Progress in neoadjuvant therapy for gastric cancer (Review)

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Abstract. Gastric cancer is one of the most common malignant tumor types in the world and the majority of patients have already reached the advanced stage at the time of initial diagnosis, owing to the subtle symptoms of gastric cancer in the early stage and the low rate of screening in the population. Surgical resection is one of the main treatments for advanced gastric cancer; however, the efficacy of surgery is limited by factors such as low radical resection rate and high distant metastasis rate. A large number of clinical trials have indicated that neoadjuvant therapy (NAT), which consists of neoadjuvant chemotherapy, neoadjuvant chemoradiotherapy and NAT combined with targeted therapy, may improve the therapeutic effect and prognosis of patients to different degrees. However, the benefit of NAT remains controversial due to the heterogeneity of clinical trials and gastric cancer itself. The present review summarizes the main research progress and key breakthrough of NAT for advanced gastric cancer and discusses its prospects.

Contents

1. Introduction

Although its incidence exhibits a downward trend as a whole, gastric cancer remains a globally common malignancy, ranking fifth in terms of frequency of diagnosis and third as the cause of cancer-related death worldwide (1). Early gastric cancer may be cured by surgery, but the majority of patients have already reached the advanced stage at the initial visit. R0 resection is the only treatment that may achieve a clinical cure for advanced gastric cancer; however, the low R0 resection rate, postoperative recurrence and distant metastasis are the main causes of poor prognosis of patients (2). Therefore, improving the R0 resection rate and reducing postoperative recurrence and distant metastasis, thus prolonging the survival and improving the prognosis of patients with advanced gastric cancer, are the focal points of gastric cancer therapy (3).

In recent years, the application of neoadjuvant therapy (NAT) in gastric cancer has become increasingly common. It aims at shrinking primary tumors and eliminating microscopic metastatic lesions, so as to achieve the purpose of degrading the staging and improving the R0 resection rate. There are still controversies regarding the selection and efficacy evaluation of NAT for advanced gastric cancer (4). Newton *et al* (5) have summarized the existing strategies and outlined a future direction for the development of NAT for gastric cancer and illustrated the benefits of NAT in the management of gastrointestinal malignancies to a certain extent. However, progress regarding NAT combined with targeted therapy and the prediction and assessment of therapeutic effects of NAT required further discussion. The present article reviewed the main research progress and key breakthroughs of NAT, including neoadjuvant chemotherapy (NACT), neoadjuvant chemoradiotherapy (NACRT) and NAT combined with targeted therapy for gastric cancer. Furthermore, it elaborated on the prediction and assessment of therapeutic effects and discussed the prospects of these therapeutic patterns.

2. NACT for gastric cancer

NACT drugs and regimens. NACT is also known as preoperative chemotherapy; the commonly used drugs are mainly based on the experience of postoperative chemotherapy, including cis-platinum (CDDP), oxaliplatin (OXA), 5-fluorouracil (5-FU), capecitabine (ECX), paclitaxel (PTX) and docetaxel (DTX). In 1993, the Dutch Gastric Cancer Group performed a randomized controlled clinical trial of NACT for gastric cancer to verify whether the preoperative chemotherapy regimen consisting of 5-FU, doxorubicin and methotrexate is able to improve the R0 resection rate; however, the result indicated that patients did not benefit from this regimen (6).

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During the subsequent long-term follow-up, this preoperative chemotherapy regimen was observed to neither prolong the median survival time nor improve the 5-year survival rate, and it was determined that the high toxicity and low efficacy of this regimen were the main reasons for the disappointing result (7). Therefore, researchers paid increasing attention to the toxicity and efficacy of regimens and their tolerability by patients in the subsequent studies.

