



## Review

## Neoadjuvant therapy strategies for advanced gastric cancer: Current innovations and future challenges

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**Abstract**

Gastric cancer, which has a high incidence and poor prognosis, remains a therapeutic challenge. Recently, neoadjuvant therapy has attracted increasing attention due to high recurrence rate and low survival rate after resection in most patients with advanced stage. Clinical trials show that neoadjuvant approaches confer a significant survival advantage for resectable locally advanced gastric cancer. The specific advantages of chemoradiotherapy compared with chemotherapy have not been clarified; optimal regimens and cycles, particularly in the preoperative setting, should be studied further; and trials aimed at determining the role of targeted and immunological therapies should be conducted.

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**Keywords:** Gastric cancer; Neoadjuvant therapy; Chemotherapy; Radiotherapy

**Introduction**

Gastric cancer (GC) has a particularly poor prognosis and high incidence rate worldwide. Cases in China account for >45% of the incidence rate and >50% of the mortality rate of the total worldwide cases of GC reported annually.<sup>1</sup> D2 radical surgery is still the most effective treatment for advanced GC (AGC).<sup>2</sup>

Despite remarkable improvements in surgical and comprehensive therapies, recurrence and metastasis are still the main causes of death from GC. Increasing R0 resection rate and reducing recurrence and metastasis rates have become the main goals of treatment. Therefore, the concept of neoadjuvant therapy has been proposed.<sup>3</sup> Adjuvant and neoadjuvant perioperative approaches, including chemotherapy and/or radiotherapy, are now increasingly being used in combination with surgery for locally AGC and even early-stage GC. Several clinical studies have confirmed the efficacy of neoadjuvant therapy and chemoradiotherapy.<sup>4–6</sup> Neoadjuvant therapy can improve the R0 surgical resection rate, reduce distant metastasis and recurrence rate, and improve survival of patients by reducing the tumor stage, but the specific regimen, optimal cycles of treatment, and histological response evaluation are

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unclear, and its indications, feasibility, and long-term survival benefit remain controversial. In this review, we summarized the current state and future challenges of neoadjuvant therapeutic approaches for AGC.<sup>7,8</sup>

## Indications

Prospective randomized controlled trials have suggested the role of neoadjuvant therapy in patients with AGC, and influential guidelines from various countries have recommended various neoadjuvant therapeutic strategies (Table 1). The National Comprehensive Cancer Network (NCCN) guidelines recommend neoadjuvant chemotherapy or chemoradiotherapy for patients with resectable GC with clinical stage  $\geq$  T2N0–3M0.<sup>9</sup> The European Society for Medical Oncology (ESMO) guidelines, based on MAGIC and FNCLCC/FFCD studies, recommend neoadjuvant chemotherapy with cisplatin combined with fluorouracil for all patients with resectable GC whose clinical stage is  $>$ T2M0 (IB).<sup>10</sup> As GC screening is extremely popular in Japan, most patients are diagnosed at the early stage, D2 lymph node dissection is widely prevalent, and surgical treatment has a good prognosis for early disease. Therefore, neoadjuvant chemotherapy was excluded in the 5th edition of the Japanese Gastric Cancer Association (JGCA) treatment guidelines released in 2018.<sup>11</sup> The JGCA guidelines indicate that the Association is awaiting the results of an ongoing clinical research. The incidence of GC in Korea is similar to that in Japan. According to the

guidelines published on March 2019, neoadjuvant chemotherapy for potentially resectable GC is not an option if D2 lymphadenectomy is considered.<sup>12</sup> Referring to the standard for diagnosis and treatment of GC of the Chinese Society of Clinical Oncology (CSCO), neoadjuvant chemotherapy is recommended for T3–4N1–3M0 of local AGC.<sup>13</sup> However, a large-scale phase III clinical research evaluation is still lacking in China. While a neoadjuvant approach can be broadly applied, its advantages may be most pronounced in specific patient subsets. Appropriate selection of patients for neoadjuvant therapy can ensure maximum benefit to patients based on precise preoperative staging and reduce the substantial morbidity rate of surgery for high-risk patient groups.

