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Current Status and Research Progress of Neoadjuvant Chemotherapy for Locally Advanced Gastric Cancer

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Abstract

Gastric cancer is one of the most common malignant tumours worldwide, with a high degree of malignancy and a poor prognosis. While early gastric cancer can be cured by surgical treatment, locally advanced gastric cancer requires neoadjuvant therapy to shrink the tumour, suppress potential metastases, achieve down-staging, and provide patients with the opportunity for radical surgery to prolong their survival. This article reviews the current status and progress of neoadjuvant chemotherapy for locally advanced gastric cancer.

Keywords

Locally Advanced Gastric Cancer, Adjuvant Chemotherapy, Neoadjuvant Chemotherapy

1. Introduction

Gastric cancer, estimated annual incidence of over 1 million new cases, is the 5th most common malignancy and the 3rd highest death rate among malignancies worldwide [1]. There are significant geographical differences in the incidence of gastric cancer globally, with the highest incidence rates in East Asia, Central and Eastern Europe and South America [1] [2]. Gastric cancer is a leading cause of cancer-related deaths in China [3]. The main clinical symptoms of progressive gastric cancer include discomfort and pain in the upper abdomen, weight loss due to loss of appetite and fatigue. Most patients do not have obvious clinical symptoms in the early stage and are already in the advanced stage when they are seen, leading to poor treatment results. Surgery is still the only radical treatment for gastric cancer [4]. However, surgery alone is still not a satisfactory treatment

for locally advanced gastric cancer (LAGC). Only 40% - 50% of advanced gastric cancers can be treated with radical resection (R0), and even after R0 resection, 50% - 90% of patients have recurrence or die, with a 5-year survival rate of less than 30% [5].

The treatment of gastric cancer is more diverse and no longer limited to surgery alone, but a combination of multiple modalities to improve the surgical outcome, the quality of life, and the survival rate of the patients. New treatment modalities for advanced gastric cancer have also emerged, such as neoadjuvant chemotherapy, neoadjuvant radiotherapy, neoadjuvant chemotherapy combined with targeted therapy, neoadjuvant chemotherapy combined with immunotherapy, etc. These treatment modalities are collectively known as neoadjuvant therapy [6].

Neoadjuvant chemotherapy for gastric cancer has received increasing clinical attention in recent years. Some meta-analyses have shown that neoadjuvant chemotherapy is most likely to be the best treatment for patients with locally advanced gastric cancer who are feasible for radical resection [7] [8]. The theoretical applications of neoadjuvant chemotherapy are: 1) Neoadjuvant chemotherapy can shrink the primary tumor foci, shrink or disappear the metastatic lymph nodes, induce preoperative downstaging, and increase the surgical R0 resection rate; 2) Timely initiation of treatment can eliminate potential micrometastases in the body and reduce the postoperative distant metastases and recurrence rate; 3) According to the clinical examination data before and after neoadjuvant chemotherapy and postoperative pathology, the clinical remission rate of primary lesions and the histopathological regression grade can be observed; 4) Neoadjuvant chemotherapy can be used to verify the sensitivity of the tumor to chemotherapeutic drugs and guide the postoperative use of drugs according to the tumor response; 5) To determine the biological behavior of the tumor to assess the patient's prognosis [6] [9]. The neoadjuvant chemotherapy regimens are mainly based on the postoperative regimens for gastric cancer, but there is no uniform chemotherapy regimen yet.

This article will review the current status and problems of neoadjuvant chemotherapy for LAGC.

2. Current Status of Neoadjuvant Chemotherapy

The surgical approaches and perioperative treatment patterns for resectable gastric cancer are not standardised worldwide, with differences between the East and West. For postoperative treatment of resectable gastric cancer, the American INT-0116 study [10] demonstrated that 5-Fu followed by radiotherapy after R0/D1 surgery improved OS compared to surgery alone, but the limitation was that only 10% of patients received D2 lymph node dissection; in Asia, the ACTS-GC study [11] in Japan and the CLASSIC study [12] in Korea, two studies of pStage II - III gastric cancer, recommended S-1 alone for one year or capecitabine combined with oxaliplatin/cisplatin chemotherapy after R0/D2 surgery. After the benefits of the surgical approach of D2 lymphadenectomy were con-

