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Review Article

Neoadjuvant Chemotherapy in Asian Patients With Locally Advanced Gastric Cancer

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ABSTRACT

Presently, surgery is the only treatment approach for gastric cancer and improving the prognosis of locally advanced gastric cancer is one of the key factors in promoting gastric cancer survival benefit. The MAGIC study was the first to demonstrate the efficacy of neoadjuvant chemotherapy (NAC) in European countries. In recent years, several clinical trials have provided evidence for the use of NAC in Asian patients with locally advanced gastric cancer. However, clinical practice guidelines vary between Asian and non-Asian populations. Optimal NAC regimens, proper target populations, and predictors of NAC outcomes in Asian patients are still under investigation. Herein, we summarized the current progress in the administration of NAC in Asian patients with gastric cancer.

Keywords: Gastric cancer; Neoadjuvant chemotherapy; Asian patients

INTRODUCTION

Gastric cancer is characterized by high incidence and mortality rates, especially in Asian countries [1]. As most patients are asymptomatic at an early stage, advanced gastric cancer (AGC) is extremely common at the time of diagnosis. Surgery is presently the only approach for the treatment of AGC, and improving prognosis is one of the key points in gastric cancer treatment.

Neoadjuvant therapy has been adopted for the treatment of several other tumor types, such as non-small cell lung cancer and head and neck cancer [2-4]. Furthermore, the feasibility of neoadjuvant chemotherapy (NAC) for gastric cancer has been explored. The MAGIC study was the first phase III randomized controlled trial (RCT) to demonstrate the superiority of NAC, where three cycles of preoperative and three cycles of postoperative epirubicin, cisplatin, and fluorouracil treatment showed superior disease-free survival (DFS) and overall survival (OS) in locally AGC compared with surgery alone [5]. Subsequently, the FLOT4 study confirmed the success of triplet regimens (four preoperative and four postoperative docetaxel and oxaliplatin plus fluorouracil); however, only European patients were recruited in these trials [6]. In America neoadjuvant chemoradiation therapy (nCRT) instead of NAC is widely accepted based on the results from CROSS trial, in which 5 weeks of preoperative paclitaxel and carboplatin plus concurrent radiation therapy prolonged OS compared to surgery alone

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[7]. However, it remains unclear whether NAC works in Asian patients with gastric cancer, and a proper preoperative treatment strategy is yet to be established. It was not until 2021 that RESOLVE and PRODIGY studies reported positive results from phase III RCT in Asian patients, where perioperative SOX (S-1 plus oxaliplatin) and DOS (docetaxel, oxaliplatin plus S-1) therapies both showed better DFS than standard surgery and adjuvant therapy [8,9].

However, there are still unanswered questions regarding NAC in gastric cancer. First, in the FLOT4 study, patients with cT2-4- or N-positive gastric cancer receiving FLOT chemotherapy before surgery showed superior DFS [6]. In contrast, the RESOLVE study demonstrated survival benefits of SOX NAC in cT4aN + or cT4bNany patients [9]. The target population varied across studies on neoadjuvant therapy. Second, the efficacy of different chemotherapy combinations has been evaluated in several clinical trials; doublet or triplet regimens both exhibited favorable outcomes, and precise regimen decisions would rely on other clinicopathological factors. Although downstaging and tumor regression were observed in most patients, some could not benefit from neoadjuvant therapy, which may be due to primary resistance to chemotherapy. The importance of predicting the pathological complete response (pCR) and clinical outcome has been demonstrated. In addition, radiomics and other biological predictors have been investigated in recent years.

Herein, we aimed to summarize the current evidence of NAC in locally AGC among the Asian population and the possible approach to precise gastric cancer surgery.