In 2006, the UK Medical Research Council published the results of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial, a phase III clinical study of NACT for gastric cancer. As compared with the surgery alone group, the perioperative chemotherapy group, which adopted ECF as the regimen, consisting of epirubicin (EPI), CDDP and 5-FU, exhibited a significantly improved R0 resection rate (79.3 vs. 70.3%, P=0.03) and 5-year survival rate (36.3 vs. 23.0%, P=0.009) (8). In spite of certain hematologic adverse effects, such as granulocytopenia, lymphocytopenia, leukopenia and thrombocytopenia, and certain nonhematologic adverse events, such as nausea, emesis and stomatitis, the MAGIC trial was still a milestone in the development of NACT for gastric cancer, and the ECF regimen was at once adopted as a category 1 recommended scheme in the NCCN guidelines and became the standard chemotherapy regimen for perioperative therapy for gastric cancer. Over the next several years, only a small number of regimens were able to achieve results comparable to those of the MAGIC trial. Even though the European Organization for Research and Treatment of Cancer (EORTC) published the result of the EORTC 40,954 trial in 2010 that the preoperative PFL regimen, which consisted of CDDP, 5-FU and leucovorin (LV), was able to improve the R0 resection rate (81.9 vs. 66.7%, P=0.036), it failed to significantly prolong the median survival time of patients [64.6 vs. 54.5 months (mo), P=0.466] (9). This situation was changed in 2011, when the result of a large multi-center phase III clinical study, FNCLCC/FFCD 9,703, was published. The result indicated that the perioperative FC regimen, consisting of FU and CDDP, significantly enhanced the R0 resection rate (84 vs. 74%, P=0.04) and 5-year survival rate (38 vs. 24%, P=0.02). The regimen not only benefited patients' survival but also had lower toxicity (grade 3 to 4 toxicity, mainly neutropenia, occurred in 38% of patients) compared with the ECF regimen in the MAGIC trial and was adopted as a category 1 recommended scheme in the National Comprehensive Cancer Network (NCCN) guidelines later (10,11). The results led to the use of NACT for gastric cancer in Europe. However, just as for the MAGIC trial, the limitation of the FNCLCC/FFCD 9,703 trial was that the recruited patients included those with gastroesophageal and lower esophageal adenocarcinoma, in whom the D2 resection rate was low and the assessment of the efficacy of NACT was influenced to a certain extent.

With the development of NACT for gastric cancer, researchers worked to further improve the efficacy of NACT. In the German FLOT4 study, Al-Batran *et al* (12) compared the efficacy of the perioperative FLOT regimen (FU, LV, OXA, DTX) and the ECF/ECX regimen (EPI, CDDP, FU/ECX). The results of the phase II study suggested that the FLOT regimen achieved a higher R0 resection rate (85 vs. 74%, P=0.02) and tumor reduction rate (≤ypT2, 44 vs. 27%, P=0.01) compared with the ECF/ECX regimen, but the rates of grade 3/4 neutropenia, diarrhea and neurotoxic effects were also higher (12). Furthermore, a phase III study illustrated that the FLOT regimen further prolonged overall survival (50 vs. 35 mo, P=0.012) (13). In addition, with the accumulation of data related to the efficacy and safety of NACT and the increasing number of reports of adverse drug reactions to chemotherapy regimens containing anthracyclines, the ECF/ECX regimen was gradually removed from the NCCN guidelines and the FLOT regimen was adopted as a category 1 recommended scheme (10,14). Of note, its methodology is not immune from the criticism that the inclusion criteria do not rule out gastroesophageal carcinoma, which has a D2 lymphadenectomy rate of just >50%.

Asia, particularly East Asia, has a high incidence of gastric cancer. Thus, it is important to focus on the research progress on NACT for patients with gastric cancer in these areas. In 2012, Chinese researchers published the result of one prospective nonrandomized controlled trial for NACT, indicating that patients who received the preoperative FOLFOX regimen (FU, LV, OXA) and surgical treatment followed by the postoperative FOLFOX regimen had a higher 4-year survival rate (78 vs. 51%, P=0.031) and disease-free survival rate (78 vs. 48%, P=0.022) (15). In addition, the most common side effect was grade 1-2 leukopenia and there were no grade 3 neuropathies, grade 4 cytopenia or treatment-related death. However, a randomized trial may further enhance the credibility of this conclusion. In Japan, a phase II clinical trial verified the safety and efficacy of the SC regimen comprising S-1 and CDDP, which, as a preoperative regimen, achieved an R0 resection rate of 87.8% and a 4-year survival rate of 48% in patients with stage II and stage III gastric cancer (16). Based on this, another phase III clinical trial performed by the Japan Clinical Oncology Group further confirmed the efficacy of the SC regimen and indicated that the major grade 3 or greater toxicities were neutropenia (29.3%), anorexia (11.6%), leukocytes (7.5%) and nausea (5.4%). This preoperative chemotherapy regimen achieved an R0 resection rate of 80.6% for type 4 and large type 3 gastric cancer; however, patients who received NAC followed by gastrectomy and adjuvant chemotherapy obtained no benefit in terms of the 3-year survival rate compared with those who received gastrectomy plus adjuvant chemotherapy (60.9 vs. 62.4%, P=0.284) (17). The docetaxel-containing regimens were considered the standard according to the result of the FLOT4 study (11,12). However, docetaxel was not included in the previous studies (15-17), and whether adding docetaxel enhances the efficacy and improves the prognosis should be further evaluated. The RESOLVE study, performed by Peking University, was the largest phase III clinical trial for comparing NACT with postoperative adjuvant chemotherapy for gastric cancer. The latest study suggested that the perioperative SOX regimen (S-1, OXA) significantly improved the 3-year disease-free survival rate when compared with the postoperative XELOX regimen (ECX, OXA) (59.4 vs. 51.1%, P=0.028) and the postoperative SOX regimen was not inferior to XELOX (18).