firmed [13], the XELOX (capecitabine, oxaliplatin) regimen became a generally accepted adjuvant chemotherapy regimen after D2 standard surgery for LAGC [5]. According to the JCOG1104 study [14], for pStage II gastric cancer, the 3-year relapse-free survival (RFS) rate was 93.1% and the 3-year survival rate was 96.1% with the use of S-1 up to 1 year after surgery, similar to the findings of ACTS-GC, and the S-1 regimen was adopted as the standard chemotherapy regimen for pStage II gastric cancer after surgery in Japan. In the latest JACCRO GC-07 study [15], postoperative S-1 plus docetaxel (DS) continued with oral S-1 monotherapy adjuvant therapy was proved to improve RFS and overall survival (OS) compared to S-1 monotherapy in 3-year follow-up data. In 2021, the ARTIST2 trial [16] confirmed that adjuvant SOX (S-1, oxaliplatin) chemotherapy for 6 months was effective in extending RFS compared to S-1 monotherapy for 1 year in patients with radical D2 resected, stage II/III, node-positive gastric cancer. Both S-1 plus docetaxel and SOX are suggested as chemotherapy for patients after R0/D2 lymph node dissection for stage III gastric cancer, but it is inconclusive which is more advantageous [17]. The RESOLVE study [18] in China showed that 8 cycles of SOX adjuvant chemotherapy after D2 surgery was non-inferior to CapOx (capecitabine, oxaliplatin) in patients with cT4aN + M0 or cT4bNanyM0 gastric or gastroesophageal junction adenocarcinoma. Several important clinical trials on postoperative adjuvant chemotherapy are presented in **Table 1**.

To further improve survival benefits, clinicians began to explore new modalities of chemotherapy. 1989 saw the first report of neoadjuvant chemotherapy in gastric cancer by Wilke *et al.* [19]. The significance of perioperative chemotherapy for gastric cancer was first demonstrated in the landmark phase III MAGIC trial [20], which showed better survival of patients who received perioperative chemotherapy using epirubicin, cisplatin, and infused fluorouracil than of those treated with surgery alone. In the FNCLCC/FFCD trial [21], perioperative chemotherapy with fluorouracil plus cisplatin significantly improved R0 resection rates, RFS and OS compared to surgery alone, further advancing the development of neoadjuvant chemotherapy in LAGC. These studies can be regarded as establishing the status of perioperative chemotherapy for gastric cancer, based on which neoadjuvant chemotherapy was formally adopted by the NCCN guidelines [22]. However, the low proportion of D2 surgery is a limitation of these studies mentioned above [21] [22]. In the FLOT4 study [23], patients with resectable adenocarcinoma of gastric or gastroesophageal junction were treated with FLOT (docetaxel, oxaliplatin, 5-fluorouracil, leucovorin) and ECF/ECX (epirubicin, cisplatin, fluorouracil or epirubicin, cisplatin, capecitabine) regimens for perioperative chemotherapy. The results showed that the FLOT and ECF/ECX regimens had an OS of 50 months and 35 months ($P = 0.012$), and PFS was 30 months and 18 months ($P = 0.004$), but FLOT is associated with more side effects such as nausea, vomiting, or infection. Since then, in Europe and the US, the FLOT regimen has replaced the previous triplet regimen as the standard of care in the perioperative treatment of LAGC [24] [25]. The efficacy

Table 1. Key trials of postoperative adjuvant chemotherapy.