EVIDENCE ON NAC IN LOCALLY AGC

Doublet vs. triplet

Fluorouracil, especially oral fluorouracil, plus oxaliplatin has been widely adopted as an NAC regimen for Asian patients. KSCC1601, a phase II single-arm multicenter clinical trial employing SOX as an NAC regimen in Japan, reported a 59.5% pathological response rate (pRR) [more than one-third of tumors affected] and a 53.2% 3-year relapse-free survival rate in patients with clinical T3-4N+ gastric cancer or T3-4Nany gastroesophageal junction adenocarcinoma [10]. Similar to KSCC1601, the OGSG 1601 study reported a close pRR and survival outcomes in T3/T4a N1-3 M0 gastric cancer patients receiving XELOX as an NAC regimen [11]. RESONANCE is a phase III RCT launched in China that reported early results of 67.6% downstaging rate and 23.3% pCR rate in gastric cancer patients with clinical stage IIA-IIIC [12]. Subsequently, the RESOLVE study reported positive results demonstrating superior DFS of peri-operative SOX (three cycles preoperatively and five cycles postoperatively) than standard surgery plus a 6-month adjuvant XELOX (hazard ratio [HR], 0.77; 95% confidence interval [CI], 0.61–0.97; P=0.027), and perioperative SOX exhibited as high as a 93% R0 resection rate. All the evidence above demonstrates the feasibility and high tolerability of doublet NAC in Asian patients (**Table 1**). Furthermore, to achieve better tumor downstaging, triplet NAC has been investigated in Asia. A retrospective cohort study from Japan reported a 97% R0 resection rate and 31% pCR rate in patients with clinical stage II-III and distant lymph node metastasis [16]. PRODIGY, a phase III RCT from Korea, subsequently demonstrated a higher R0 resection rate (84% vs. 95%) and better progression-free survival (PFS) (HR, 0.70; 95% CI, 0.52–0.95; P=0.023), but not OS (HR, 0.84; 95% CI, 0.60–1.19; P=0.338), in patients receiving three cycles of neoadjuvant DOS treatment followed by D2 surgery and eight cycles of S-1 adjuvant chemotherapy compared to surgery and standard S-1 adjuvant therapy [8].

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Table 1. Key phase II/III NAC clinical trials in Asian gastric cancer patients

Name/NCT number	Design	Sample size	pCR rate	DFS	OS
ISRCTN12206108 [13]	Arm A: NAC SOX Arm B: NAC XELOX Arm C: Adjuvant SOX Arm D: Adjuvant	135	SOX: 12% XELOX: 4%	-	5-year OS rate Arm A: 78% Arm B: 66% Adjuvant: 74%
Dragon-II [14]	XELOX Arm A: NAC FLOT	326	FLOT: 2.5%	-	-
KSCC1601 [10]	Arm B: NAC SOX NAC SOX	47	SOX: 0% 9.50%	3-year DFS rate: 53.2%	3-year OS rate: 62.9%
OGSG 1601 [11]	NAC CapeOx	37	2.70%	-	-
NCT01516944 [15]	Arm A: Adjuvant SOX Arm B: NAC SOX Arm C: NAC XELOX	749	-	2-year DFS rate Arm A: 66.7% Arm B: 82.4%	2-year OS rate Arm A: 70.0% Arm B: 86.7% Arm C: 80.6%
RESOLVE [9]	Arm A: Adjuvant CapeOX Arm B: Adjuvant SOX Arm C: NAC SOX	1,094	-	Arm C: 80.0% 3-year DFS rate Arm A: 51.1% Arm B: 56.5%	-
PRODIGY [8]	Arm A: adjuvant S-1 Arm B: NAC DOS	530	10.40%	Arm C: 59.4% 3-year PFS rate Arm A: 60.2% Arm B: 66.3%	3-year OS rate Arm A: 73.4% Arm B: 74.2%

Name	NCT	Design	Sample size	Inclusion criteria	Primary endpoint
-	NCT05264896	Arm A: Pre: FLOT × 4 cycles, Post: FLOT × 4 cycles Arm B: Pre: -, Post: XELOX	110	≥T3 or N+	DFS
-	NCT05149807	Arm A: Pre: SHR-1701+SOX, Post: SHR-1701+SOX Arm B: Pre: placebo+SOX, Post: placebo+SOX	846	Investigator's assessment	EFS
-	NCT04139135	Arm A: Pre: HLX10+SOX × 3 cycles, Post: HLX10 × 17 cycles Arm B: Pre: placebo+SOX × 3 cycles, Post: SOX × 5 cycles	642	≥T3N+	EFS
-	NCT02555358	Arm A: Pre: DOX × 4 cycles, Post: XELOX × 4 cycles Arm B: Pre: XELOX × 4 cycles, Post: XELOX × 4 cycles Arm C: Pre: -, Post: XELOX × 8 cycles	300	Stage III	pCR rate
Dragon III	NCT04384601	Arm A: Pre: SOX × 3 cycles, Post: SOX × 3 cycles Arm B: Pre: FLOT × 4 cycles, Post: FLOT × 4 cycles	246	Stage III	OS, DFS
Keynote-585	NCT03221426	Arm A: Pre: Pembrolizumab+XP/FP/FLOT × 3 cycles, Post: Pembrolizumab+XP/FP/FLOT × 3 cycles followed by pembrolizumab x 11 cycles Arm B: Pre: placebo+ XP/FP/FLOT × 3 cycles, Post: placebo+ XP/FP/FLOT × 3 cycles followed by placebo 11 cycles	1,007	≥T3 or N+	OS, EFS, pCR rate
MATTERHORN	NCT04592913	Arm A: Pre: Durvalumab+FLOT × 2 cycles, Post: Durvalumab+FLOT × 2 cycles followed by Durvalumab × 10 cycles Arm B: Pre: placebo+FLOT × 2 cycles, Post: placebo+FLOT × 2 cycles followed by placebo × 10 cycles	955	>T2 N0–3 M0 or T0–4N1–3 M0	EFS