Based on the research progress on NACT for gastric cancer (Table I), it may be concluded that different NACT regimens may improve the R0 resection rate and the prognosis of patients with gastric cancer to various degrees. However, owing to differences among regions and in completion rates

Table I. Key studies on neoadjuvant chemotherapy for gastric cancer.

Study or author (year)	Groups	Patients	R0 rate	DFS	OS or MST	(Refs.)
FAMTX	FAMT x 3 + surgery;	27;	56 vs. 62%,	NA;	5-year OS rate: 21% vs. 34%,	(6,7)
	surgery alone	29	P: NA	NA	P=0.17	
MAGIC	ECF x 3 + surgery + ECF x 3;	250;	69.3 vs. 66.4%,	NA;	5-year OS rate: 36.3 vs. 23%,	(8)
	surgery alone	253	P: NA	NA	P=0.009	
EORTC 40954	PFL x 2;	72;	81.9 vs. 66.7%,	NA;	MST: 64.6 vs. 52.5 mo,	(9)
	surgery alone	72	P=0.036	NA	P=0.466	
FFCD 9703	FC x 2-3 + surgery + FC x 3-4;	113;	84 vs. 73%,	5-year DFS rate: 34 vs. 19%,	5-year OS rate: 38 vs. 24%,	(11)
	surgery alone	111	P=0.04	P=0.003	P=0.02	
FLOT 4-AIO	FLOT x 4 + surgery + FLOT x 4;	356;	85 vs. 78%,	Median DFS: 30 vs. 18 mo,	Median OS: 50 vs. 35 mo,	(12,13)
	ECF/ECX x 3 + surgery + ECF/ECX x 3	360	P=0.0162	P=0.0036	P=0.012	
Li (2012)	FOLFOX x 2-4 + surgery + FOLFOX x 2-4;	36;	86 vs. 55%,	4-year DFS rate: 78 vs. 48%,	5-year OS rate: 78 vs. 51%,	(15)
	surgery + FOLFOX x 6	37	P=0.011	P=0.022	P=0.031	
Kochi (2017)	SC x 2 + surgery + S-1	50	87.8%	3-year DFS rate: 44.9%	3-year OS rate: 48%	(16)
Terashima (2019)	SC x 2 + surgery + S-1;	151;	80.6 vs. 72.1%,	NA	3-year OS rate: 60.9 vs. 62.4%,	(17)
	surgery + S-1	149	P: NA	NA	P=0.284	
RESOLVE	i) SOX x 3 + surgery + SOX x 5+ S-1;	337;	92.9 vs. 87.8	3-year DFS rate:	NA	(18)
	ii) Surgery + SOX x 8;	340;	vs. 86.4%,	i) 59.4% vs. iii) 51.1%, P=0.03;		
	iii) Surgery + XELOX x 8	345	P: NA	ii) 56.5% vs. iii) 51.1%, P=0.17		

FAMTX, 5-fluorouracil + doxorubicin + methotrexate; ECF, epirubicin + cisplatinum + 5-fluorouracil; PFL, cisplatinum + 5-fluorouracil + leucovorin; FC, 5-fluorouracil + cisplatinum; FLOT, 5-fluorouracil + leucovorin + oxaliplatin + docetaxel; FOLFOX, 5-fluorouracil + oxaliplatin + leucovorin; SC, S-1 + cisplatinum; SOX, S-1 + oxaliplatin; XELOX, capecitabine + oxaliplatin; NA, not available; DFS, disease-free survival; OS, overall survival; MST, median survival time; mo, month; NA, not available.

of perioperative chemotherapy and surgical resection, there has not yet been a NACT regimen with overwhelming advantages and suitability for all patients. With the accumulation of data from clinical trials such as the classic MAGIC study, the FNCLCC/FFCD9703 study and the FLOT4 study, the two-drug regimen or multi-drug regimen based on fluorouracil and platinum have demonstrated their advantages and achieved good efficacy in clinical practice. Furthermore, research to optimize the NACT regimen has been underway.