## Neoadjuvant chemotherapy

Since the 1990s, neoadjuvant chemotherapy for AGC has been used in clinical practice.<sup>14</sup> A large number of clinical studies on the efficacy of neoadjuvant chemotherapy or different chemotherapeutic regimens have been conducted (Table 2). The MAGIC trial in 2006 was a milestone, which identified the efficacy of neoadjuvant chemotherapy for GC.<sup>4</sup> It is the largest randomized phase III clinical trial to date that has studied the effects of neoadjuvant chemotherapy in gastric and gastroesophageal cancers and included nine centers or hospitals in the UK and several other countries. A total of 503 patients were randomly assigned to surgery alone or surgery plus perioperative

Table 1  
Current clinical indications of neoadjuvant chemotherapy and chemoradiotherapy for gastric cancer.

Guidelines	Neo-chemotherapy			Neo-chemoradiotherapy		
	Stage	Regimen	Evidence	Stage	Regimen	Evidence
NCCN (2018.V2)	$\geq$ cT2, Nany	TX, TC, PFL, XELOX, FOLFOX, FLOT	1	$\geq$ cT2, Nany	TX, TC, PFL, FOLFOX, XELOX, CRT – 45 Gy	2B
JGCA Guideline (5th edition)	Tany, Bulky N	–	–	–	–	–
ESMO (2016)	$>$ T1N0	5-FU and platinum-based	1A	–	–	–
CSCO (2019)	Stage III (T2N3M0, T3N2-3M0, T4aN1-3M0)	ECF (2A), PF (2A), XELOX (2A)	2A	EGJ Stage III (T2N3M0, T3N2-3M0, T4aN1-3M0)	CRT 45–50 Gy (5-FU/platinum-based/Taxol)	1
Korean Practice Guideline (2018)	Not considered for resectable GC	–	Not considered for resectable GC	–	–	–

NCCN: National Comprehensive Cancer Network; JGCA: Japanese Gastric Cancer Association; ESMO: European Society for Medical Oncology; CSCO: Chinese Society of Clinical Oncology; TX: Taxol+ capecitabine; TC: Taxol, cisplatin; PFL: cisplatin, fluorouracil, leucovorin; ECF: epirubicin, cisplatin, fluorouracil; PF: cisplatin, fluorouracil; XELOX: capecitabine, oxaliplatin; FOLFOX: fluorouracil, oxaliplatin. FLOT: docetaxel, oxaliplatin, fluorouracil; EGJ: esophagogastric junction; CRT: Chemoradiotherapy; GC: gastric cancer.

Table 2  
Summary of clinical trials investigating the impact of neoadjuvant chemotherapy for locally advanced gastric cancer.

Author	Studies	Year	Inclusion criteria	Group	Patients	R0 rate (%)	CR rate (%)	OS or median survival time
Ajani et al <sup>50</sup>		1991	Resectable gastric M0 + EGJ cancer	EFP × 2 + surgery + EFP × 3	25	72	0	15 months
Ajani et al <sup>51</sup>		1993	Resectable gastric M0 cancer	EAP × 3 + surgery + EAP × 2	48	90	0	16 months
Rougier et al <sup>52</sup>		1994	Locally advanced gastric cancer M0 + EGJ	FP × 6 + surgery	30	78	0	16 months
Songun et al <sup>14</sup>		1999	T2–4M0	1.FAMTX × 3 + surgery/2.surgery	27/29	75/75	NS	18/30 months
Schuhmacher et al <sup>53</sup>		2001	Locally advanced gastric cancer III–IV (M0) + EGJ	EAP + surgery	42	86	0	19 months
D'Ugo et al <sup>54</sup>		2006	T3–4 Nx M0 or T ≤ 2N + M0	EEP × 3/ ECF × 3 + surgery + EEP × 3/ ECF × 3	34	82	3	>28 months
Cunningham et al <sup>4</sup>	MAGIC	2006	Resectable gastric + EGJ cancer	1. ECF × 3 + surgery + ECF × 3/2. surgery	250/253	74/68	NS	5 years, 36.3% vs. 23.0%, P = 0.009
Tsuburaya et al <sup>16</sup>	JCOG0405	2007	Bulky N2/3	S-1/CDDP × 2 –3 + surgery + D2 + PAND	53	82.4	NS	5 years, 53%
Ychou et al <sup>5</sup>	FNLCC and FFCO	2011	Resectable gastric + EGJ cancer	1. FP × 2–3 + surgery + FP × 3–4/ 2. surgery	113/111	84/73	NS	5 years 38% vs. 24%, P = 0.02
Schuhmacher et al <sup>6</sup>	EORTC	2010	T3–4NxM0	1. PFL × 2/2. surgery	72/72	81.9/66.7	NS	64.62/52.53 months
Kinoshita et al <sup>55</sup>		2009	T2–3/N+ or T4aN0	S-1 × 2 + surgery	55	80.8	0	NS
Biffi et al <sup>56</sup>		2010	T3–4 Nx or Tx N1–3 M0 + EGJ	1. TCF × 4 + surgery/2. surgery	34/35	85	11.7/-	NS
Iwasaki et al <sup>57</sup>	JCOG0210	2013	Resectable gastric cancer	SC × 2 + surgery	36	73.5	NS	17.3 months, 3 years, 24.5%
Yoshikawa et al <sup>15</sup>	COMPASS	2014	T2–3/N+ or T4aN0 + EGJ	1. SC × 2 + surgery/2. SC × 4 + surgery	21/20	NS	NS	NS
Cunningham et al <sup>29</sup>	ST03	2017	Resectable gastric + EGJ + esophageal cancer	1. Bevacizumab + ECX + surgery/2. ECX + surgery	530/533	64/61	NS	33.97 vs. 34.46 months, 3 years, 48.9% vs. 47.6%