TRIAL	Stage	NO. of patients	Arms	Lymphadenectomy	RFS (%)	OS (%)	Hazard ratio for OS (RFS if no OS) (95% CI)
INT-0116 [10]	pStage IB-IVA	281	I: Surgery + Leucovorin, fluorouracil + RT	D0/D1/D2	-	***36	(C:I) 1.35 (1.09 - 1.66, P = 0.005)
		275	C: Surgery alone		-	***27	
ACTS-GC [11]	pStage II/III	529	I: Surgery + S-1	D2	**65.4	**71.7	0.669 (0.54 - 0.82)
		530	C: Surgery alone		**53.1	**61.1	
CLASSIC [12]	pStage II/III	520	I: Surgery + CapOx	D2	**68	**78	0.66 (0.51 - 0.85)
		515	C: Surgery alone		**53	**69	
JACCRO GC-07 [15]	pStage III	454	I: Surgery + DS	D2	*50	-	0.63 (99.99% CI, 0.400 - 0.998)
		459	C: Surgery alone		*66	-	
JCOG1104 [14]	pStage II	295	C: Surgery + 8 courses SOX	D2	*93.1	-	2.52 (1.11 - 5.77)
		295	I: Surgery + 4 courses SOX		*89.8	-	
ARTIST 2 [16]	pStage II/III	182	I_1: Surgery + S-1	D2	*64.8	-	(I_1:I_2) 0.692 (P = 0.042)
		181	I_2: Surgery + SOX		*74.3	-	(I_2:I_3) 0.971 (P = 0.879)
		183	I_3: Surgery + SOX + RT		*72.8	-	(I_1:I_3) 0.724 (P = 0.074)
RESOLVE [18]	cStage III-IVA	345	C: Surgery + CapOx	D2	*51.1	-	-
		340	I_1: Surgery + SOX		*56.5	-	0.86 (0.68 - 1.07 P = 0.17)
		337	I_2: Preoperative SOX		*59.4	-	0.77 (0.61 - 0.97 P = 0.028)

I: Intervention Group; C: Control Group; RT: Radiotherapy; *: 3 year; **: 5 year; ***: median (months).

of neoadjuvant chemotherapy has been certified in phase II studies in patients with gastric cancer with extensive nodal metastases. The JCOG0405 trial [26] demonstrated the benefits of 2 - 3 courses of neoadjuvant therapy with S-1 plus cisplatin and showed an R0 resection rate of 82% and OS rates of 59% and 53% at 3 and 5 years. For these patients mentioned above, the triplet regimen with docetaxel, cisplatin, and S-1 in the Japanese JCOG1002 study [27] did not achieve more favorable results. The ongoing JCOG1509 trial [28] is exploring the effectiveness of neoadjuvant chemotherapy with the SOX regimen. 530 patients with locally progressive gastric or gastroesophageal junction adenocarcinoma (clinical TNM staging: T2-3N1 or T4Nany) were randomly divided into two groups in the PRODIGY trial [29]. CSC group: neoadjuvant DOS (docetaxel, oxaliplatin, S-1) before R0/D2 surgery, followed by adjuvant S-1 (n = 266); SC

group: R0/D2 surgery followed by adjuvant S-1 (n = 264). CSC compared to SC improved PFS (adjusted hazard ratio, 0.70; 95% CI, 0.52 to 0.95; stratified log-rank P 5.023) and was found to be well-tolerated. For the applicability of the FLOT neoadjuvant regimen in the East, the Chinese DRAGON III trial [30] compared neoadjuvant FLOT versus SOX, showing a higher proportion of complete or subtotal tumor regression grading (TRG) in the SOX group, but no significant difference (P > 0.05). However, only 20% of patients in the FLOT group achieved complete or subtotal TRG, which scholars have speculated is due to ethnic differences. Specific RFS and OS are being traced.

3. Specific Regimens for Neoadjuvant Chemotherapy

Based on these researches, neoadjuvant chemotherapy has been adopted as the standard of care in Europe and the USA: the NCCN [24] in the USA and the ESMO [25] guidelines in Europe recommend neoadjuvant chemotherapy for patients with cStage ≥ IB, for a relatively wide range of patients, with the FLOT regimen preferred for all specific regimens, and fluorouracil plus platinum as the preferred regimen in the perioperative period for patients who are intolerant to triple chemotherapy or have poor physical performance. The JGCA guidelines [17] recommend neoadjuvant chemotherapy with S-1 and cisplatin only for patients with enlarged lymph nodes (bulky N). The CSCO guidelines [31] recommend neoadjuvant chemotherapy for gastric cancer patients with cStage III T3-4aN + M0. The first-choice regimen is SOX (class IA), followed by DOS (IB), FLOT4 (IB) and others. Currently, the KGCA in Korea has not classified neoadjuvant chemotherapy as a guideline recommendation, but they are conducting clinical trials with Asia as the research setting [32]. **Table 2** gives details of representative clinical trials relating to preoperative chemotherapy