NAC = neoadjuvant chemotherapy; pCR = pathological complete response; DFS = disease-free survival; OS = overall survival; XELOX/CapeOX = capecitabine+oxaliplatin; FLOT = docetaxel+oxaliplatin+5-fluorouracil+leucovorin.

However, contradictory results were observed in two independent cohorts comparing the efficacy of triplet and doublet NAC in China. Zhang et al. [17] reported that patients receiving neoadjuvant DOS showed better tumor response, R0 resection rate, and OS than patients SOX in cT2-4bN0-3M0 gastric cancer patients. However, another retrospective study demonstrated comparable R0 resection rates, DFS, and OS after propensity score matching between DOS and platinum plus fluorouracil doublet groups in cT2-4N+M0 patients [18]. Nevertheless, both studies consistently showed higher adverse event rates or post-operative complications in patients receiving triplet NAC. Thus, the risk of toxicity should be carefully evaluated during the implementation of triplet NAC. It is worth mentioning that although NAC increases tissue fibrous adhesion and make surgery more challenging, surgical complications and chemotherapy adverse events were comparable in patients receiving NAC and standard treatment, regardless of whether the treatment was doublet or triplet [19]. A

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meta-analysis in 2021 reported an even lower anastomotic leakage and reoperation rate in NAC patients than in patients receiving standard treatments [20].

NAC vs nCRT

Few RCTs have investigated the feasibility of nCRT in Asian patients with gastroesophageal junction adenocarcinomas. Comparison with the National Cancer Database demonstrated the highest pCR rate in the nCRT group. Meta-analyses in 2015 and 2019 demonstrated survival benefits from nCRT; however, clinical evidence between Asian and non-Asian countries were heavily biased in both meta-analyses [21,22]. A large-scale retrospective study from China reported a higher pCR rate, better DFS, and local recurrence-free survival benefits, but not OS, in patients receiving nCRT compared with those in patients receiving NAC [23]. Short-term tumor control and survival benefits were improved by administering radiation therapy before surgery; however, nCRT may not prolong long-term outcomes. Meanwhile, postoperative chemoradiation has been investigated in gastric cancer to minimize the risk of recurrence; however, neither DFS nor OS was prolonged based on the results from the ARTIST series studies [24,25]. Patients with high tumor burden, especially borderline resectable tumors at the first evaluation at the gastroesophageal junction, may benefit better from nCRT for tumor shrinkage and achieve eligibility surgery. The use of nCRT may also be influenced by personal preferences in different cancer centers.

IMPACTS OF NAC IN CLINICAL PRACTICE

Operation

Laparoscopic gastrectomy has received increasing attention in the recent years. CLASS-01 and KLASS-02 studies have demonstrated safety and faster postoperative recovery of laparoscopic gastrectomy than open gastrectomy [26,27]. However, chemotherapy-induced tissue fibrotic changes and edema increase technical challenges during surgery. Retrospective studies in Japan and China demonstrated comparable short- and long-term outcomes of laparoscopic gastrectomy surgery and even shorter hospital stays in NAC gastric cancer patients [28,29]. A prospective non-inferiority RCT in China demonstrated a significantly lower postoperative complication rate (20% vs. 46%), lower analog scale score for pain, and better adjuvant chemotherapy completion in patients receiving distal gastrectomy after NAC, where three cycles of preoperative XELOX plus five cycles of postoperative XELOX were administered [30]. Thus, laparoscopic gastrectomy is safe for patients undergoing NAC.