(continued on next page)

Table 2 (continued)

Author	Studies	Year	Inclusion criteria	Group	Patients	R0 rate (%)	CR rate (%)	OS or median survival time
Katayama et al <sup>58</sup>	JCOG1002	2013	Bulky N2/3	CDDP/S-1 × 2 -3 + surgery + D2 + PAND	53	84.6	NS	5 years, 55%
Al-Batran et al <sup>59</sup>	FLOT-AIO	2017	cT2-4/cN-any/cM0 or cT-any/cN+/cM0	1. ECF/ECX + surgery/2. FLOT + surgery	360/356	78/85	NS	35/50 months, P = 0.012
Terashima et al <sup>60</sup>	JCOG0501	2019	Resectable gastric cancer	1. Surgery + S1/2. SC × 2 + surgery + S-1	149/151	NS	NS	3 years, 62.4% vs. 60.9%, P = 0.916
	PRODIGY	Ongoing	cT2-3/N(+), T4/N(+/-)	DOS + surgery + S-1 vs. surgery + S-1				

CR: complete response; OS: overall survival; EGI: esophagogastric junction; EEP: etoposide, fluorouracil, cisplatin; PFL: cisplatin, fluorouracil, leucovorin; SC: S-1, cisplatin; TCF: Taxol, cisplatin, fluorouracil; EEP: etoposide, epirubicin, cisplatin; EAP: etoposide, adriamycin, cisplatin; FP: fluorouracil and cisplatin; F: fluorouracil; ECX: epirubicin, cisplatin, capecitabine; TC: Taxol, cisplatin; SC: Systemic chemotherapy; FAMTX: fluorouracil-adriamycin-methotrexate; DOS: docetaxel, oxaliplatin, S-1; CDDP: cisplatin; ECF: epirubicin, cisplatin, fluorouracil; PAND: para-aortic nodes dissection; NS: Not Sure.

chemotherapy with epirubicin, cisplatin, and fluorouracil (ECF); the regimen consisted of three preoperative and three postoperative cycles. The results showed that neoadjuvant chemotherapy significantly increased R0 resection rate (79% vs. 70%) and reduced tumor size (T1/T2 52% vs. 37%) and regional nodal metastases (N0/N1 84% vs. 71%) than surgery alone preoperatively. Furthermore, the perioperative regimen improved overall survival (OS) rate (5-year OS, 36% vs. 23%;  $P = 0.009$ ) and progression-free survival rate compared with surgery alone. In the French FFCD9703 trial, 224 patients were randomly divided into the preoperative group (5-fluorouracil [5-Fu] + cisplatin, 2–3 cycles) and control group (surgery alone).<sup>5</sup> Statistically significant R0 resection rates (84% vs. 73%,  $P = 0.04$ ), improved OS (38% vs. 24%,  $P = 0.02$ ), and improved 5-year disease-free survival (DFS) (34% vs. 19%,  $P = 0.01$ ) were achieved in the neoadjuvant group compared with the surgery alone group.