Indications for NACT. The surgical cure rate of early gastric cancer is as high as 90% and the main purpose of NACT is to improve the R0 resection rate and the prognosis of patients; therefore, the majority of clinical studies on NACT for gastric cancer included patients with advanced gastric cancer (≥cT2 N0-3 M0). Based on the results of the MAGIC study and the FNCLCC/FFCD9703 study, the European Society for Medical Oncology recommended NACT for patients with potentially resectable advanced gastric cancer with clinical stage ≥T2 (19). Correspondingly, the NCCN guidelines recommended NACT as the primary therapy for resectable advanced gastric cancer with clinical stage T2-4N0-3M0 (14). In 2021, the Chinese Society of Clinical Oncology (CSCO) included patients with non-esophagogastric junction gastric cancer, whose clinical stage was T3-4aN1-3M0, as the suitable population for NACT and the SOX regimen was adopted as a recommended scheme for grade 1 (20). However, the Japanese Gastric Cancer (JGCA) treatment guidelines just recommended NACT with low-grade evidence for patients with late-stage or poor prognosis, rather than adopting NACT as a conventional therapeutic regimen (21). There is no uniform standard for the indications of NACT for gastric cancer and further research is required to combine reasonable indications with accurate preoperative staging and provide personalized and precise treatment for patients with gastric cancer, so as to maximize the benefit for these patients.

Therapeutic cycles of NACT. The majority of clinical studies in Japan recommended 2 cycles of NACT for gastric cancer (16,17). The classic MAGIC study and the FNCLCC/FFCD9703 study adopted 3 cycles of NACT and the RESOLVE study adopted 3 cycles of the chemotherapeutic SOX regimen prior to surgery, while 4 cycles of the FLOT regimen were recommended in the FLOT4 study (8,11,13,18). Therefore, there is currently no uniform standard for the cycles of NACT for gastric cancer. The COMPASS study (22) was performed to compare the efficacy of NACT with 2 and 4 cycles of the SC (S-1, CDDP) and PC (PTX, CDDP) regimens for potentially resectable advanced gastric cancer by a two-by-two factorial design. The 3-year overall survival rate was 60.9 and 64.3% in the SC arm and PC arm (P=0.921), and 64.3 and 61.0% in the 2-cycles arm and 4-cycles arm, respectively (P=0.700). Furthermore, the 3-year survival rate of the groups with 2 and 4 cycles of the SC regimen was 67 and 55%, respectively, and the proportion was 67 and 62% for the PC regimen, while there were no significant intergroup differences. The OE05 study indicated that NACT with 4 cycles of the ECF regimen failed to benefit patients compared with more than 2 cycles of the FC regimen; on the contrary, 4 cycles of the ECF regimen were associated with more toxicity and adverse reactions to the chemotherapy (10). The optimal duration of NACT requires a higher level of evidence to verify; in addition, timely and accurate clinical staging and evaluation after NACT are particularly necessary and the selection of the cycles of NACT requires to be balanced between ensuring the efficacy of preoperative chemotherapy and seizing the best time-point for surgery.

3. NACRT for gastric cancer

Macdonald *et al* (23) performed the INT 0116 study to compare the effectiveness of surgery combined with postoperative chemoradiotherapy with surgery alone for gastric or gastroesophageal cancer. The result indicated that postoperative chemoradiotherapy was able to significantly improve the median survival time of patients (36 vs. 27 mo, P=0.005). The result of the ARTIST study suggested that postoperative chemoradiotherapy significantly improved the 3-year disease-free survival rate compared with postoperative chemotherapy for gastric cancer with lymphatic metastasis (77.5 vs. 72.3%, P=0.036) (24). Regarding the effectiveness of postoperative chemoradiotherapy, research studies for NACRT have been gradually performed and certain achievements have been obtained.

