	
No. of NCT cycles	4.0 (3.0–4.0)	3.0 (3.0–4.0)	3.0 (3.0–5.0)	4.0 (3.0–4.0)	0.017
Completion of NCT (yes)	131	34	63	34	0.215
Tumor location					0.894
Upper	54	19	24	11	
Middle	62	19	27	16	
Lower	113	32	52	29	
Clinical response[a]					0.757
PR	158	50	69	39	
SD/PD	71	20	34	17	
Severe NCT toxicity[b]	87	25	37	25	0.498

[a], according to the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1); [b], according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). IQR, interquartile range; ASA, American Society of Anesthesiologists; NCT, neoadjuvant chemotherapy; SOX, oxaliplatin + S-1; XELOX, oxaliplatin + capecitabine; PR, partial remission; PD, progressive disease; SD, stable disease.

the optimal timing of surgery after NCT and the current clinical guidelines do not present specific guidelines on an optimal interval. In default of relevant data, clinicians had to extrapolate from interval data in the context of adjuvant therapy, although its applicability in preoperative settings had not been validated (16-19).

Table 2 Reasons for surgery delay among patients with time to surgery (TTS) >6 weeks

Reasons	Number of patients (%)
Hematologic toxicity	15 (26.8)
Gastrointestinal symptoms	12 (21.4)
Nutritional support requirement	7 (12.5)
Poor performance status	9 (16.1)
Patient choice	4 (7.1)
Logistic reasons	4 (7.1)
Economic reasons	2 (3.6)
Unknown	3 (5.4)

Table 3 Independent factors associated with TTS >6 weeks

Variables	OR (95% CI)	P value
Number of NCT cycles	1.071 (0.876–1.308)	0.504
NCT regimen	0.444 (0.230–0.854)	0.015

TTS, time to surgery; NCT, neoadjuvant chemotherapy; OR, odds ratio.

In contrast to previous results from esophageal, rectal and GC showing that prolonged TTS significantly increased the odds of pCR (10,20-22), we did not observe any impact of TTS on the tumor histopathological response or tumor downstaging. Data on the influence of delaying TTS on the pathologic response rate are conflicting. An increased time interval (>6 weeks) between NCT and surgery revealed a significantly increased pCR rate among patients with locally advanced GC in a study conducted by Liu and colleagues (10). They speculated that a prolonged NCT-surgery interval during which tissue swelling and local inflammation induced by chemotherapy was allowed to subside could lead to a greater extent of tumor regression (e.g., downsizing and downstaging) through apoptosis and necrosis. In the current study, the association between the TTS and pathological response was not observed. The rate of pCR was 22.7% in the study conducted by Liu and colleagues compared with 7.0% in our study, although more than 40% of patients were given paclitaxel in addition to platinum plus fluorouracil chemotherapy. The reason for such an uncommon high probability of pCR in the study by Liu *et al.* is unclear. Investigating whether prolonged TTS increased the odds of pCR was not allowed due to the inferior chemosensitivity of GC and limited cases of complete responders in the current single institutional cohort. A multi-institutional study is needed to address this issue in the future.

There was a concern that delayed surgical treatment after NCT can lead to a poor survival outcome. The survival outcomes in our study did not differ across groups, a finding that was supported by previous studies, suggesting that postponing surgery beyond the currently accepted schedule did not impair survival. The association between TTS and survival varied with the cancer type. TTS had been shown to impair survival in many cancers, such as breast, esophageal, rectal and ovarian cancers. Sanford *et al.* analyzed data from a large breast cancer patient cohort treated with NCT at a single institution, revealing worse outcomes when surgery was scheduled after longer than 8 weeks (23). A recent study correlated the time interval between the end of NCT and initiation of adjuvant chemotherapy to survival in patients with stage III or IV ovarian cancer. The longer time intervals were independently predictive of higher risks of recurrence and death (24). In esophageal cancer, the perioperative mortality and OS are significantly correlated with the time interval between preoperative chemoradiation therapy and esophagectomy (25). Therefore, the correlation between TTS and prognosis vary with the cancer type, and this was probably due to distinct tumor characteristics and treatments.

