

# Current status and future perspectives on neoadjuvant therapy in gastric cancer

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## Abstract

Gastric cancer, with high morbidity and mortality rates, is one of the most heterogeneous tumors. Radical gastrectomy and postoperative chemotherapy are the standard treatments. However, the safety and efficacy of neoadjuvant therapy (NAT) need to be confirmed by many trials before implementation, creating a bottleneck in development. Although clinical benefits of NAT have been observed, a series of problems remain to be solved. Before therapy, more contributing factors should be offered for choice in the intended population and ideal regimens. Enhanced computed tomography (CT) scanning is usually applied to evaluate effectiveness according to Response Evaluation Criteria in Solid Tumors (RECIST), yet CT scanning results sometimes differ from pathological responses. After NAT, the appropriate time for surgery is still empirically defined. Our review aims to discuss the abovementioned issues regarding NAT for GC, including indications, selection of regimens, lesion assessment and NAT-surgery interval time.

**Keywords:** Gastric cancer; neoadjuvant therapy; regimens; lesion assessment; NAT-surgery interval time

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## Introduction

Gastric cancer (GC) is the fifth most common type of cancer and the third leading cause of cancer-related death worldwide (1). Although the incidence is decreasing, 1,089,103 individuals worldwide were diagnosed with GC in 2020, with approximately 44% (478,508 cases) in China (2). Curative treatment for GC is mainly surgery. However, surgery alone is not sufficient for the best survival outcomes. Neoadjuvant therapy (NAT) is a multimodal strategy developed to optimize prognosis and includes neoadjuvant chemotherapy (NACT), neoadjuvant chemoradiotherapy (NACRT), targeted therapy and even immunotherapy. The efficacy of NACT has been confirmed by the MAGIC trial, which showed better

survival among patients who received perioperative chemotherapy with epirubicin, cisplatin, and infused fluorouracil than among those not treated with perioperative chemotherapy [hazard ratio (HR), 0.75; 95% confidence interval (95% CI), 0.60–0.93] (3). In addition, the advantages of NACRT have been demonstrated by the POET trial in Germany (4) and further confirmed by the Australian TOPGEAR study and Dutch phase I/II CROSS trial. The abovementioned studies showed that preoperative synchronous NACRT can not only improve R0 resection rates but also reduce distant metastasis and recurrence rates and improve survival in advanced GC (AGC) by degrading the primary tumor stage, especially among those with a pathologic complete response (pCR) (5,6). The German HER-FLOT study demonstrated that

targeted drugs may also be incorporated in NAT for GC, with an R0 resection rate of 93%, and 23% of patients achieved pCR (7). Atezolizumab is proven safe as a kind of perioperative immunotherapy in combination with FLOT in patients with resectable esophagogastric adenocarcinoma. Nevertheless, the benefit of NAT differs among regions, and in general, NAT is more preferred in Western countries than in Eastern countries. In Japan, the phase III study JCOG0501 failed to demonstrate the efficacy of preoperative NACT with S-1 plus cisplatin for patients with type 4 or large type 3 ( $\geq 8$  cm in maximum diameter) GC (8), with 3-year relapse-free survival (RFS) rates of 60.9% and 62.4% for patients who received preoperative NACT vs. those who did not, respectively (HR, 0.916; 95% CI, 0.679–1.236) (9). Therefore, NACT is not strongly recommended for GC, with the exception of patients with extensive nodal metastasis, as defined as bulky ( $\geq 30$  mm in diameter) suprapancreatic lymph nodes or enlarged ( $\geq 10$  mm in diameter) para-aortic lymph nodes (10). Conversely, NACT has become more accepted in China and Korea since many clinical trials, such as the RESOLVE and PRODIGY studies, have shown a better response and prognosis (11,12).

The tolerance to and efficacy of various treatment protocols differ. Trumbull DA *et al.* (13) found that the use of NACT led to a significant increase in overall survival (OS) compared with NACT for those who achieved pCR in gastric adenocarcinoma (5-year survival rate: 94% vs. 60%). Nonetheless, the time interval until surgery after the

completion of NAT is a common question without a definite answer. Neoadjuvant targeted therapy and immunotherapy are hot topics, though concrete details need to be studied. Overall, as neoadjuvant therapeutic strategies are sophisticated, we review the current status and future perspectives of NAT in GC in this article.