However, the limitation in both the MAGIC and FFCD9703 trials was that the enrolled patients included those with lower esophageal adenocarcinoma and esophagogastric junction cancer, in which D2 lymph node dissection was only recommended but not the standard operation. Moreover, D2 resection rate was low, which could not prove the value of neoadjuvant chemotherapy in patients who underwent D2 lymph node dissection. To further confirm the efficacy of neoadjuvant chemotherapy alone in patients with GC who underwent D2 lymph node dissection, a European cancer research group conducted studies, such as EORTC 40954 and FLOT. Compared with ECF or epirubicin, cisplatin, and capecitabine (ECX), the FLOT regimen increased the R0 resection rate and improved OS and DFS. These results confirmed that FLOT is efficacious as a novel standard treatment for perioperative therapy of gastric or esophagogastric junction adenocarcinoma.

In 2014, the COMPASS clinical trial from Japan reported that four cycles of S-1/cisplatin or paclitaxel/cisplatin neoadjuvant chemotherapy regimen could achieve 10% of the postoperative pathological complete response (pCR) rate without significant increase in drug toxicity.<sup>15</sup> For patients with distal lymph node metastasis, Japanese studies suggest that preoperative adjuvant chemotherapy combined with surgery could be better than surgery alone. The JCOG 0405 study enrolled 53 patients with AGC and completed a 5-year follow-up.<sup>16</sup> The neoadjuvant chemotherapy consisted of two cycles of S-1 plus cisplatin, which was followed by D2 gastrectomy plus para-aortic lymph node dissection. Eventually, R0 resection rate reached 82%, and the 3- and 5-

year OS rates were 59 and 53%, respectively. The study suggests that D2 resection combined with para-aortic lymph node dissection after preoperative S-1 plus cisplatin for patients with AGC with distant lymph node metastasis is effective and safe. To further explore the efficacy of preoperative targeted therapy and three-drug regimen for patients with extensive lymph node metastasis, JCOG 1301 and JCOG 1002 studies were launched based on JCOG 0405 in Japan.

The abovementioned studies confirmed that neoadjuvant chemotherapy has a significant downstaging pathological effect, increasing the R0 resection rate and improving the 5-year OS rate. Moreover, there was no significant difference between the neoadjuvant chemotherapy group and surgery alone group with regard to postoperative complications, mortality, and length of hospital stay. Recently, meta-analysis and systematic reviews of neoadjuvant chemotherapy have also shown that neoadjuvant chemotherapy can significantly improve the survival and R0 resection rates of patients. Moreover, patients with esophagogastric junction cancers benefit more from neoadjuvant chemotherapy. As for the neoadjuvant chemotherapy regimens, the classic MAGIC trial and subsequent high-level evidence gradually established the standard two- or three-drug regimen based on fluorouracil and cisplatin. Capecitabine, docetaxel, oxaliplatin, and S-1 also can be incorporated in neoadjuvant chemotherapy.

Regarding the effect of preoperative chemotherapy cycle on efficacy, most related clinical trials generally recommended 2–4 cycles. Recently, a phase III study of preoperative chemotherapy for GC compared the pathological response rate between patients with two or four cycles using docetaxel + cisplatin or S-1 + cisplatin.<sup>17</sup> The results suggested that complete response was noted only in the group with four cycles, and there was no association with the regimens. In contrast, some researchers hold a view that patients with four cycles of preoperative chemotherapy have a higher nutritional risk. Despite significant advances in neoadjuvant chemotherapy in the past few decades, so far, there is insufficient high-level evidence to support the contention that patients can achieve survival benefits from neoadjuvant chemotherapy combined with D2 radical gastrectomy.<sup>5,6,18–20</sup> Patient selection for personalized therapy and optimal tolerated neoadjuvant regimens and cycles are other important issues to be addressed.