In clinical practice, it is common to encounter dilemmas in distinguishing NAC and conversion treatment in patients with limited metastasis, especially with para-aortic node (PAN) enlargement, which is not typical on computed tomography (CT) scans [31]. Although JCOG 9501 PAN dissection did not prolong recurrence-free survival or OS [32], the extent of lymph node dissection should be further discussed in this new NAC treatment setting. In JCOG0405 study, patients with bulky lymph node metastasis along the celiac artery and its branches and/or PAN metastasis were enrolled; two or three cycles of neoadjuvant cisplatin plus S-1 followed by extended surgery with PAN dissection achieved 65% clinical response and 51% pathological response, and the 3-year and 5-year OS rates were 59% and 53%, respectively [33]. Although JCOG1002 confirmed the response rate, neither short- nor long-term outcomes were improved by the addition of neoadjuvant docetaxel to cisplatin plus S-1 [34,35]. All evidence points to the feasibility of preoperative chemotherapy in patients with para-aortic lymph node metastasis. Furthermore, in JCOG0405, \xcb\x8240%

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of PANs was pathologically confirmed as a metastasis. Ri et al. further confirmed that limited PAN dissection where only clinically metastatic PAN and D2 were dissected showed higher recurrence-free survival and OS than complete No.16 a2 and b1 node dissection [36]. In addition to PAN, No. 14v, No. 10, No. 13, and No. 8p lymph node metastases may meet this condition [37], but not peritoneal metastasis, based on the negative results from JCOG0501 [38]. Implementation of NAC in newly defined patients undergoing surgery and the extent of node dissection could be considered.

Adjuvant therapy

CLASSIC and ACTS-GC studies provided standard 6-months XELOX or 1-year S-1 options for gastric cancer adjuvant therapy; both modalities showed prolonged survival compared to surgery alone [39,40]. However, in patients receiving NAC, the decision to administer adjuvant therapy could be influenced by various factors such as tumor regression grade (TRG), pathological residue, and chemotherapy tolerability. To a great extent, the TRG reflects a patient's sensitivity to chemotherapy. Comprehensive evidence has demonstrated a close relationship between pCR and long-term survival [41-43]. The need for adjuvant therapy, especially in patients who achieve a pCR, has been widely debated. Retrospective studies in China and USA reported that patients who received adjuvant therapy after neoadjuvant treatment could gain survival benefits, especially when the lymph node ratio was above 9% and in patients who completed at least four cycles of adjuvant chemotherapy [44,45]. However, contradictions were observed in patients who achieved a pCR. Mokdad et al. [45] reported that adjuvant therapy showed favored results in even patients with ypT0 (HR, 0.63; 95% CI, 0.41–0.97) or ypN0 (HR, 0.68; 95% CI, 0.54–0.87). However, data from China did not show the survival benefit of adjuvant therapy in ypT0-1 (HR, 0.52; 95% CI, 0.04–7.07) or ypN0 (HR, 0.79; 95% CI, 0.38–1.65) subgroups [44]. It is difficult to draw conclusions based on current data; and other factors, especially the management of adverse effect and patients' intention to undergo chemotherapy, should be considered. Therefore, we still encourage patients to complete 6 months of peri-operative chemotherapy, especially patients with an advanced tumor stage, if tolerability is permitted.

In contrast, the choice of adjuvant chemotherapy when a high TRG grade is reported after surgery is undefined. Kang et al. [46] reported data from China that although higher Mandard scores correlated with advanced ypT and ypN stages and shorter survival, hazard should not be simply judged by TRG. In Mandard score 4-5 group, the median OS of patients who achieved clinical PR during NAC was 68.5 months, which was significantly longer than that of Mandard score 1–2 patients who showed PD during NAC, where the median OS was only 15.6 months [46]. The decision to modify the regimen for adjuvant therapy still needs to be investigated by other studies based on information on clinical response and biological features.

