

# Implications of clinical research on adjuvant chemotherapy for gastric cancer: Where to go next?

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## Abstract

Postoperative adjuvant chemotherapy (ACT) confers superior gastric cancer (GC) survival in the Eastern cohort. However, is the current standard of ACT already excessive, or is it still necessary to increase its intensity for specific subgroups? Tailored ACT strategies for GC depend on gradual exploration by clinical trials in selected patients. Thus, understanding the implications of previous and current research can help us respond wisely and design effective, rational trials, save medical resources and make better decisions in clinical practice. After reviewing and analyzing studies on ACT for GC patients undergoing curative resection, we found that research strategies for conducting “addition” ACT for specific stages of the disease have achieved great progress in making ACT more tailored and personalized in consideration of pathology stages. Furthermore, trials indicate that “addition” ACT strategies for GC patient subgroups based on histological characteristics might be helpful to move toward a more specific tailored and personalized management approach. Designing ACT research focused on different node statuses should also be conducted according to the biological specificity of lymph node (LN) metastasis. Therefore, future trials designed to determine tailored treatment based on histological and biological characteristics for specific subgroups are urgently needed and conducted as the theme of the 2019 American Society of Clinical Oncology (ASCO): Caring for Every Patient, Learning from Every Patient.

**Keywords:** Gastric cancer (GC); adjuvant chemotherapy (ACT); clinical trial; tailored

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## Introduction

Surgery remains the cornerstone of curative treatment for gastric cancer (GC). And currently, for locally advanced GC, laparoscopic gastrectomy is becoming the mainstream of surgical approach (1-2) while D2 lymphadenectomy is considered the standard of lymph node dissection (3-5). Compared with surgery alone, postoperative adjuvant chemotherapy (ACT) for GC can significantly improve survival in the Eastern cohort (6,7). A meta-analysis by the Global Advanced/Adjuvant Stomach Tumor Research International Collaboration (GASTRIC) group further

confirmed that some regimes of postoperative ACT may promote survival (8). However, the limit of the expansion remains unknown, and it is unclear whether the current standard of ACT is already excessive or whether it is still necessary to increase its intensity. These questions need to be explored through clinical trials, as designing rational clinical trials to efficiently answer clinical questions requires gaining insight into the implications of previous and current clinical research on ACT. A rational approach can help save medical resources and permit better decisions in clinical practice. Thus, where should we go in the next trial?

This review aims to summarize subsequent directions for ACT exploration in selecting GC patients and improving efficiency of rational design of relevant clinical trials.

### “Addition” tendency in ACT trials for GC

In 2011, the Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) laid the foundation of ACT for curatively resected local advanced GC with the regimen of postoperative S-1 single-agent for 12 months (6). The 5-year follow-up data of 1,059 participants showed that the 5-year overall survival (OS) rate was 71.7% in the group receiving S-1 after surgery and 61.1% in the group receiving surgery only [hazard ratio (HR), 0.669; 95% confidence interval (95% CI), 0.540–0.828], respectively. The 5-year relapse-free survival (RFS) rate was 65.4% and 53.1%, respectively (HR, 0.653; 95% CI, 0.537–0.793). However, subgroup analysis showed that the 5-year OS rate of stage IIIB GC patients was 50.2% in the group receiving S-1 after surgery and 44.1% in the group receiving surgery-only (HR, 0.791; 95% CI, 0.520–1.205), indicating that some room for improvement remains. Therefore, further trials based on the pathology stage are needed to identify optimal adjuvant strategies.