### Why should we have NAT?

With the MAGIC study (3) confirming the benefits of NACT for patients with GC for the first time, the results of a number of clinical studies (14–18) in recent years have shown the advantages of NACT over surgery alone (Table 1). For example, a meta-analysis (19) compared multiple preoperative chemotherapy regimens with surgery alone and found that NACT improved OS [odds ratio (OR): 1.32; 95% CI: 1.07–1.64] and progression-free survival (PFS) (OR: 1.85; 95% CI: 1.39–2.46). In addition, NACT significantly enhanced the complete (R0) tumor resection rate (OR: 1.38; 95% CI: 1.08–1.78) but did not significantly increase the incidence of surgical complications, perioperative mortality, or grade 3–4 adverse reactions (19).

NACT and adjuvant chemotherapy (ACT) have been compared in some studies. The RESONANCE trial (20) for patients with clinical stage II and III gastric adenocarcinoma showed that NACT with the SOX regimen effectively controlled tumors, with a disease control rate of over 97%, significantly increasing the R0

**Table 1** Trials of NACT in GC

Trails	Year	Cases	Arms	Patients (n)	R0 rate (%)	OS or HR for OS (95% CI)	Results
MAGIC (3)	2006	Resectable gastric + EGJ cancer	E: ECF + surgery S: surgery	E: 250 S: 253	E: 74 S: 68	HR=0.75 (0.60–0.93)	Positive
JCOG0405 (17)	2007	Bulky N2/3	SP + D2 + PAND	53	82.4	5-year OS: 53%	–
FNLCC/FFCD (15)	2011	Resectable gastric + EGJ cancer	E: FP + surgery S: surgery	E: 113 S: 111	E: 84 S: 73	HR=0.69 (0.50–0.95)	Positive
EORTC (14)	2010	cT3–4NxM0	E: PFL + surgery S: surgery	E: 72 S: 72	E: 81.9 S: 66.7	HR=0.84 (0.52–1.35)	Negative
JCOG0501 (9)	2018	Type 4/Large type 3	E: SP + surgery + S-1 S: surgery + S-1	E: 149 S: 151	E: 51 S: NS	HR=0.92 (0.68–1.23)	Negative
FLOT-AIO (18)	2017	cT2–4/cNany/cM0 or cTany/cNt/cM0	E: FLOT + surgery S: ECF/ECX + surgery	E: 356 S: 360	E: 85 S: 78	HR=0.77 (0.63–0.94)	Positive
RESOLVE (12)	2020	cT4b/N+ or cT4aN+	E: SOX + surgery + SOX S: surgery + XELOX	E: 353 S: 353	NS	HR=0.79 (0.62–0.99)	Positive

NACT, neoadjuvant chemotherapy; GC, gastric cancer; OS, overall survival; HR, hazard ratio; 95% CI, 95% confidence interval; EGJ, esophagogastric junction; ECF, epirubicin, cisplatin, fluorouracil; PAND, para-aortic node dissection; FP, fluorouracil and cisplatin; PFL, cisplatin, fluorouracil, leucovorin; SP, S-1 + cisplatin; FLOT, fluorouracil, leucovorin, oxaliplatin and docetaxel; ECX, epirubicin, cisplatin, capecitabine; SOX, S-1 and oxaliplatin; XELOX, capecitabine and oxaliplatin; NS, not sure.

resection rate, and R0 resection was achieved in 95% of patients. According to the multicenter RESOLVE trial (12) based on the same research background, SOX regimen NACT significantly improved the 3-year disease-free survival rate of GC patients compared with the standard treatment of D2 surgery combined with XELOX regimen ACT (P=0.045; HR: 0.79; 95% CI: 0.62–0.99).

There is no doubt regarding the effectiveness of NACT for GC, but the population for whom such treatment is indicated and the selection of specific options remains the focus of current research.