### Neoadjuvant chemoradiotherapy

In 2001, the efficacy and advantages of adjuvant chemoradiotherapy were demonstrated by the INT0116 trial,

and the neoadjuvant approach used in other aggressive malignancies has prompted the transfer to the application of neoadjuvant chemoradiotherapy in GC.<sup>18</sup> The preliminary phase II clinical study showed that 63% of patients receiving preoperative radiotherapy and chemotherapy (fluorouracil + 45 Gy/5 weeks) achieved pCR and 83% of patients underwent D2 radical surgery.<sup>19</sup> In 2006, Ajani retrospectively analyzed and found that, in most randomized controlled studies, combined radiotherapy (35–37.5 Gy/4–5 weeks + 5-Fu) in patients with locally AGC significantly improved survival compared with radiotherapy alone.<sup>20</sup> Many studies have also confirmed the survival benefits of preoperative radiotherapy and chemotherapy in patients with AGC (Table 3). In the German POET studies published in 2009, patients were randomly divided into neoadjuvant chemotherapy with surgery group and neoadjuvant chemoradiotherapy with surgery group.<sup>21</sup> The results showed that neoadjuvant chemoradiotherapy significantly increased the 3-year OS rate (47.4% vs. 27.7%,  $P = 0.07$ ) and pCR rate (15.6% vs. 2.0%,  $P = 0.03$ ). It confirmed that the efficacy of preoperative chemoradiotherapy was better than that of chemotherapy alone. The radiotherapy regimens of the follow-up studies included mainly cisplatin or paclitaxel or three-drug regimens based on fluorouracil. A series of studies conducted in MD Anderson Cancer Center showed that neoadjuvant chemoradiotherapy improves not only the postoperative pCR rate and R0 resection rate but also the tumor stage reduction rate.<sup>22–24</sup> The RTOG 9904 study showed similar results: 77% of patients received R0 radical treatment, and 27% achieved pCR.<sup>23</sup> Similar results were observed in the recent Dutch phase I/II CROSS, which included 25 patients with locally AGC who received preoperative radiotherapy of 45 Gy and capecitabine + paclitaxel chemotherapy.<sup>25</sup> In this study, the R0 resection rate was 72%, and the pCR rate was 16%.

The abovementioned studies initially confirmed that, in patients with AGC, preoperative synchronous neoadjuvant chemoradiotherapy can not only improve the R0 resection rate but also reduce distant metastasis and recurrence rate and improve survival of patients by degrading primary tumor stage, especially those with pCR. Importantly, this therapeutic strategy is safe and tolerable. This is further confirmed by the Australian TOPGEAR study in 2018.<sup>25</sup> It also indicated that patients receiving neoadjuvant chemoradiotherapy had significantly improved survival benefit compared with patients who underwent surgery alone.<sup>26</sup> Preoperative chemoradiotherapy is also recommended for advanced gastroesophageal junction cancer in the NCCN guidelines. The current evidence is mostly based on the

Table 3  
Summary of clinical trials investigating impact of neoadjuvant chemoradiotherapy for locally advanced gastric cancer.

Author	Studies	Year	Inclusion criteria	Group	Patients	R0 rate (%)	CR rate (%)	OS or median survival time
Shchepotin et al <sup>61</sup>		1994	Resectable gastric cancer	1. Surgery/ 2. 20 Gy EBRT/ 3. 20 Gy EBRT + Hy	98/100/95	NS	NS	5 years, 21% vs. NS vs. NS
Safran et al <sup>62</sup>		1997	Unresectable gastric cancer	45 Gy EBRT + paclitaxel	27	NS	11	2 years, 35% vs. NS
Lowy et al <sup>19</sup>	INT0116	2001	T > 2, N±, M0	45 Gy EBRT, 5-FU	24	75	11	NS
Ajani et al <sup>22</sup>		2004	T > 2, N±	5-FU, LV, P + 45 Gy EBRT, 5-FU	33	70	30	34 months
Ajani et al <sup>20</sup>		2005	Resectable gastric + EGJ cancer	FP, paclitaxel + 45 Gy EBRT	41	78	20	>36 months
Allal et al <sup>63</sup>		2005	T3-T4, N+	FP, LV + 31.2–45.6 Gy EBRT	19	NS	5	NS
Stahl et al <sup>7</sup>	POET trial	2009	EGJ	1. PFL × 3 + 30 Gy + cisplatin/surgery/ 2. PFL × 2 + surgery	62/64	72/69	15.6/2	33.1/21.1 months
Van Hagen et al <sup>8</sup>	CROSS trial	2012	Esophageal cancer + EGJ cancer	1. Paclitaxel + carboplatin + 41.1 Gy + surgery/ 2. surgery	178/188	92/69	NS	49.9/24 months
Cats A et al <sup>25</sup>	TOPGEAR	2018	Resectable gastric cancer	ECF + surgery vs. ECF + 45 Gy + surgery	393/395	80/82	6	43/37 months, <i>P</i> = 0.9; 5 years, 42% vs. 40%
	Neo-Aegis	Ongoing	Esophageal cancer + EGJ cancer	ECF × 3 + surgery vs. Paclitaxel + carboplatin + 41.1 Gy	620			
	CRITICS-2	Ongoing	Resectable gastric + EGJ cancer	DOS × 3 weeks (45 Gy in 1.8 Gy + surgery vs. DOS × 3 + surgery	540			
	NEO-CRAG	Ongoing	Resectable gastric + EGJ cancer	RT (45 Gy)+ XELOX × 3 + surgery + XELOX × 3 vs. XELOX × 3 + surgery + XELOX	632			
	PREACT	Ongoing	Resectable gastric + EGJ cancer	SOX × 1 + CRT (45 Gy/ S1) + SOX × 1 + surgery + SOX × 3 vs. SOX × 3 + surgery + SOX × 3				