Differences in neoadjuvant treatment choices are relevant to the history of gastric cancer treatment in each country region and the characteristics of the patient population [6]. Take Japan as an example, distal gastric cancer is prevalent due to the high prevalence of chronic H. pylori infection [33]. At the same time, a comprehensive screening policy for gastric cancer led to an early detection rate of 50% in Japan by 2009 [34]. They value radical surgical treatment and have high surgical standards. Therefore, the benefits of neoadjuvant treatment in their country are yet to be investigated. In the USA and other western countries, the incidence of adenocarcinoma of both the oesophagus and gastric cardia is increasing due to GERD, Barrett's oesophagus, diet, obesity, etc. [35], making those tumours a higher percentage of some of their large clinical trials, which differs from Asia. In China, more than eighty per cent of gastric cancer patients are already in the progressive stage when they are first diagnosed [34], making the need for some options to improve resection rates and OS even greater. The economic level and the relative lag in drug development have made clinical research more difficult for Chinese clinicians, and the design of clinical trials often refers to some of the findings of Japanese and Korean studies.

Table 2. Key trials of perioperative adjuvant chemotherapy.

TRIAL	Stage	No. of patients	Arms	Lymphadenectomy	RFS (%)	OS (%)	Hazard ratio for OS (RFS if no OS) (95% CI)
MAGIC [20]	cStage II-IVa	250	I: Preoperative ECF	D1/D2	-	**36	0.75 (0.60 - 0.93 P = 0.009)
		253	C: Surgery alone		-	**23	
FNCLCC/ FFCD [21]	cStage M0	113	I: Preoperative cisplatin + fluorouracil	D1/D2	**34	**38	0.69 (0.50 - 0.95 P = 0.02)
		111	C: Surgery alone		**19	**24	
FLOT4 [23]	cStage I-IVA	356	I:Preoperative FLOT	D2	***30	***50	0.77 (0.63 - 0.94)
		360	C: Preoperative ECF/ECX		***18	***35	
PRODIGY [29]	cStage II-IVA	266	I_1: DOS + Surgery + S-1	D2	*66.3	*74.2	0.84 (0.60 - 1.19 P = 0.338)
		264	I_2: Surgery + S-1		*60.2	*73.4	
RESOLVE [18]	cStage III-IVM0	345	C: Surgery + CapOx	D2	*51.1	-	-
		340	I1: Surgery + SOX		*56.5	-	0.86 (0.68 - 1.07 P = 0.17)
		337	I2: Preoperative SOX		*59.4	-	0.77 (0.61 - 0.97 P = 0.028)

I: Intervention group; C: Control group; RT: Radiotherapy; *: 3 year; **: 5 year; ***: Median (months).

4. Selection of Cycles for Neoadjuvant Chemotherapy

The length of treatment for neoadjuvant chemotherapy is usually 2 - 4 cycles, less than or equal to three months. For example, the MAGIC study [20] chose 3 cycles of neoadjuvant chemotherapy, while the FNCLCC/FFCD study [21] chose 4 cycles. However, there is no standard neoadjuvant chemotherapy cycle. In a Japanese 2 × 2 randomised phase II trial [36], patients with stage III gastric cancer, patients with prognosis equivalent to stage III gastric cancer and largely resectable stage IV cases were randomised to receive two or four courses of S-1 plus cisplatin (SC) or paclitaxel plus cisplatin (PC) as neoadjuvant chemotherapy regimens. 3-year OS was 60.9% for SC and 64.3% for PC. 64.3% for two courses of treatment and 61.0% for four courses. Subgroup analysis showed that PC did not show any potential survival advantage compared to SC, nor did four courses of treatment show any potential survival advantage compared to two courses of treatment. It is concluded that two courses of SC are recommended as neoadjuvant chemotherapy as a trial group for future phase III studies in patients with LAGC. COMPASS-D [37] is another trial evaluating neoadjuvant chemotherapy regimens, also in a 2 × 2 analytic design, with 2 and 4 courses of S-1 plus cisplatin or S-1 plus cisplatin plus docetaxel in patients with largely resectable and plasma layer-positive gastric cancer. 120 patients will be enrolled in the study with a primary endpoint of 3-year OS. The RESONANCE-2 trial [38] was subsequently commenced to compare a neoadjuvant 3-cycle SOX regimen to a 6-cycle SOX regimen with the primary endpoint of pathologic complete remission rate and the secondary endpoints of R0 resection rate, 3-year RFS, 5-year

OS and safety. The great novelty is that patients on 6 cycles of neoadjuvant chemotherapy can be considered to have completed all perioperative chemotherapy, and the results may suggest the feasibility of using chemotherapy only before surgery for gastric cancer. We look forward to the final results of several of these studies.