However, it is not clear how subsequent studies should be conducted to further explore this topic. Previous research has implications for oncologists. The S-1 Plus cisplatin vs. S-1 In the Treatment for Stomach cancer (SPIRITS) trial (9) showed that the addition of cisplatin to S-1 significantly extended progression-free survival (PFS), whereas the V325 study (10) demonstrated that docetaxel plus cisplatin and fluorouracil is superior to cisplatin and fluorouracil with respect to survival in advanced GC. These studies have suggested that S-1 plus cisplatin and S-1 plus docetaxel are potentially better regimens for postoperative ACT for GC. Additionally, some trials have confirmed the feasibility of these regimes in a postoperative setting for GC (11,12). Therefore, it appears that enhancing the ACT intensity in later-stage GC subgroups is worth exploring. In the same way, a phase III RCT (RESCUE-GC study, ClinicalTrials.gov/NCT02867839), which focused on evaluating S-1 plus oxaliplatin compared with S-1 alone in the adjuvant setting for stage II or IIIA gastric adenocarcinoma, is accruing patients in 13 Chinese institutions (13).

Accordingly, step-by-step “addition” ACT trials for specific-stage GC have been conducted. Shitara *et al.* proved that S-1 plus oxaliplatin ACT for stage III GC was

manageable and safe based on the Japanese model (14). Fujitani *et al.* also demonstrated the feasibility and safety of postoperative ACT with S-1 plus docetaxel for stage III patients who had undergone D2 gastrectomy (15). The 3-year follow-up data further showed that the S-1 plus oxaliplatin regimen resulted in promising OS and DFS in stage IIIa GC patients, suggesting that this regime is a candidate for future phase III trials exploring optimal ACT strategies for selected GC patients. Additionally, Yoon *et al.* investigated the efficacy and safety of docetaxel, capecitabine and cisplatin (DXP) in patients with curatively resected stage IIIB–IV(M0) GC (16). Consistently, the adjuvant DXP regime was demonstrated to be feasible and effective in this trial, and the sequent phase III study comparing triplet and doublet regimens for these patients is ongoing. Similarly, a meta-analysis aimed at investigating the role of combination vs. single-agent ACT for GC also reported survival superiority for “addition” strategies of postoperative ACT in resectable GC (17). Compared with single-agent chemotherapy, postoperative combination chemotherapy conferred a 13% (HR, 0.87; 95% CI, 0.79–0.95; P=0.004) fixed reduction and a 19% (HR, 0.81; 95% CI, 0.68–0.97; P=0.02) random reduction in the risk of death in GC patients who had undergone radical resection. Aiming at determining more reasonable ACT strategies for stage III GC, the Japan Clinical Cancer Research Organization (JACCRO) randomly assigned 915 participants to an S-1 plus docetaxel group or S-1 group in the JACCRO GC-07 trial (18,19). The second interim analysis showed that the 3-year RFS of the S-1 plus docetaxel group (65.9%) was significantly superior to that of the S-1 group at 49.6% (HR, 0.632; 99% CI, 0.400–0.998; P=0.0007); furthermore, the addition of docetaxel inhibited multiple types of recurrence, including hematogenous, lymphatic and peritoneal recurrence, in stage III GC. The stage II GC subgroup has also been exclusively studied. The Japan Clinical Oncology Group (JCOG) conducted the JCOG1104 trial (20) focused on identifying the optimal duration of S-1 for stage II GC, and the primary endpoint also highlighted the “addition” trend. The 3-year RFS in the 8-course arm was 93.1%, and that of the 4-course arm was 89.8% (HR, 1.84; 95% CI, 0.93–3.63); while the 3-year OS in the 8-course arm (96.1%) was significantly superior to that of the 4-course arm at 92.6% (HR, 3.34; 95% CI, 1.22–9.12), indicating the effectiveness of this “addition” ACT duration for GC. Moreover, considering the efficacy, acceptable toxicity and