CR: complete response; OS: overall survival; EBRT: external beam radiotherapy; IORT: intraoperative radiation therapy; CRT: Chemoradiotherapy; Hy: hyperthermia; FP: fluorouracil and cisplatin; PFL: cisplatin, fluorouracil, leucovorin; LV: leucovorin; DOS: docetaxel, oxaliplatin, S-1; ECF: epirubicin, cisplatin, fluorouracil; XELOX: capecitabine and oxaliplatin; SOX: S-1 and Oxaliplatin; NS: Not Sure.

findings of gastroesophageal junction tumors, and clinical guidance value of neoadjuvant chemoradiotherapy for distal GC is limited. Furthermore, it has not been included in the guidelines of the JGCA, CSCO, etc. Because distal GC is more common in Asian countries, we expect the advent of more large-scale phase III clinical trials on the treatment of distal GC.

### Targeted drugs in neoadjuvant therapy

In addition to traditional chemotherapeutic regimen, targeted drugs are also incorporated in neoadjuvant therapy. For human epidermal growth factor receptor 2 (HER2)-positive locally progressive GC, current phase II clinical studies have shown that trastuzumab combined with chemotherapy is highly effective.<sup>27</sup> Neoadjuvant targeted therapy for GC with different regimens have emerged: trastuzumab (anti-HER2), ramucirumab and apatinib (anti-vascular endothelial growth factor 2), cetuximab (anti-epidermal growth factor receptor), and some targeted miRNAs have shown an important role in tumor proliferation, invasion, and metastasis recently (Table 4).

The German HER-FLOT study reported in the 2014 American Society of Clinical Oncology (ASCO) conference showed that four cycles of trastuzumab combined with FLOT neoadjuvant chemotherapy resulted in an R0 resection rate of 93%, and 23% of patients achieved pCR.<sup>28</sup> The Spanish NEOHX study reported in the 2015 ASCO meeting revealed that trastuzumab combined with XELOX regimen for resectable GC or gastroesophageal junction cancer achieved an objective response rate of 39% and pCR of 8%. However, large-scale phase III randomized controlled studies are still needed to confirm the efficacy. The ST03 study published in 2017 is a comparative study on ECX combined with bevacizumab in resectable GC, esophagogastric junction cancer, and esophageal cancer.<sup>29</sup> A total of 1063 patients (530, bevacizumab combined with ECX; 533, ECX) were enrolled in this study. There was no significant difference in 3-year OS (48.1% vs. 50.3%) and DFS rates between the combined bevacizumab group and control group. The incidence of anastomotic leakage was higher in the bevacizumab group. This study revealed that increasing bevacizumab dose did not improve patient survival.

A newly completed clinical trial demonstrated that trastuzumab significantly improved the survival of HER2(+) patients with AGC, which was consistent with the ToGA trial.<sup>30</sup> Additionally, there are several ongoing clinical trials, such as JCOG 1301 (S-1 + cisplatin + trastuzumab), that analyzed the efficacy

Table 4  
Summary of clinical trials investigating targeted drugs of neoadjuvant chemotherapy for locally advanced gastric cancer.