PREDICTORS OF NAC OUTCOMES IN GASTRIC CANCER

Radiomics

Radiomics is an emerging technology that involves image feature extraction and establishment of predictive models, which are thought to represent the biological behavior of primary tumors. Different studies have investigated possible radiomics models to predict surgical outcomes to select eligible patients for NAC based on pretreatment information. Most existing predictive models are based on CT imaging. By training and validating separately, the area under the receiver operating characteristic curve (AUC) of the currently

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reported models was approximately 0.8 [47-49]. In addition to CT scans, dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) has been used to develop prediction models. Zhu et al. [50] reported an AUC of 0.922 by combining parameters from DCE-MRI and intravoxel incoherent motion diffusion-weighted imaging to predict 2-year DFS in patients receiving NAC.

Biological features

Tumoral molecular features significantly define the response pattern. Microsatellite instability (MSI-H)/mismatch repair deficient (dMMR) and Epstein-Barr virus (EBV)-associated gastric cancer are special subgroups of gastric cancer based on multi-omics analysis from TCGA (The Cancer Genome Atlas), which is characterized by massive lymphocyte infiltration and higher sensitivity to immunotherapy [51]. Post-hoc analysis from the MAGIC study found that none of the dMMR (mismatch repair-deficient) gastric cancers reached TRG1 or TRG2, whereas 14% of patients with proficient mismatch repair showed good pathological response to chemotherapy [52]. As for long-term outcomes, a single meta-analysis concluded that although MSI-H was a robust prognostic factor for OS, NAC did not prolong DFS or OS of MSI-H gastric cancer [53]. EBV-associated gastric cancer showed poorer DFS after NAC in a retrospective study [54]. The response rate of EBV-positive gastric cancer is limited [54]. Except for MSI and EBV, other biomarker-positive gastric cancer patients also showed a response pattern to NAC. After propensity score matching, a retrospective study found no improvement in the survival of patients with stomach cancer and hepatoid adenocarcinoma [55]. In addition, patients with positive MET had significantly shorter PFS and OS than those with other gastric cancers who received NAC [56].

Based on multi-omics analysis, several translational studies have provided comprehensive insights into biological predictors of NAC. T>G base substitutions, which are linked to the by-products of oxidative damage, MYC signaling activation, and DNA repair pathway upregulation, may contribute to a patient's response to NAC. In contrast, consistent with the observation of dMMR/MSI gastric cancer insensitivity to NAC, high tumor mutation burden and MSI score were more often observed in non-response patients. Other somatic variations, such as C10orf71 mutation and MDM2 amplification, also correlated closely with gastric cancer NAC outcomes [57]. Correspondingly, another translational study confirmed high single-nucleotide variant (SNV) in Becker-3 gastric cancer patients; however, DNA cluster alteration was not detected based on the TRG after NAC [58]. In addition to genomic changes in primary tumors, other factors related to the tumor immune microenvironment also contribute to the response to NAC, and are correlated with long-term survival. High-density FoxP3 and PD-L1 expressions on immune cells in pre-NAC specimens were a favorable prognostic factors for NAC; in contrast, CD8+ density was related to worse DFS and OS. In addition, high FoxP3 and PD- L1 expressions in tumor cells post-NAC were indicators of shorter survival [59].

Although many studies have focused on finding effective biomarkers for NAC response, some results have been contradictory, and next-generation sequencing of DNA, RNA, and other factors related to the microenvironment may be unavailable for some patients. As gastric cancer is characterized by high heterogeneity, NAC outcome, especially survival outcomes, is difficult to predict based on a single parameter. A predictive model that combines both clinical features and biological characteristics based on a large-scale NAC population is required for further investigation.

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Table 2. Ongoing phase III neoadjuvant chemotherapy or neoadjuvant immunotherapy clinical trials in Asia