high compliance, the study concluded that S-1 ACT for stage II GC should continue for 12 months. After a serious amount of research based on staging workup explorations, we may provide better ACT strategies for local GC: S-1 for 1 year is necessary for stage II disease; S-1 plus docetaxel for 6 months and followed by S-1 alone for 6 months is a good choice for stage III disease. Furthermore, survival outcomes of the full analysis set of the SOXaGC trial and J-CLASSIC trial were assessed to evaluate which strategies have a better benefit for GC: S-1 plus oxaliplatin (SOX) or capecitabine plus oxaliplatin (CAPOX/XELOX) (21). The analysis suggested that although SOX and CAPOX have similar efficacy for stage III GC patients after D2 gastrectomy, adjuvant SOX appeared to be more favorable than CAPOX with regard to DFS among subgroups of patients younger than 65 years with stages IIIB and IIIC disease. The analysis put forward another clinical research direction about the differences in the treatment efficacy regarding sex and histologic type, which need further evaluation. Additionally, on the basis of the superiority of “addition” ACT, some trials to investigate whether further “addition” ACT may benefit selected GC subgroups are ongoing. For example, to validate the superiority of triplet over doublet regimens, the GASTFOX trial is comparing 5-fluorouracil and oxaliplatin (FOLFOX) without or with docetaxel (TFOX protocol) as first-line treatment for locally advanced or metastatic GC (22). Thus far, research on “addition” ACT trials for GC subgroups at specific stages has achieved great progress in making ACT more tailored and personalized with consideration of pathology stages. Additionally, for more selected high-risk GC patients (stage IIIB/IIIC), a longer duration or more intensive ACT might be worthy of further exploration.

Inspired and enlightened by this development, we suggest that more specific stage subgroups, such as stage IIa/IIb/IIIa/IIIb/IIIc or N1/N2/N3a/N3b, should be evaluated. Moreover, future trials may be designed based on histological and biological characteristics to assess the tailored ACT for specific subgroups [e.g., signet ring cell (SRC)].

### Designing ACT trials focused on node status

Recently, a study conducted by Massachusetts General Hospital (MGH) showed that cancer cells from metastatic LNs can escape into the blood circulation and become the main source of cancer cells for distant metastasis in mouse

models (23). At almost the same time, the same conclusion was independently obtained at the Medical University of Vienna using different methodologies (24). If human GC is comparable to the mouse model that LNs are active hubs for systemic tumor cell spread, GC patients with extensive LN metastasis are liable to the status that cancer cells have been widely released into the blood circulation from metastatic LNs. Consistently, LN metastasis has been demonstrated to be the strongest predictor of disease recurrence for GC (3, 25-27). Thus, high-LN-burden (e.g., N3a and N3b status) GC patients, regardless of T stage, might need more intense ACT (if patients have a good performance status and are able to tolerate more aggressive cytotoxic chemotherapeutics), even after radical gastrectomy and lymphadenectomy. Moreover, some researchers have found that the status of micrometastasis in regional LNs, which cannot be detected by conventional pathologic examination, may be associated with recurrence in node-negative status (pN0) patients (28-33). Some studies have reported that LN micrometastasis confers a poor prognosis (34,35). Hence, for locally advanced GC patients with a pN0 status, ACT may also decrease the risk of cancer cell release from potential micrometastatic LNs. Of note, the optimal extent of lymphadenectomy for local advanced GC remains controversial; D2 lymphadenectomy is routinely performed for locally advanced GC in East Asia, whereas surgeons in Western countries tend to perform D1 lymphadenectomy (5). Thus, we might need to distinguish these two types of patients in ACT programs when postoperative pathology confirms LN metastasis and picks relatively intense ACT regimens for Western patients who received D1 lymphadenectomy.

In addition, based on the above analysis, we sought to determine whether the “addition” trend of postoperative ACT might be extended to early GC with limited LN metastasis (e.g., pT1N1M0). At present, there is no consensus on whether postoperative ACT for diagnosed pT1N1M0 cases can improve patient’ prognosis. The retrospective analysis at Asia Centre suggested that patients with pT1N1 (1 or 2 LN involvement) GC might not benefit from postoperative ACT (21). However, we note that 95% of the patients in this trial underwent D2 lymphadenectomy, with different histology types; the extent of LN dissection might be attributed to marked disparities in outcomes between Eastern and Western patients, and histology characteristics might also affect the prognosis (5,36). The same situation has occurred in other