As many clinical trials have lower completion rates of postoperative treatment than preoperative, this may affect survival outcomes. Therefore, total neoadjuvant therapy (TNT) may be a promising treatment modality to explore. In a previous study of TNT in rectal cancer, the application of the TNT modality in patients with locally advanced rectal cancer did not improve prognosis, but the high response rate may allow more patients to retain their rectum [39]. It also gives us a hint: what would be the benefit of a TNT model in gastric cancer? A TNT study protocol will recruit patients with (cT3 - 4 and cN+) gastric cancer and adenocarcinoma of the gastroesophageal junction. Patients will initially receive radiotherapy and concurrent S-1 chemotherapy, followed by six cycles of combined SOX chemotherapy and surgery. The primary objective will be to assess the pathological complete response; secondary objectives will include the assessment of toxicity, surgical complications, the tumor downstaging rate and the R0 resection rate [40].

5. Neoadjuvant Chemotherapy in Combination with Other Treatments

Targeted therapy: Currently, the main types of targeted therapies for gastric cancer are human epidermal growth factor receptor 2 (HER-2), such as trastuzumab, pertuzumab and lapatinib; human epidermal growth factor receptor (EGFR1/HER-1), for example, cetuximab and panitumumab; and vascular endothelial growth factor receptor (VEGFR) like bevacizumab, ramucirumab and apatinib, etc. For patients with HER-2-positive gastric cancer, the addition of trastuzumab to perioperative cytotoxic chemotherapy is a seemingly viable treatment option to improve survival outcomes [41]. The randomised phase II study JCOG1301C [42] investigated the superiority of preoperative neoadjuvant S-1 and cisplatin plus trastuzumab. The preoperative chemotherapy regimen was feasible and often showed better radiological and pathological response rates. In locally advanced HER2-positive gastric cancer with extensive nodal metastases, the addition of trastuzumab to preoperative chemotherapy is expected to result in better survival outcomes. An international multicentre collaborative clinical trial, EORTC-1203-GITCG-the "INNOVATION" Trial [43], in 14 countries, will include a total of 215 patients with HER2-positive gastric cancer and AEG, divided into perioperative chemotherapy alone group, chemotherapy + trastuzumab group and chemotherapy + trastuzumab + pertuzumab group, using any of the chemotherapy regimens FLOT, CapOx and FOLFOX (oxaliplatin, leucovorin, fluorouracil). The aim was to compare pathological remission rates, resection rates and survival rates between the three groups. The UK ST03 study [44] investigated the efficacy and safety of preoperative ECX in combination with

bevacizumab in resectable gastric or esophagogastric junction cancer. The results showed no statistical difference between the two groups in terms of R0 resection rate, 3-year OS rate and RFS. There was a higher incidence of postoperative anastomotic fistula in the combined bevacizumab treatment group, and the study demonstrated no survival benefit from chemotherapy combined with bevacizumab. In some Chinese studies, neoadjuvant apatinib in combination with chemotherapy followed by surgery has shown good efficacy and a manageable safety profile in patients with locally advanced gastric or GEJ adenocarcinoma [45] [46] [47] the true validity of these non-randomised controlled trials needs to be validated by large RCTs.

Immunotherapy: Immunotherapy, especially with immune checkpoint inhibitors, has changed the traditional treatment paradigm for several malignant solid tumours. The addition of immune checkpoint inhibitors to neoadjuvant chemotherapy for gastric cancer is another promising neoadjuvant treatment strategy [48]. The double-blind phase III clinical trial KEYNOTE-585 [49] is evaluating the role of pembrolizumab in the perioperative treatment of gastric adenocarcinoma. Interim results from the DANTE study, which was conducted in combination with atezolizumab on top of the conventional FLOT regimen for perioperative procedures, were reported at the ASCO 2022 Congress. The results showed a pCR (pathological complete response) rate of approximately 16% for the FLOT regimen and an efficacy similar to that of the small sample size phase II study of approximately 25% after the combination of PD-L1 antibody. In terms of safety, there was no significant increase in adverse events with the combination of atezolizumab, which was generally manageable and well tolerated by patients. In patients with high PD-L1 expression, atezolizumab in combination with FLOT has advantages in terms of phase down and pathological remission [50]. In addition, a single-arm phase II study of tislelizumab in combination with SOX for the neoadjuvant treatment of locally advanced gastric/gastroesophageal junction adenocarcinoma achieved a pCR of 23.8% and a major pathological remission rate (MPR) of 61.9% with a favorable safety profile of grade 3 and above adverse reactions < 10% [51].