NACT is common in Western countries. This is because existing clinical evidence for NACT for GC is mainly based on trials of EGJ cancer (21). Radiotherapy is considered to be an effective method for the treatment of EGJ cancer, yet distal GC is more common in Asian countries/regions. In addition, before the 15-year follow-up results of the Dutch D1D2 trial (22) in 2010 were announced, D2 lymph node dissection was still considered controversial among Western researchers (23). As a result, the proportion of D2 surgery in most clinical trials is relatively low (3). As the INT-0116 trial (24) in 2001 proved the effectiveness and advantages of adjuvant radiotherapy and chemotherapy, a series of clinical trials initially confirmed that for patients with AGC, preoperative NART and NACT could improve R0 resection (4,5,25) over surgery alone. It also decreased the rate of distant metastasis and recurrence by reducing the primary tumor stage and improved survival rates (Table 2). Importantly, this treatment strategy was found to be safe and well tolerated. In EGJ cancer, the POET trial (4) compared the effectiveness of neoadjuvant chemoradiation and NACT and found that the former improved the 3-year OS rate (47.4% vs. 27.7%, P=0.07) and pCR rate (15.6% vs. 2.0%, P=0.03). Although the efficacy of preoperative chemoradiotherapy in EGJ cancer has been confirmed, for

non-EGJ GC, the TOPGEAR trial (5) failed to verify that NART and NACT leads to higher survival benefits than NACT.

For patients with non-early GC, the addition of trastuzumab to cytotoxic chemotherapy might improve survival in those with human epidermal growth factor receptor 2 (HER2)-overexpressing tumors (26). HER2 is also one of the most widely studied and widely used molecular targets for GC. Although a series of small phase II clinical studies of HER2-positive GC yielded optimistic data, the NEOHX trial showed that the R0 resection rate of patients with trastuzumab combined with XELOX regimen NAT could reach 78%; in the HER-FLOT trial, trastuzumab + FLOT NAT resulted in an R0 resection rate of 93% and a pCR rate of 23%. In the TRAP trial, the PH (Patuzumab and Trastuzumab) dual target combined with radiotherapy and chemotherapy had a pCR rate of 34%. However, there is currently no high-level medical evidence for anti-HER2 therapy in the perioperative period. The 2020 ASCO meeting revealed the results of the PETRARCA trial, in which a perioperative FLOT regimen was combined with trastuzumab and pertuzumab for the treatment of HER2-positive GC. The results showed that the combination of two anti-HER2 drugs could increase the pCR rate (35% vs. 12%) and prolong OS (84% vs. 77%) and median disease-free survival (mDFS) (not reached vs. 26 months; HR=0.58; P=0.14). In terms of safety, diarrhea and leukopenia in the test group were improved. However, because the survival benefit of the combined use of two anti-HER2 drugs in the JACOB trial (ClinicalTrials.gov identifier NCT01774786) was not significantly different from trastuzumab alone, the PETRARCA trial (7) was terminated early. At present, the JCOG1301 study is evaluating the effectiveness of NACT with trastuzumab+S-1/cisplatin for GC with confluent lymph nodes.

Table 2 Trials of NACT in GC

Trails	Year	Cases	Arms	Patients (n)	R0 rate (%)	OS or HR for OS (95% CI)	Results
POET (4)	2009	EGJ	E: PFL+ 30 Gy + surgery S: PFL+ surgery	E: 62 S: 64	E: 72 S: 69	HR=0.67 (0.41–1.07)	Negative
CROSS (6)	2012	Esophageal cancer + EGJ cancer	E: Paclitaxel + carboplatin + 41.1 Gy + surgery S: surgery	E: 178 S: 188	E: 92 S: 69	HR=0.657 (0.495–0.871)	Positive
TOPGEAR (5)	2018	Resectable GC	E: ECF + 45 Gy + surgery S: ECF + surgery	E: 395 S: 393	E: 82 S: 80	5-year OS E: 40% S: 42% (P=0.9)	Negative

NACT, neoadjuvant chemotherapy; GC, gastric cancer; OS, overall survival; HR, hazard ratio; 95% CI, 95% confidence interval; EGJ, esophagogastric junction; PFL, cisplatin, fluorouracil, leucovorin; ECF, epirubicin, cisplatin, fluorouracil.

With the success of a series of clinical trials of AGC immunotherapy (27), the application of immunotherapy in the perioperative period is being explored. For instance, the ongoing KEYNOTE-585 trial (28) is evaluating pembrolizumab combined with chemotherapy (cisplatin/capecitabine or 5-FU) in the perioperative period for GC and EGJ cancer.

### Who should receive NAT?

At present, the four major international gastric cancer guidelines recommend NACT. Although the indications are still controversial, their importance is being increasingly recognized.

The population indicated for NACT for GC is based on the results of different clinical studies, with large differences between regions, which can be roughly divided into Europe (European Society for Medical Oncology, ESMO), the United States (National Comprehensive Cancer Network, NCCN) and East Asia. In East Asia, there is much experience in the field of perioperative treatment of GC because of its high incidence.