In 2009, the POET study, a phase III clinical trial, drew the conclusion that NACRT achieved a higher 3-year survival rate (47.4 vs. 27.7%, P=0.07) and 5-year survival rate (39.5 vs. 24.4%, P=0.055) than NACT for gastroesophageal adenocarcinoma; although the difference was not statistically significant, NACRT still demonstrated a tendency to prolong the survival (25,26). Klevebro *et al* (27) performed a multi-center phase II clinical trial to further verify the advantage of NACRT over NACT. This study included patients with resectable esophagogastric junction or esophageal cancer. Although there was no significant difference in the 3-year survival rate (49 vs. 47%, P=0.77), the R0 resection rate reached 87% after NACRT, vs. 74% after NACT (P=0.04), and the lymphatic metastasis rate was lower in the NACRT group (35 vs. 62%, P=0.001). Furthermore, the result of the CROSS trial illustrated that NACRT combined with surgery markedly improved the R0 resection rate (92 vs. 69%, P<0.001) and median survival time (49.4 vs. 24.0 mo, P=0.003) for patients with resectable esophagogastric junction or esophageal cancer compared with surgery alone, and 8% of patients who received NARCT experienced grade 3 or worse haematological toxicity and 11% had grade 3 or worse non-haematological toxicity. In addition, subgroup analysis indicated that patients with squamous carcinoma achieved a markedly longer median survival time (81.6 vs. 21.1 mo, P=0.008) (28,29). However, the above studies (Table II) mainly included patients with esophagogastric junction or esophageal cancer rather than non-esophagogastric junction gastric cancer and the information from evidence-based medicine for NACRT was mainly derived from the clinical trial of NACRT for patients with esophagogastric junction or esophageal cancer. Prospective randomized phase III clinical trials for resectable gastric cancer (except for gastroesophageal cancer) to verify the role of NACRT are still lacking. The latest NCCN guidelines recommended NACRT for resectable advanced gastric cancer with category IIB evidence and the CSCO guidelines only included

Table II. Key studies on (neo-)adjuvant chemoradiotherapy for gastric cancer.

Study or author (year)	Groups	Patients	R0 rate	DFS	OS or MST	(Refs.)
INT-0116	Surgery + FL + RT; Surgery alone	281; 275	NA	NA	Median OS: 36 vs. 27 mo, P=0.005	(23)
ARTIST	Surgery +XP x 2 + XRT +XP x 2; Surgery +XP x 6;	230; 228	NA	3-year DFS rate: 78.2 vs. 74.2%, P=0.0862	NA	(24)
POET	2xPFL+ RT + CE + surgery; 2xPFL+ surgery	60; 59	72 vs. 69.5%, P: NA	NA	Median OS: 30.8 vs. 21.1 mo, P=0.055	(25,26)
Klevebro (2016)	FC x 3 + RT + surgery; FC x 3 + surgery	90; 91	87 vs. 74%, P=0.004	NA	3-year OS rate: 49 vs. 47%, P=0.77	(27)
CROSS	PC + RT + surgery; Surgery alone	178; 188	92 vs. 69%, P<0.001	NA	Median OS: 49.4 vs. 24.0 mo, P=0.003	(28)
TOPGEAR	ECF x 2 + RT + surgery + ECF x 3; ECF x 3 + surgery + ECF x 3	60; 60	NA	NA	NA	(30)
CRITIC	ECC/EOC x 3 + surgery + XP + RT; ECC/EOC x 3 + surgery + ECC/EOCx3	395; 393	82 vs. 80%, P: NA	82 vs. 80%, P: NA	Median OS: 37 vs. 43 mo, P=0.9	(64)

FL, 5-fluorouracil + leucovorin; RT, radiotherapy; XP, capecitabine + cisplatinum; XRT, capecitabine + radiotherapy; PFL, cisplatinum + 5-fluorouracil + leucovorin; CE, cisplatinum + etoposide; FC, 5-fluorouracil + cisplatinum; ECF, epirubicin + cisplatinum + 5-fluorouracil; ECC, epirubicin + cisplatinum + capecitabine; EOC, epirubicin + oxaliplatin + capecitabine; NA, not available; DFS, disease-free survival; OS, overall survival; MST, median survival time; mo, month.

Table III. Key studies of targeted therapy in combination with (neo-)adjuvant therapy for gastric cancer.