The prolonged interval between NCT and surgery is driven by multiple factors. One of the most frequently encountered is the time period required for the resolution of short-term chemotherapy toxicities. Chemotherapy-related toxicities is a well-known contributor to postoperative complications after immediate surgery (5). Poor physical conditions and comorbidities of patients may also prolong this time interval, explaining why a difference was not detected in TTS between patients with or without NCT toxicity. Patients would experience psychological pressure, a deteriorated quality of life and satisfaction worrying about an impaired survival during the delay (7,8). No negative influence of postponed surgery on postoperative complications or survival suggested by our results should reassure patients and surgeons when scheduling surgery after NCT, but it did not support delaying surgery without reason. If a prolonged preoperative wait time is necessary for recovery from chemotherapy-related toxicity, physical condition improvement or comorbidity control, active surveillance is warranted and the initiation of treatment should occur as soon as possible.

Table 4 Surgical and histopathological characteristics by the interval from the completion of neoadjuvant chemotherapy to surgery.

Characteristic	Total patients (n=229)	Time to surgery ≤4 weeks (n=70)	Time to surgery 5–6 weeks (n=103)	Time to surgery >6 weeks (n=56)	P value
Extent of gastrectomy					0.491
Subtotal	151	43	72	36	
Total	78	27	31	20	
Additional organs resection	24	8	6	6	0.367
Differentiation					0.452
Well/moderate	65	16	31	18	
Poor/undifferentiated	164	54	72	38	
Pathologic T stage					0.750
T0–T2	70	21	29	19	
T3–T4	166	49	74	37	
Pathologic N stage					0.166
N0	75	17	36	22	
N+	154	53	67	34	
Pathological stage (pCR)	16	4	6	6	0.015
I	29	8	13	8	
II	59	17	28	14	
III	125	41	56	28	
HPR[a] [1–3]	96	30	45	21	0.539
Resection margin					0.993
R0	216	66	97	53	
R1	13	4	6	3	
Number of LNs, median (IQR)	29.0 (21.0–38.0)	26.5 (18.8–38.0)	29.0 (21.0–41.0)	31.0 (22.5–37.5)	0.171
Postoperative complications[b]					0.850
None	161	50	72	39	
Clavien-Dindo I–II	56	18	24	14	
Clavien-Dindo III+	12	2	7	3	
Operative duration (min), median (IQR)	190.0 (164.0–240.0)	180.0 (153.8–240.0)	194.0 (165.0–230.0)	197.5 (164.8–254.3)	0.664
Intraoperative blood loss (mL)	200 (164–240)	200 (100–300)	200 (100–300)	150 (100–300)	0.344
Postoperative hospital stay (day), median (IQR)	11.0 (9.0–13.0)	11.0 (9.0–13.0)	12.0 (10.0–14.0)	11.0 (9.0–14.0)	0.279
No. of postoperative cycles	3.0 (0.0–4.0)	3.0 (1.0–5.3)	3.0 (0.0–4.0)	2.0 (0.0–4.0)	0.129
Adjuvant chemotherapy					0.164
None	64	15	27	22	
Incomplete	79	24	40	15	
Complete	86	31	36	19	

[a], according to Mandard score; [b], according to the Clavien–Dindo classification system. pCR, pathologically complete response; HPR, histopathological response; LNs, lymph nodes; IQR, interquartile range.