Studies	Year	Inclusion criteria	Group	Patients	R0 rate (%)	CR rate (%)	OS or median survival time
HER-FLOT	2014	uT2–4,N+,M0	HER-FLOT	52	NS	23%	NS
NEOHX	2015	T1–2N + M0 or T3–4NxM0	XELOX-T	36	NS	8	NS
STO-080 <sup>64</sup>	2017	Locally advanced gastric cancer + EGJ	Panitumumab + ECX 3 vs. ECX 3	83/80	84%/82%	NS	10.3 vs. 9.6, HR = 1.17, P = 0.43
ST03 <sup>65</sup>	2017	Resectable lower esophageal, EGJ, or gastric cancer	ECX 3 vs. bevacizumab + ECX 3	530/533	64/61	NS	33.97 vs. 34.46, HR = 1.067, P = 0.4784, 3 years, 48.9% vs. 47.6%
FLOT6	Ongoing	T 2–4 any N, M0 OR any T N + M0	FLOT vs. FLOT + pertuzumab + trastuzumab				
INNOVATION	Ongoing	HER2 + resectable gastric and GEJ cancer	Chemotherapy vs chemotherapy + trastuzumab				
PERIHER	Ongoing	T2N2–3, T3/T4N+, T4bN any, M0	XELOX vs. XELOX + trastuzumab				
Trigger	Ongoing	Extensive lymph node metastasis	SP vs. SP + trastuzumab				
NCT03229096	Ongoing	T3–4 N any M0	SOX vs. SOX + trastuzumab				
NCT03192735	Ongoing	Locally advanced gastric cancer	Apatinib plus XELOX				
NCT03599778	Ongoing	Locally advanced gastric adenocarcinoma	Apatinib				
NCT03355612	Ongoing	Locally advanced gastric signet ring carcinoma	Apatinib vs. XELOX				
NCT03878472	Ongoing	Resectable gastric cancer	Camrelizumab vs. apatinib vs. S1				

ECX: epirubicin, cisplatin, capecitabine; XELOX: capecitabine and oxaliplatin. FLOT: docetaxel, fluorouracil, SP: S-1, cisplatin; SOX: S-1 and Oxaliplatin; NS: not sure.

of neoadjuvant chemotherapy combined with targeted drug therapy for HER2(+) GC. Although early prediction of chemosensitivity and prognosis by molecular biology is challenging, neoadjuvant chemotherapy combined with targeted therapy has great potential as a new therapeutic regimen in the future.

### Efficacy prediction and evaluation

Evaluation of efficacy of neoadjuvant chemotherapy and timely adjustment of treatment strategies play an important role in improving the overall treatment effect of patients with GC. Chiari et al<sup>31</sup> suggested prediction of sensitivity of neoadjuvant chemotherapeutic regimens by gene testing, such as HER2 and EGFR. Other studies, with serum anti-survivin and systemic immunoinflammatory index as predictive factors, also lack sufficient evidence.<sup>32,33</sup> So far, prediction of efficacy of neoadjuvant regimens by molecular markers has not yet been fully recognized.

Anatomical imaging evaluation, including computed tomography (CT), magnetic resonance imaging, endoscopy, and ultrasound, is the main method of determining the efficacy of neoadjuvant therapy. Generally, the Response Evaluation Criteria in Solid Tumors (RECIST), based on CT, is used to calculate the length of lesion before and after treatment to evaluate the degree of response.<sup>34</sup> However, with shrinkage and fibrosis of the tumor, the accuracy of TNM staging by CT decreases. The accuracy of T staging decreased to 57% and N staging to 37%.<sup>35</sup> With the development of endoscopic technology, endoscopic ultrasound (EUS) has received increasing attention. Redondo et al<sup>36</sup> believe that EUS has advantages over CT and positron emission tomography, especially in T1-T2 stage.