Study or author (year)	Groups	Patients	R0 rate	DFS	OS or MST	(Refs.)
ToGA	FC/XC x 6 + trastuzumab; FC/XC x 6	298, 296	NA	NA	Median OS: 13.8 vs. 11.1 mo, P=0.0046	(33)
CGOG 1001	Trastuzumab + XELOX	51	NA	NA	Median OS: 19.5 mo	(34)
AVAGAST	Bevacizumab + XP; Placebo + XP	387, 387	NA	NA	Median OS: 12.1 vs. 10.1 mo, P=0.1002	(35)
AVATAR	Bevacizumab + XP; Placebo + XP	100, 102	NA	NA	Median OS: 10.5 vs. 11.4 mo, P=0.56	(36)
ST03	Bevacizumab + ECX + surgery; ECX + surgery	530, 533	61 vs. 64%, P=0.47	NA	3-year OS rate: 48.1 vs. 50.3%; P=0.36	(38)
Zheng (2020)	SOX + apatinib	29	96.6%	NA	NA	(39)
HER-FLOT	FLOTA x 4 + FLOTA x 4 + trastuzumab x 9	56	92.9%	Median DFS: 42.5 mo	3-year OS rate: 82.1%	(40)
EORTC-INNOVATION	SOX/FLOT x 3 + surgery + SOX/FLOT x 3; SOX/FLOT x 3 + trastuzumab + surgery + SOX/FLOT x 3 + trastuzumab; SOX/FLOT x 3 + trastuzumab + pertuzumab + surgery + SOX/FLOT x 3 + trastuzumab + pertuzumab	NA	NA	NA	NA	(41)

FC, 5-fluorouracil + cisplatinum; XC, capecitabine + cisplatinum; XELOX, capecitabine + oxaliplatin; XP, capecitabine + cisplatinum; ECX, epirubicin + cisplatinum + capecitabine; SOX, S-1 + oxaliplatin; FLOTA, 5-fluorouracil + leucovorin + oxaliplatin + docetaxel + apatinib; NA, not available; DFS, disease-free survival; OS, overall survival; MST, median survival time; mo, month.

patients with esophagogastric junction cancer as the suitable population for NACRT with grade IB evidence; these guidelines were lacking persuasiveness and instructions for gastric body cancer or distal gastric cancer (20). The TOPGEAR study is an international multi-center phase III clinical trial aiming to compare the efficacy of NACRT and NACT; it is worth noting that numerous study subjects were patients with non-esophagogastric junction gastric cancer (30). Early results indicated that preoperative chemotherapy combined with radiotherapy did not increase adverse reactions and the results regarding prognosis are to be anticipated.

4. NAT combined with targeted therapy for gastric cancer

Current status of targeted therapy for gastric cancer. Cancer is a type of genetic disease and with the progression of research on the mechanisms of onco-molecular biology, several target genes associated with the pathogenesis and progression of gastric cancer were discovered; explorations of drugs targeting these genes have been rapidly developing in the field of gastric cancer therapy. The targeted drugs for gastric cancer mainly comprise anti-human epidermal growth factor receptor-2 antibody (anti-HER-2 antibody) and anti-vascular endothelial growth factor receptor antibody (anti-VEGFR antibody) (31). As a recombinant human anti-HER-2 antibody, trastuzumab selectively binds to the extracellular region of the receptor, thereby inhibiting the activity of the receptor kinase and antagonizing the signaling cascade reaction to exert its anti-tumor effect (32). The ToGA study was an international multi-center phase III clinical trial of targeted therapy for late gastric cancer and the result indicated that trastuzumab combined with chemotherapy significantly improved the median survival time when compared with chemotherapy alone (13.8 vs. 11.1 mo, P=0.0046) (33). The CGOC1001 study further verified the efficacy and safety of trastuzumab for patients with HER-2-positive late gastric cancer and trastuzumab combined with chemotherapy has become the first-line treatment for HER-2-positive late gastric cancer (34). However, the AVAGAST study (35) and AVATAR study (36) indicated that, compared with chemotherapy alone, bevacizumab combined with chemotherapy failed to improve the median survival time (12.1 vs. 10.1 mo, P=0.100; 10.5 vs. 11.4 mo, P=0.56). The selection of targeted drugs and indications of targeted therapy were limited and trastuzumab was the only drug that was proved to be effective in the targeted therapy for gastric cancer. However, only 20% of patients with gastric cancer were suitable for this targeted medical therapy (37). Further progress of targeted drugs and detectable biomarkers is required to promote the development of targeted therapy for gastric cancer.