Asian studies (37,38). In contrast, analysis of pT1N1 patients in Western population using the National Cancer Database (NCDB), with most participants undergoing D1/D1+lymphadenectomy, resulted in the opposite conclusions (39). Among pT1N1 patients, ACT and adjuvant chemoradiation therapy (ACRT) significantly improved OS compared with surgery alone (HR, 0.37; 95% CI, 0.22–0.65 and HR, 0.40; 95% CI, 0.28–0.57). Therefore, this trial suggested that ACT, with or without concomitant radiation, might have a valuable role in Western pT1N1 GC patients. Considering the biological characteristics of metastatic LNs and the potential micrometastasis in regional LNs, pT1N1 GC patients not treated with D2 lymphadenectomy should be assessed for ACT. Further studies are necessary to reveal specific pT1N1 GC subgroups who might benefit from adjuvant treatments.

### Designing ACT research based on histological and biological characteristics

As discussed above, research strategies of conducting “addition” ACT trials for specific stages of GC have achieved great progress in making ACT more tailored and personalized with consideration of pathology stages. Nonetheless, these ACT strategies can be even more tailored and personalized. Enlightened by previous and current research, we propose that future trials should be designed based on the histological and biological characteristics.

For example, SRC has specific biological potential features, including less differentiated and more infiltrative behavior and the potential of chemoresistance. Analyzing a cohort in Europe, Piessen *et al.* reported that SRC is a major and independent predictor of a dismal prognosis due to the aggressive behavior, such as a higher rate of peritoneal carcinomatosis and lymph node invasion (40). In contrast, analyses of a cohort of Western patients and patients in a high-volume center in Asia showed that when stratifying survival by tumor stage, the prognosis is paradoxically better for SRC tumors at early stages but worse as the disease progresses compared to non-SRC tumors (41,42). These findings suggest that driver mutations controlling the potential of SRC infiltration and metastasis may proceed as carcinogenesis develops. Additionally, studies have reported chemoresistance in SRC GC. In a cohort in Europe, the response to neoadjuvant chemotherapy was rare in SRC, though it was

associated with improved outcomes (43). Another multicenter comparative study in Europe demonstrated that perioperative chemotherapy with fluorouracil-platinum doublet or triplet regimens did not provide any survival advantage in SRC GC, which continued to progress during treatment (44). These results suggest that chemotherapeutic insensitivity is attributed to the absence of both cytotoxic and cytostatic effects. However, intriguingly, the FLOT (fluorouracil, leucovorin, oxaliplatin, and docetaxel) scheme as perioperative chemotherapy can achieve a good response in SRC tumors according to the preliminary data of the phase 2 part of the phase 2/3 FLOT4-AIO trial (45).

Therefore, tailored therapeutic strategies for SRC cancers, not only surgical approaches but also the chemotherapy regimens, should be highlighted. By reviewing the literature of SRC GC, Mengardo *et al.* proposed that multimodal treatment of SRC require special considerations with regard to the choice of the best therapeutic option (46). Thus, stratification based on SRC GC (or stratification according to the SRC subtype) to examine different therapeutic strategies and/or chemotherapeutic regimens and studies of chemoresistance biology to find specific signaling pathway targets for SRC should be included in subsequent clinical trials to identify more specific strategies. For example, considering the inherent chemotherapy resistance of SRC GC, the benefits of delaying surgery to pursue a neoadjuvant approach for SRC GC arouse doubts. Accordingly, a prospective multicenter controlled randomized phase II/III trial (PRODIGE-19-FFCD1103-ADCI002) was conducted to compare the strategy of perioperative chemotherapy (2×3 cycles of epirubicin, cisplatin, 5-fluorouracil) with a management of surgery followed by adjuvant chemotherapy (6 cycles of epirubicin, cisplatin, 5-fluorouracil) (47). The results of this trial may further help in devising individualized protocols of patient care in GC group in which diversity increasingly demands assessment of alternative strategies. More trials dedicated to this histological subtype to determine tailored treatment are awaited.