Targeted therapy, immunotherapy combined with chemotherapy: In TAOS-3B-Trial [52], 25 patients with locally progressive gastric/gastroesophageal junction adenocarcinoma Borrmann type IV, large volume Borrmann type III and Bulky N + /Her2 negative, were given neoadjuvant therapy with tislelizumab in combination with apatinib and SOX regimen for 3 to 6 cycles before surgery.23 achieved a partial response and 2 had stable disease, resulting in an overall response rate of 92% and a disease control rate of 100%. The rate of R0 resection was 100%. Six cases were diagnosed with pathological complete response, and safety and tolerability were also acceptable.

6. Screening of Suitable Patients for Neoadjuvant Chemotherapy

The effectiveness of neoadjuvant chemotherapy varies greatly depending on gas-

tric cancer's type and degree of differentiation, so screening of suitable patients for neoadjuvant chemotherapy is a problem that needs to be solved. A Japanese study showed that the cTNM staging was in line with pathological TNM staging in the range of 25.1% to 88.8% [53] [54]. This puts a number of patients at risk of over-treatment due to inaccurate pre-operative staging [17]. A prospective cross-sectional study, JCOG1302A, evaluated the correlation between clinical and pathological staging. The primary endpoint was the proportion of cT3/T4 patients with pathological stage I tumours. 1260 patients were included, and the proportion of pathological stage III tumours met expectations (87.7%), but the proportion of pathological stage I tumours in the study was 12.3%, which was much higher than expected and did not meet the study's primary study endpoint. Patients with cStage III (cT3-4N1-3) according to the seventh edition of the TNM classification were judged to be suitable candidates for preoperative neoadjuvant chemotherapy based on the results of JCOG1302A. PStage I had a contamination rate of 6.5% and pStage III had a sensitivity of 64.5% [28]. Based on the results of this study, the JCOG1509 study [28] aims to explore the efficacy and safety of the SOX regimen in the neoadjuvant treatment of these patients. The results of the Japanese phase II clinical study JCOG 0210 [55] and the phase III clinical trial JCOG 0501 [56] both showed that neoadjuvant chemotherapy did not provide a survival benefit for patients with Borrmann type IV or bulky type III hypofractionated sclerosing gastric cancer, and neoadjuvant chemotherapy was not recommended for patients with this type of gastric cancer. Studies such as JCOG 1301 [57] and JCOG 1002 [58] have further explored the benefit population of neoadjuvant chemotherapy and attempted to screen for those sensitive to neoadjuvant chemotherapy.

Besides, a deep learning-based radiomics nomogram exhibited a promising performance for predicting therapeutic response and clinical outcomes, especially RFS, in patients with LAGC, which could provide valuable information for individualized treatment [59].

7. Problems and Perspectives of Neoadjuvant Chemotherapy

At present, there are still issues regarding the implementation of neoadjuvant chemotherapy for progressive gastric cancer: 1) The indications for neoadjuvant chemotherapy, *i.e.* which patients are suitable for neoadjuvant chemotherapy and how to identify them; 2) The dosing regimen and treatment period of neoadjuvant chemotherapy; 3) Whether neoadjuvant chemotherapy can bring survival benefits to patients; 4) Whether patients who have achieved complete pathological remission after neoadjuvant chemotherapy can wait and see; 5) How to accurately determine the efficacy of neoadjuvant chemotherapy and accurately re-stage; 6) How to choose further treatment for patients who have failed neoadjuvant chemotherapy; 7) Differences in treatment between East and West, etc.

For LAGC, radical surgery is still a necessary treatment of choice. While standard perioperative chemotherapy differs between the west and east, the superiority of perioperative chemotherapy is still being explored and may become standard in the future. It is believed that with the continuous development of relevant clinical studies, neoadjuvant chemotherapy will become more and more perfect so that patients with LAGC can be treated with better and better results.

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Author Contributions

JL designed the review, collected the trials, and drafted the paper. ZX and TW assisted in collection of the data and edited the final paper. All authors read and approved the paper for publication.

Conflicts of Interest

The authors declare no competing interests.

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