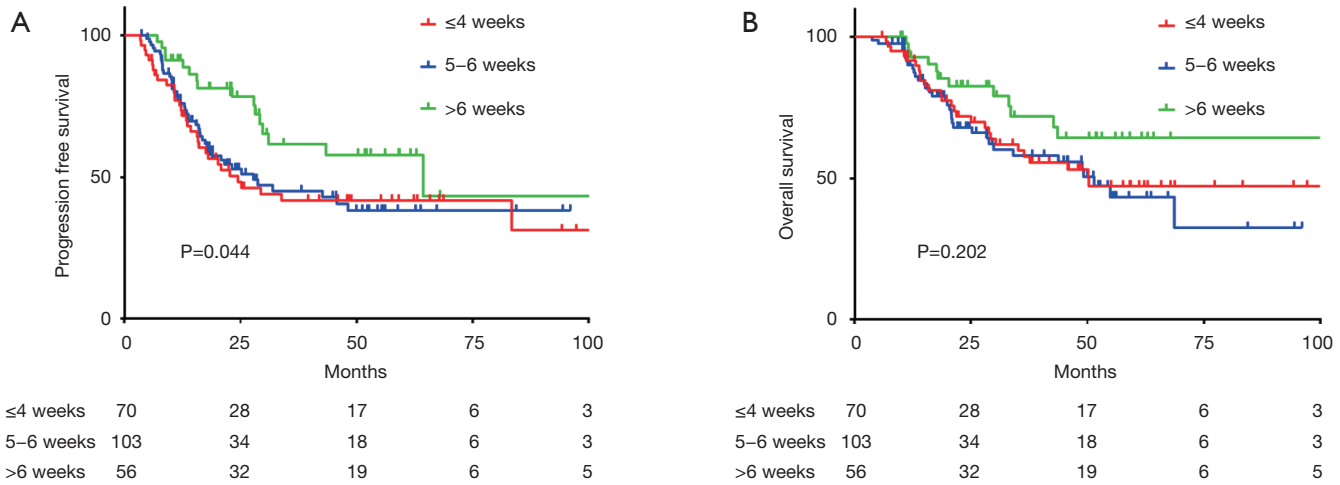

Figure 1 Kaplan-Meier analyses of progression-free survival (A) and overall survival (B) according to time to surgery.

Table 5 Univariate and multivariate analysis of the factors affecting OS

Variables	Univariate analysis	Multivariate analysis		
	P value	HR	95% CI	P value
Age (year)	0.422			
Gender (male *vs.* female)	0.949			
ASA score (1–2 *vs.* 3–4)	0.118			
Comorbidity (reference, no)	0.754			
1				
≥2				
NCT regimens (SOX/XELOX *vs.* paclitaxel plus SOX/XELOX)	0.345			
Completion of NCT (yes)	0.540			
Time to surgery (reference, ≤4 weeks)	0.202			
5–6 weeks				
>6 weeks				
Extent of gastrectomy (subtotal *vs.* total)	<0.001	1.766	1.093–2.855	0.020
Additional organs resection	0.329			
Differentiation (well/moderate *vs.* poor/undifferentiated)	0.003	1.563	0.822–2.972	0.174
HPR (1–3 *vs.* 4–5)	0.324			
pT stage (pT0–2 *vs.* pT3–4)	<0.001	2.231	1.099–4.527	0.026
pN stage (pN0 *vs.* pN+)	<0.001	1.919	1.017–3.621	0.044
Resection margin (R0 *vs.* R1)	0.007	2.944	1.194–7.257	0.019
Adjuvant chemotherapy (reference, none)	0.004			
Incomplete		0.727	0.423–1.250	0.249
Complete		0.343	0.180–0.652	0.001

OS, overall survival; HR, hazards ratio; CI, confidence interval; ASA, American Society of Anesthesiologists; NCT, neoadjuvant chemotherapy; SOX, oxaliplatin + S-1; XELOX, oxaliplatin + capecitabine; HPR, histopathological response.