Similarly, some research has demonstrated that the diffuse histological type according to Lauren is the determinant for positive peritoneal cytology and peritoneal recurrence after surgery (48). It has been proven that S-1 chemotherapy might decrease the risk of peritoneal recurrence (6,21). By combining full analysis of the SOXaGC and J-CLASSIC trials, Nakamura found that



diffuse-type disease, female sex, age younger than 65 years, and stages IIIB and IIIC disease appeared to be favorable factors for adjuvant SOX (21). Thus, differences in treatment efficacy concerning sex and histologic type may be useful for selecting treatment among several options, though more solid evidence by further evaluation is needed. Similarly, the ARTIST 2 trial randomly allocated 538 local AGC patients with LN metastasis to receive S-1 alone for 12 months, S-1 plus oxaliplatin (SOX group) for 6 months or SOX plus radiotherapy with 45 Gy (SOXRT group) (49). The results were consistent with the trend of “addition” ACT in these subgroups, indicating that SOX/SOXRT is superior to S-1 alone for DFS among locally advanced GC patients with positive LNs.

Therefore, future trials designed based on histological and biological characteristics to determine tailored treatment for specific subgroups are urgently needed.

### Further extension of “addition” tendency in ACT for specific subgroups

Further extension in the “addition” tendency in ACT for specific subgroups of GC patients might be local ACT [hyperthermic intraperitoneal chemotherapy (HIPEC)]. Breaking the “plasma-peritoneal barrier” and increasing the cytotoxic activity of chemotherapy by a synergistic effect with hyperthermia, prophylactic HIPEC (P-HIPEC) can eradicate free cancer cells and micrometastases in the peritoneal cavity, intraoperatively or soon after curative gastrectomy, to reduce peritoneal recurrences. Similar to the role of HIPEC in GC with peritoneal carcinomatosis (50), many clinical trials have also proven that P-HIPEC can reduce peritoneal recurrence and improve prognosis of locally advanced GC patients (51-56). Future trials should be designed to include more specific subgroups with a high risk of peritoneal recurrence. There are some ongoing trials to identify the efficacy of specific management for specific subgroups. For example, the phase III HIPEC-01 trial (ClinicalTrials.gov NCT02240524) investigated Paclitaxel (PTX)-based P-HIPEC for T3-T4b GC patients undergoing radical gastrectomy with D2 lymphadenectomy. In addition, the GAPS trial (UMIN000013109) evaluated intraperitoneal (IP) PTX plus S-1/PTX for curatively resectable GC with serosal invasion (57). We suggest that the addition of P-HIPEC in other subgroups with risk factors of peritoneal recurrences, such as Bormann type 4, venous invasion, diffuse-type classification or positive peritoneal washing cytology (CY+) (58-62), should be further verified in future trials.

### Implications and concerns

“Addition” ACT research based on GC subgroups at specific pathology stages has achieved great progress in making ACT more tailored and personalized with the consideration of pathology stages. Thus, “addition” ACT strategies for subgroups of GC patients based on histological characteristics should be promoted. Considering the biological specificity of LN metastasis in GC, ACT trials focused on different node statuses should also be investigated. Indeed, future trials designed based on histological and biological characteristics to determine tailored treatment for specific subgroups are urgently needed and conducted as the theme of 2019 ASCO: Caring for Every Patient, Learning from Every Patient.

Of course, in the West, other multidisciplinary adjunctive approaches in addition to surgery, such as neoadjuvant chemotherapy (63), neoadjuvant chemoradiotherapy (64) and adjuvant chemoradiotherapy (65), have also confirmed a survival benefit compared with surgery alone. Perioperative chemotherapy has become the standard approach based on the positive results of the FLOT4 trial in the West (66). Hence, these investigations raise solid doubt about the role of ACT. However, there is also concern about the applicability of treatment models in the West to the East. Comparisons among all these treatment models have not been performed and are awaited.

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### Footnote

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

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