To date, ESMO guidelines recommend NACT for patients with GC at a clinical stage >T1N0. This is based on the results of the pioneering MAGIC trial (3) and the FLOT-AIO4 trial (18). US guidelines are based on the INT0116 trial (24), recommending clinical stage  $\geq$  T2Nany. The patient was treated with neoadjuvant chemoradiation. In Japan, the standard treatment is still surgery combined with postoperative chemotherapy. Preoperative NACT is only performed on some patients, mainly those with gross sclerosis, large Borrmann III (longest diameter  $\geq$ 8 cm) and Borrmann IV cases, those with additional lymph node metastasis (mainly para-aortic lymph node metastasis) and fused lymph nodes and those with expected poor survival. These indications are based on the JCOG0501 (8), JCOG0405 and JCOG1002 trials (17). In South Korea, the PRODIGY trial is in progress; the NACT-adapted population included in this study involved cT2-3N+ or cT4 cases, and the chemotherapy regimen was DOS (docetaxel + oxaliplatin + S-1). Compared with ACT, NACT significantly prolonged PFS of patients for 3 years (66.3% vs. 60.2%). The Chinese 2020 version of the CSGO Gastric Cancer Guidelines recommends NACT for patients with locally AGC at clinical stage T3/4N+. The chemotherapy regimen included SOX (oxaliplatin + S-1), but unfortunately, clinical research results were lacking for the Chinese guidelines for a long time; support was only

based on the consensus of clinical experience and expert opinions. This situation was improved in 2019. The results of RESOLVE and RESONANCE studies confirmed the value of NAT based on the SOX program in the II/III GC population.

### What is the most important point in NAT?

#### *Tumor staging before NAT*

Clinical staging may guide the selection of the initial treatment plan, and accurate staging is very important for clinical decision-making. The current preoperative staging is mainly based on the results of endoscopic and imaging examinations. The methods include computerized tomography scan (CT), endoscopic ultrasonography (EUS), magnetic resonance imaging (MRI), positron emission tomography (PET-CT), and staging laparoscopy. The depth of tumor invasion of the stomach wall (T staging), the extent and location of lymph node metastasis (N staging), and the presence or absence of distant metastasis (M staging) were comprehensively evaluated, and preoperative clinical TNM staging was carried out with reference to the AJCC eighth edition staging system (29).

The significance of correct preoperative staging for NACT is as follows: 1) to avoid unnecessary treatment for patients with early GC; 2) subdividing patients such that they receive the most suitable chemotherapy regimen more in line with the principle of individualized and precise treatment.

As a highly accessible noninvasive examination, CT is the most popular and appropriate for the assessment of extensive tumor metastases. Indeed, most studies have been based on the staging results of CT examinations. Nevertheless, CT scans easily miss metastatic lesions <5 mm (30), and approximately 20%–30% of peritoneal metastases cannot be diagnosed by CT (31,32). In addition, CT scanning may not be able to accurately assess the depth of primary tumor invasion (T stage) and lymph node involvement (N stage). The accuracy of CT for T staging also varies greatly among studies, with most reporting 50%–70% (33,34), even though the accuracy of specific staging (cT2) in some studies can be as low as 25.1% (35). The accuracy of CT in judging N staging is limited by the lack of tissue-specific identification methods. Lymph nodes with a diameter less than 0.8 cm are difficult to detect (36), and inflammatory lymphadenopathy might lead to false positives (37). Meta-analyses have shown that the sensitivity

of CT for N staging is 62.5%–91.9%, with a specificity of 50.0%–87.9%.(38-40). Multidetector-row CT combined with serum tumor biomarkers can be adopted to improve preoperative sensitivity (up to 89.3%) of lymph node metastasis for GC patients (41). Interestingly, a CT-based radiomics nomogram for predicting HER2 status is built and validated in patients with GC so as to guide clinical treatment (42).

EUS examination is considered to be the most reliable method that to assess the invasion depth of primary GC (43), and it is especially suitable for preoperative evaluation of ESD/EMR (21). A number of comparative studies have shown that the accuracy of EUS for T staging is higher than that of CT (44-46), reaching more than 75% (44). However, due to the limitation of the scanning range and depth of the EUS probe, it is difficult to assess advanced tumors that infiltrate the serous membrane of the stomach wall or adjacent organs. Overall, the accuracy of EUS in judging N staging is slightly better than that of CT (47), and the overall sensitivity for the diagnosis of lymph node metastasis is 83% (95% CI: 79%–87%), with an overall specificity of 67% (95% CI: 61%–72%) (48). The poor consistency of EUS inspection between different studies might be due to the professional technical ability and experience of the operator, which limits the wide application of this technology.