Research progress in NAT combined with targeted therapy for gastric cancer. As for anti-VEGFR-targeted drugs, the ST03 study enrolled 1,063 patients with resectable gastric, esophagogastric junction or oesophageal cancer, and randomly assigned these patients to receive perioperative chemotherapy using the ECX regimen or chemotherapy plus bevacizumab (38). The result indicated that bevacizumab in combination with perioperative chemotherapy did not improve the R0 resection rate or 3-year survival rate (61 vs. 64%, P=0.47; 48.1 vs. 50.3%, P=0.36, respectively). Apart from neutropenia, no other toxic effects were reported with grade 3 or worse severity in >10% of patients, but the postoperative anastomotic leak rate was higher in the bevacizumab plus perioperative chemotherapy group (24%) than that in the perioperative chemotherapy alone group (10%). Combined with the results of the AVAGAST study (35) and AVATAR study (36), it may be concluded that the efficacy of bevacizumab was unsatisfactory as a targeted therapy for gastric cancer. Even though the results of the abovementioned clinical trials are unsatisfactory, these data still guide the direction of future research in the field of targeted therapy for gastric cancer. A single-arm phase II clinical study indicated that preoperative use of the SOX regimen in combination with apatinib achieved a 96.6% R0 resection rate and 87.9% pathologic response rate for advanced gastric cancer. Furthermore, the adverse reactions were tolerable and controllable. The survival data were not obtained due to the short follow-up and research on the efficacy and impact on the prognosis of patients was ongoing (39).

Regarding clinical trials for anti-HER-2 targeted drugs, the German HER-FLOT4 study verified the efficacy and safety of the perioperative FLOT regimen plus trastuzumab for patients with HER-2-positive advanced gastric cancer. The R0 resection rate and 3-year survival rate reached 92.9 and 82.1%, respectively, and the most frequently observed grade 3 and 4 adverse events were leukopenia (17.9%), neutropenia (46.6%), diarrhea (17.9%) and infections (21.4%). However, this study mainly enrolled patients with esophagogastric junction adenocarcinoma (40). The ongoing EORTC-INNOVATION study aimed to investigate the added efficacy of trastuzumab alone or combined with pertuzumab, making NAT in combination with targeted therapy one of the standard treatments for HER-2-positive advanced gastric cancer (41). It is worth noting that this study mainly enrolled non-esophagogastric junction rather than esophagogastric junction or esophageal cancer cases.

It may be concluded from the abovementioned studies (Table III) that NAT in combination with targeted therapy has been a hotspot in the field of gastric cancer therapy, and even though multiple studies failed to achieve satisfactory results, this treatment strategy is still promising and NAT combined with targeted therapy has potential to be a novel therapeutic regimen for gastric cancer. For this, further progress on targeted drugs and detectable biomarkers and more data from clinical studies are required.

5. Prediction and assessment of the therapeutic effects of NAT

Prediction of therapeutic effects of NAT. Predicting the therapeutic effect of NAT is of great significance for improving the survival benefit and socioeconomics benefit, and the exploration of predictive factors of the therapeutic effect is underway. Chiari *et al* (42) retrospectively analyzed the expression of HER-2 in the tumor tissue of 35 patients with advanced gastric cancer prior to and after NAT and the results indicated that the expression status of HER-2 prior to NAT (positive or negative), was not significantly associated with the regression of tumor grading or pathological reaction (χ^2=5.90, P=0.005; χ^2=2.55, P=0.029). However, a significant association between HER-2 reduction after NAT and regression of tumor grading and