The most accurate evaluation criterion for neoadjuvant chemotherapy is pathological evaluation, which is usually in accordance with tumor regression grading (TRG). However, some studies found that TRG has no predictive value for postoperative long-term survival, and the predictive effect of pCR rate is not as good as that of lymph node metastasis rate.<sup>37,38</sup> Furthermore, in the latest 8th edition of the American Cancer Association guidelines for GC, post-neoadjuvant therapy pathological staging has been added. On one hand, neoadjuvant chemotherapy is gradually being adopted as a new treatment concept; on the other hand, the evaluation criteria are further completed, and then neoadjuvant chemotherapy will have an independent evaluation standard so as to avoid confusion of clinical staging previously used.

### Current problems and future prospective

There are significant differences in treatment strategies for GC being implemented in Asian and European countries. Neoadjuvant chemotherapy has become the standard mode of treatment of GC in America and European countries. The reason for the differing treatment strategies is mainly that GC is usually detected at an earlier stage in Asian countries, such as Korea and Japan, due to the national screening programs for GC. The therapeutic efficacy of oral regimens also differs between Asian and European populations.<sup>39,40</sup> S-1 is safe and effective in the treatment of GC in the Asian population. Due to differences in CYP2A6 gene polymorphism in Asian, European, and American populations, S-1 is difficult to promote in European and American countries.<sup>41</sup>

Scholars who oppose neoadjuvant therapy for GC believe that neoadjuvant chemotherapy only makes up for the lack of extent of lymphadenectomy.<sup>4,21</sup> The EORTC 40954 trial also supports this view, and neoadjuvant therapy is more beneficial for patients with insufficient lymph node dissection.<sup>6</sup> In the ACTS-GC clinical trial of adjuvant chemotherapy with an oral regimen for GC in the Asian population, the efficacy of surgery combined with chemotherapy was better than that of surgery alone for patients with GC undergoing total D2 lymph node dissection.<sup>42</sup>

Clinical trials, such as CROSS, confirmed the role of neoadjuvant radiotherapy and chemotherapy in esophagogastric junction cancer. The difference in tumor location and tumor biological behavior is crucial for the conclusion of clinical trials. The proportion of esophagogastric junction cancer in Asia is relatively lower than that in Europe and America.<sup>43–45</sup> Meta-analyses and retrospective studies showed that patients with esophagogastric junction cancer were more likely to benefit from neoadjuvant therapy.<sup>46,47</sup>

Although studies have suggested that neoadjuvant chemotherapy does not tend to increase perioperative risk, the related risks showed a higher trend compared with surgery alone. The conundrum is that neoadjuvant chemotherapy may delay surgery in patients who are not sensitive to chemotherapy, and remedial strategies are limited for these patients.<sup>48,49</sup> This could explain why the 5-year survival rate did not improve in these studies.

Additionally, many issues regarding neoadjuvant therapy for GC should be addressed, such as indications for patients from different regions, chemotherapeutic regimens, treatment cycles, extent of surgery after neoadjuvant chemotherapy, and



significance of perioperative radiotherapy. All these issues necessitate clarification with clinical research. Exploration and optimization of precision therapy, selection and review of personalized therapy, efficacy evaluation, and timely adjustment of treatment strategy are other important issues to be addressed.

Recently, immune checkpoint inhibitors, such as PD-1/PD-L1 and CTLA-4, have demonstrated innovative progression in cancer therapy. However, so far, anti-PD-1 therapy failed to show benefit in phase III trials, and few ongoing clinical trials on GC, including immunotherapy, showed promising results in improving clinical outcomes, safety, and tolerability. In 2017, pembrolizumab became the first immunotherapy agent approved to treat stomach cancer in some patients whose treatment did not work or stopped working ( $\geq 2$  lines). Ongoing randomized trials will be expected to confirm immunotherapy as a validated therapeutic option for AGC, especially in neoadjuvant and earlier-line strategy.

## Conclusion

Presently, some consensus has been reached on the treatment mode of AGC, and postoperative adjuvant therapy combined with surgery is deemed better than surgery alone. Neoadjuvant chemoradiotherapy is superior to surgery alone in esophagogastric junction cancer. However, there are still several issues worth exploring further, such as evaluation of efficacy of neoadjuvant chemoradiotherapy and the role of targeted and immunological therapies. More well-designed and high-quality clinical trials are needed to validate the significance and efficacy of neoadjuvant therapy for GC in greater detail.

## Conflicts of interest

None.

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