As an imaging method for assessing tissue function and metabolism, PET-CT can effectively determine whether enlarged lymph nodes have metastasized, and it is more sensitive than CT for detecting distant metastasis of tumors (49-51). However, high FDG uptake does not occur in approximately one-third of GC (diffused GC) (52-54), and PET-CT is of limited value for peritoneal metastasis (sensitivity was only 50%) (55,56). Hence, PET-CT is not routinely used as a staging method.

Although staging laparoscopy is an invasive procedure, it is still the most accurate method of judging peritoneal metastasis and might alter the treatment plan for more than half of patients (57,58). At the same time, peritoneal cytology may be performed during the operation, which helps to find undetected evidence of peritoneal dissemination. In fact, NCCN guidelines recommend preoperative laparoscopic staging for all patients planning to undergo NACT (21).

MRI is an alternative to other imaging methods (59). The accuracy of MRI for T and N staging of GC is similar to that of CT (60-62). The accuracy of MRI assessment of T stage varies from 64% to 88% (63-65). The combined

application of diffusion-weighted imaging (DWI) further enhances the accuracy of T staging by 7% (63). For N staging, there are no statistically significant differences reported between MRI and CT or EUS for accurate detection of lymph node metastasis (59). MRI has been widely used to diagnose liver metastases and has shown potential for diagnosing peritoneal seeding (66,67). Based on recent studies, functional MRI may contribute to treatment response assessment and the detection of lymph node metastasis (such as diffusion-weighted imaging and dynamic contrast enhancement) (68-70).

The application of artificial intelligence using deep learning models and radiomics has revolutionized the field of cancer imaging (71). CT-based deep learning models are currently making progress in distinguishing the histopathological characteristics of GC and in predicting the efficacy of chemotherapy as well as prognosis (72). Researchers have also established a deep learning radiomic model based on preoperative CT that can effectively predict the lymph node metastasis of locally AGC (73).

#### *Lesion assessment during NAT*

The assessment of lesions during NAT is a prerequisite for accurately evaluating the effects of NAT, which is mainly achieved by imaging methods. At present, the evaluation method commonly used for clinical efficacy is still tumor burden evaluation using Response Evaluation Criteria for Solid Tumors (RECIST) version 1.1 released in 2009 (74). Based on changes in the maximum length of target lesions and nontarget lesions before and after treatment in imaging examinations, the curative effect is divided into complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD) (74). The concepts of objective remission rate and disease control rate thereby derived have been used in many studies to evaluate the efficacy and safety of treatment (75). Researchers have also confirmed that changes in tumor size measured by imaging before and after NAT correlate with pTRG (76,77) and prognosis (78).

In terms of functional imaging, some small-sample studies have confirmed the correlation between changes in CT perfusion imaging parameters before and after NAT and pTRG (79,80), but further research is needed. MRI-DWI can indirectly reflect the microstructure of the tissue through the apparent diffusion coefficient (ADC), and it is believed that the necrosis of tumor cells can be detected earlier than by relying on morphological changes (81).

Some studies have also found that the change in ADC before and after NAT effectively predicts the long-term prognosis of patients (60,82,83) and helps identify those who will not respond to chemotherapy (84,85).

### *What is the appropriate time for surgery?*

Some studies have proven that a longer interval is significantly related to increased pCR rates, increased tumor downstaging, and superior OS in rectal cancer (86,87), whereas the results are conflicting in esophageal cancer (88). It has been argued that delaying the operation too long might result in tumor repopulation and that dissection may be more difficult because of fibrosis. The question of whether delaying the operation until after NAT is beneficial is a topic of current debate in GC (Table 3) (89-92). In general, the NACT-surgery interval time is commonly 4–6 weeks based upon empirical observations (93). However, Liu *et al.* showed that the NACT-surgery interval time was associated with pCR but had no impact on survival and that an interval time >6 weeks was associated with 74% higher odds of pCR than an interval time of 4–6 weeks (41.18% vs. 12.50%) (89). The authors stressed that the underlying mechanism might be the result of multiple factors, including the ongoing effect of chemoradiotherapy, changes in the tumor micro-