pathological reaction was obtained (χ^2=5.90, P=0.005; χ^2=2.55, P=0.029). The association between HER-2 and the prognosis of patients requires to be verified by further prospective studies. Similar to HER-2, the baseline levels of serum survivin prior to NAT were neither associated with the median disease-free survival nor median overall survival time, but the serum survivin levels were markedly reduced after NAT in patients without progression; on the contrary, serum survivin levels were increased in patients with progression (43). The serum level of survivin may be an adequate predictor of the therapeutic effect. Immunoglobulin G (IgG) is one of the most common glycoproteins in serum and the abnormal glycosylation of IgG may be a biomarker for the early detection and progression surveillance of gastric cancer (44,45). Qin *et al* (46) reported that the increased level of galactosylated IgG after NACT was able to predict a favorable response to NACT with a specificity of 100% and sensitivity of 64%. In addition, the decreased level of miRNA-145 and miRNA-185 in peripheral blood after NACT was able to indicate a poor response to NACT, in contrast to miRNA-27a (47,48). A multi-center prospective clinical study illustrated that ^{18}F-FDG PET/CT was able to recognize suspected metastasis in potentially resectable esophagogastric junction cancer prior to NAT; furthermore, the change of ^{18}F-FDG uptake exhibited a good correlation with the pathological reaction to NAT and may also be a potential predictor of prognosis (49). However, certain other studies pointed out that the low uptake of ^{18}F-FDG in several specific pathological types such as signet-ring cell carcinoma and mucinous adenocarcinoma may affect the accuracy of prediction (50,51).

Assessment of the therapeutic effect of NAT. Evaluating the therapeutic effect of NAT for gastric cancer is of great importance for adjusting or modifying NAT regimens; anatomical evaluation with imaging systems including endoscopy, ultrasound, CT and MRI as the main assessment methods is most commonly used. In the Response Evaluation Criteria in Solid Tumors (RECIST) proposed by the Euramerican research organization in 2000, the criteria adopted single-path measurement and clearly defined measurable, unmeasurable and target lesion (52). In 2008, the European Cancer Organization analyzed the test data of >6,500 patients and 18,000 target lesions from the experimental database of the EORTC and then released the RECIST 1.1 criteria (53). In the new version, the assessment criteria for tumor progression were improved, with the addition of the assessment for lymph nodes, and the application value of PET-CT was affirmed. However, NAT caused coagulated necrosis, interstitial fibrosis and scar tissue formation in the gastric cancer lesion, which made it difficult to distinguish the layers of gastric wall by imageological examination (54). Therefore, functional imaging has been gradually used for the assessment of the therapeutic effect of NAT; it assessed the efficacy not only from the perspective of anatomical changes, but also the functional and metabolic changes. Thus, functional imaging methods such as double contrast examination of the stomach, multispiral CT perfusion imaging and ^{18}F-FDG PET/CT have been gradually emerging, and their application and promotion require further supporting clinical evidence (49,55,56).

Tumor regression grading (TRG) is another commonly used method to assess the efficacy of NAT; the response to NAT is assessed on the basis of pathological characteristics and the tumor residue of postoperative specimens. Becker's scoring criteria have been commonly used in European and American countries: Level 1 is assigned for total or subtotal regression (tumor residue <10%); level 2 represents partial regression (tumor residue between 10 and 50%); and level 3 represents minor regression or no tumor regression (tumor residue >50%); furthermore, level 1 indicates effective response to NAT, while level 2 and 3 represent no response (57). Correspondingly, the JGCA scoring criteria have been widely used in Asian countries: Level 0 resembles no response to treatment; level 1a represents tumor residue >2/3, while level 1b indicates tumor residue between 1/3 and 2/3; level 2 represents tumor residue <1/3; and level 3 represents no tumor residue (58). However, certain studies pointed out that TRG was not significantly correlated with the prognosis of patients and was inferior to the assessment of the lymph node status (59,60). The evaluation criteria for the therapeutic effect need to be further improved and NAT requires an independent evaluation standard to obtain a more accurate clinical staging evaluation.

6. Summary and outlook

Shrinking primary tumors and eliminating microscopic metastatic lesions, so as to degrade the staging and improve the R0 resection rate, are the advantages and objectives of NAT, which also requires accurate tumor staging and timely assessment for therapeutic effects (61,62). While to date, no standard NAT regimens have been established, the regimens based on fluorouracil and platinum have demonstrated their efficacy in clinical practice and studies to optimize NAT regimens also have been ongoing. Furthermore, with the research progress of targeted therapy, molecular marker and evaluation methods for gastric cancer, NAT may develop in the direction of precision and individualization based on molecular classification (63).

NAT has proven its efficacy and feasibility and is gradually becoming the mainstay for the treatment of advanced gastric cancer. Highly efficacious NAT drugs or regimens, more reasonable indications and accurate evaluation systems are necessary for the further development of NAT.

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Authors' contributions

PFS conceptualized and wrote the manuscript. PFS and JCY performed the literature review. JCY edited the manuscript.

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Competing interests

The authors declare that they have no competing interests.

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