Name	NCT	Design	Sample size	Inclusion criteria	Primary endpoint
-	NCT05264896	Arm A: Pre: FLOT × 4 cycles, Post: FLOT × 4 cycles Arm B: Pre: -, Post: XELOX	110	≥T3 or N+	DFS
-	NCT05149807	Arm A: Pre: SHR-1701+SOX, Post: SHR-1701+SOX Arm B: Pre: placebo+SOX, Post: placebo+SOX	846	Investigator's assessment	EFS
-	NCT04139135	Arm A: Pre: HLX10+SOX × 3 cycles, Post: HLX10 × 17 cycles Arm B: Pre: placebo+SOX × 3 cycles, Post: SOX × 5 cycles	642	≥T3N+	EFS
-	NCT02555358	Arm A: Pre: DOX × 4 cycles, Post: XELOX × 4 cycles Arm B: Pre: XELOX × 4 cycles, Post: XELOX × 4 cycles Arm C: Pre: -, Post: XELOX × 8 cycles	300	Stage III	pCR rate
Dragon III	NCT04384601	Arm A: Pre: SOX × 3 cycles, Post: SOX × 3 cycles Arm B: Pre: FLOT × 4 cycles, Post: FLOT × 4 cycles	246	Stage III	OS, DFS
Keynote-585	NCT03221426	Arm A: Pre: Pembrolizumab+XP/FP/FLOT × 3 cycles, Post: Pembrolizumab+XP/FP/FLOT × 3 cycles followed by pembrolizumab x 11 cycles Arm B: Pre: placebo+ XP/FP/FLOT × 3 cycles, Post: placebo+ XP/FP/FLOT × 3 cycles followed by placebo 11 cycles	1,007	≥T3 or N+	OS, EFS, pCR rate
MATTERHORN	NCT04592913	Arm A: Pre: Durvalumab+FLOT × 2 cycles, Post: Durvalumab+FLOT × 2 cycles followed by Durvalumab × 10 cycles Arm B: Pre: placebo+FLOT × 2 cycles, Post: placebo+FLOT × 2 cycles followed by placebo × 10 cycles	955	>T2 N0–3 M0 or T0–4N1–3 M0	EFS

FLOT = docetaxel+ oxaliplatin+ 5-fluorouracil+ leucovorin; XELOX = capacitabine+oxaliplatin; DFS = disease-free survival; SHR-1701 = anti-PD-L1/TGF-βR fusion protein; EFS = event-free survival; HLX10 = a humanized PD-1 inhibitor; DOX = docetaxel+oxaliplatin+capecitabine; pCR = pathological complete response; XP = cisplatin+capecitabine; FP = cisplatin+5-fluorouracil.

FUTURE OF NEOADJUVANT STRATEGY IN LOCALLY AGC

Programmed cell death protein 1 (PD-1) inhibitors, which reshape the phenotype of T cells and the immune microenvironment, have been promising choices for gastric cancer treatment in recent years. Based on the results of Checkmate-649, nivolumab plus chemotherapy has recently become the standard first-line treatment [60]. In addition, the feasibility of neoadjuvant immunotherapy has been investigated in recent years (**Table 2**).

In a phase I clinical trial launched in Japan, neoadjuvant single-agent nivolumab showed a 16% major pathological response, one patient achieved pCR, safety profile was acceptable with 6% incidence of treatment-related adverse events, and only one patient reported grade 3–4 adverse event [61]. Furthermore, several other phase II clinical trials demonstrated a high response rate to PD-1 inhibitor plus chemotherapy in neoadjuvant treatment. Sintilimab, a recombinant humanized IgG4 PD-1 inhibitor produced in China, showed a 19.4% pCR rate, 47.2% major pRR, and 97.2% R0 when combined with XELOX as a neoadjuvant regimen [62]. Toripalimab and camrelizumab also showed promising results in neoadjuvant therapy combined with chemotherapy in an Asian cohort of gastric cancer patients. For MSI-H gastric cancer, PD-1 plus CTLA-4 inhibitors showed a pCR rate as high as 59% [63]. The occurrence of immune-related adverse events did not affect surgery completion. However, questions regarding the era of neoadjuvant immunotherapy remain. Should PD-1 inhibitors be combined with triplet or doublet chemotherapies? As anti-PD-1 antibody works synergistically with radiation therapy, could nCRT plus PD-1 inhibitors achieve survival benefits? Further prospective studies are needed to confirm the appropriate duration of neoadjuvant and adjuvant PD-1 inhibitors.

NAC is a new treatment strategy for locally AGC. Doublet and triplet regimens have shown favorable outcomes in Asian patients. The implementation of NAC not only prolonged DFS and OS but also changed the currently available surgical methods and perioperative

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management for locally AGC. However, details on precise population selection, duration of NAC, and formulation of an appropriate regimen still require multidisciplinary treatment to give full consideration, where tumor burden, biological features, and tolerability should be discussed jointly to achieve the goal for the precise operation. Although there is no evidence from phase III RCT demonstrating the superiority of combining PD-1 inhibitors with NAC, immunotherapy could change the current treatment landscape of locally AGC in the future.

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