environment, and recovery of immunity from chemotherapy. However, the number of patients with interval time >6 weeks (only 17) was not enough to be convincing and was not sufficient to explore more timing groups or the maximum interval time (such as 6–8 weeks, 8–12 weeks, and >12 weeks). In 2019, Wu *et al.* expanded the sample but found no impact on the histopathological response or survival outcomes of patients with locally AGC who underwent preoperative chemotherapy (90). A similar result was reported by Juan Ocana *et al.* from Spain (91). To have more probabilities to discuss the deep meaning of the NACT-surgery interval time, Wang *et al.* compiled a cohort of 426 patients divided into five groups by weeks of TTS (0–84 d). The study revealed a better prognosis among patients with TTS within 22–35 d (OS: HR, 1.78; 95% CI, 1.25–2.54; P=0.001; PFS: HR, 1.49; 95% CI, 1.07–2.08; P=0.017). The postoperative stay was significantly higher in the ≤21-day group, while no statistical significance was observed for the other parameters (P>0.05) (92).

In terms of chemoradiotherapy, patients underwent surgery 4–6 weeks following completion of preoperative therapy in the TOPGEAR and CROSS studies. Klevebro *et al.* (94) analyzed Swedish national data and suggested that it is safe and effective for patients to wait at least 7–10 weeks after completing NACT for surgery. However,

**Table 3** Studies of NACT-surgery interval time for GC after NAT

Author	Year	Group (interval time)	No. of patients (N)	pCR [n (%)]	Impact on OS/DFS
Liu <i>et al.</i> (89)	2018	<4 weeks	111	27 (24.3)	No statistical difference
		4–6 weeks	48	6 (12.5)	
		>6 weeks	17	7 (41.2)	
Wu <i>et al.</i> (90)	2019	≤4 weeks	70	4 (5.7)	57.7*
		5–6 weeks	103	6 (5.8)	58.0*
		>6 weeks	56	6 (10.7)	68.2*
Juan Ocana <i>et al.</i> (91)	2020	<4 weeks	18	1 (5.6)	No statistical difference
		4–6 weeks		0 (0)	
		>6 weeks	16	1 (6.3)	
Wang <i>et al.</i> (92)	2020	≤21 d	49	3 (6.1)	22–35 d revealed a better OS and PFS#
		22–28 d	93	5 (5.4)	
		29–35 d	108	5 (4.6)	
		36–42 d	84	10 (11.9)	
		43–84 d	92	6 (6.5)	

NACT, neoadjuvant chemotherapy; GC, gastric cancer; NAT, neoadjuvant therapy; OS, overall survival; DFS, disease-free survival; HR, hazard ratio; \*, 3-year OS (%), P=0.202; #, OS (≤21 vs. 22–28 d: HR, 1.54, P=0.185; 36–42 d vs. 22–28 d: HR, 2.20, P=0.004; 43–84 d vs. 22–28 d: HR, 1.83, P=0.022) and PFS (≤21 d vs. 22–28 d: HR, 1.54, P=0.256; 36–42 vs. 22–28 d: HR, 2.20, P=0.111; 43–84 d vs. 22–28 d: HR, 1.83, P=0.047).

there was no evidence in favor of recommending prolonged TTS after NACRT for esophageal and EGJ cancer.

Overall, there is no compelling evidence about the ideal NACT-surgery interval time. Most studies have focused on NACT and NARCT, and neoadjuvant targeted therapy and neoadjuvant immunotherapy are similarly empirically treated as NACT. Thus, basic clinical studies might be needed to provide information on environmental changes before and after NAT, especially the cellular immune function and residual drug concentration. On the other hand, randomized controlled trials should be explored to define the ideal surgery time to gain more benefits.

### Conclusions and perspectives

The safety and efficacy of NAT for GC has been proven, though many problems need to be solved. The indications for NAT are wider and regimens stronger in Western countries. Tumor staging and lesion assessment during NAT have important roles, but there is no ideal noninvasive measure; nevertheless, staging laparoscopy is a good choice. Until more trials focus on this issue, the recommended NACT-surgery interval time is 3–5 weeks. Regarding the future, more regimens such as immunotherapy and more modern devices should be introduced into NAT for GC; however, cost control and measures of indication and adverse effects are also research focuses.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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