Table 6 Univariate and multivariate analysis of the factors affecting PFS

Variables	Univariate analysis	Multivariate analysis		
	P value	HR	95% CI	P value
Age (year)	0.112			
Gender (male *vs.* female)	0.927			
ASA score (1–2 *vs.* 3–4)	0.872			
Comorbidity (reference, no)	0.757			
1				
≥2				
NCT regimens (SOX/XELOX *vs.* paclitaxel plus SOX/XELOX)	0.295			
Completion of NCT (yes)	0.643			
Time to surgery (reference, ≤4 weeks)	0.044	1	Reference	
5–6 weeks		1.176	0.742–1.865	0.490
>6 weeks		0.637	0.345–1.176	0.149
Gastrectomy (subtotal *vs.* total)	<0.001	1.870	1.205–2.902	0.005
Additional organs resection	0.478			
Differentiation (well/moderate *vs.* poor/undifferentiated)	<0.001	2.787	1.473–5.272	0.002
HPR (1–3 *vs.* 4–5)	0.049	0.827	0.529–1.291	0.403
pT stage (pT0–2 *vs.* pT3–4)	<0.001	1.369	0.751–2.495	0.305
pN stage (pN0 *vs.* pN+)	<0.001	2.051	1.187–3.545	0.010
Resection margin (R0 *vs.* R1)	<0.001	2.188	1.068–4.482	0.032
Adjuvant chemotherapy (none)	0.201			
Incomplete				
Complete				

PFS, progression-free survival; HR, hazards ratio; CI, confidence interval; ASA, American Society of Anesthesiologists; NCT, neoadjuvant chemotherapy; SOX, oxaliplatin + S-1; XELOX, oxaliplatin + capecitabine; HPR, histopathological response.

There are several inherent limitations that should be noted. Patients who underwent neoadjuvant radiotherapy were excluded because they were inherently different from those receiving chemotherapy alone. Resulting from the paucity of high-level evidence regarding a survival benefit for NCT plus surgery over surgery followed by adjuvant chemotherapy in patients with locally advanced GC, patients treated with NCT at our center mostly had clinically stage III disease as they carry a high risk of poor prognosis. This precluded our conclusion from being solid enough among patients with less advanced disease. The ethnicity, chemotherapy regimen, and postoperative treatment modality in the current study were also different from those in European studies. The range of TTS was narrow, and the selection of cut-off points were arbitrary to some extent. Patients could differ by as little as two weeks between the first and third tertiles because patients undergoing radiotherapy whose preoperative waiting time was usually longer were excluded because they were inherently different. The arbitrary cut-off points were selected based on previous retrospective studies addressing the same issue demonstrating that TTS >6 weeks increased the probability of pCR. TTS is usually 5–6 weeks, which is most commonly adopted by clinicians in China. Although the longest TTS group was the least likely to receive paclitaxel, the survival curves seem to be better than those of the other two groups together in the univariate analysis. However, TTS was not recognized as a significantly

independent predictor of survival in the multivariate analysis. We believed that the limited number of patients with the longest TTS (>6 weeks), a narrow range of TTS and relatively short follow-up time in this study might prevent us from reaching a statistically significant result. A large-sampled multi-institutional cohort is warranted to further investigate this issue. Finally, the median follow-up period was relatively short. However, because the first recurrence of GC usually develops within the first two years postoperatively, the follow-up period may have been sufficient to draw a conclusion (26).

Conclusions

Our findings suggest that TTS did not impact the histopathological response or survival outcomes. It reassures surgeons to delay surgery for patients experiencing chemotherapy-toxicity, a worsened nutritional status or serious comorbidities. On the other hand, when the patient is fit for surgery, delaying surgery appears to bear no additional benefits. Conclusive evidence from a clinical trial are necessary to define the optimal timing of surgery after NCT and to determine whether prolonged TTS could benefit patients.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.08.42). The authors have no conflicts of interests 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. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Institutional Review Board of National Cancer Center/ National Clinical Research Center for Cancer/Cancer Hospital has reviewed and approved this study, and has also agreed that individual patient consent was not required to report clinical outcomes alone (No. 17-156/1412).

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