Review

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# An update of adjuvant treatments for localized advanced gastric cancer

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Although adjuvant therapy has become the standard of care worldwide for resectable localized gastric cancer, geographic differences exist in standard adjuvant treatments: postoperative chemoradiation in North America, perioperative chemotherapy in Europe, and postoperative chemotherapy in East Asia. Global differences in standard surgical methods or study populations may influence the discrepancies in adjuvant therapy. However, now that D2 gastrectomy has been recognized as the optimal surgery for localized gastric cancer in the West, the standard adjuvant treatments used may need to be reconsidered. One of the most pertinent issues surrounding adjuvant therapy is how to improve the outcomes of current standard treatments. Negative results of recent Phase III trials suggest that simply intensifying the adjuvant chemotherapy is insufficient to enhance its efficacy in patients with localized gastric cancer. However, the AMC 0101 study showed that new strategies, such as the early initiation of chemotherapy and/or intraperitoneal chemotherapy, may further improve the efficacy of current standard adjuvant therapy.

**Keywords:** adjuvant • chemoradiotherapy • chemotherapy • gastric cancer • neoadjuvant

Surgery is the only curative treatment option for patients with localized advanced gastric cancer. However, many patients experience recurrence even after complete resection [1]. To improve survival outcomes of patients with localized resectable gastric cancer, many clinical trials have evaluated adjuvant treatments over several decades. These studies have produced conflicting results, mainly due to modest sample sizes and problematic study designs. Nonetheless, meta-analyses have consistently described a small but significant improvement in survival, suggesting the benefit of adjuvant chemotherapy [2,3]. This finding was recently confirmed by a large patient-level meta-analysis conducted by the Global Advanced/Adjuvant Stomach Tumor Research International Collaboration group [4]. Recently, multiple Phase III studies that enrolled large numbers of patients have demonstrated the survival benefits of adjuvant treatments in localized gastric cancer compared with surgery alone. There is now global agreement that adjuvant therapy improves outcomes in patients with curatively resectable stage II–IV (without distant metastasis) gastric cancer. In this review, we explore recent events in the evolution of adjuvant treatments for localized gastric cancer, as well as future perspectives for the enhancement of adjuvant therapy.

## Current standard adjuvant treatments

Currently, no single regimen has been accepted as the global standard for the adjuvant therapy of resectable gastric cancer. In addition, geographical differences still exist in therapeutic strategies; postoperative chemoradiation, peri- and

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Table 1. Major pivotal Phase III trials for adjuvant treatments of gastric cancer.

| Study name | Treatment arms | Total patients | Patients with lower esophageal or EGJ cancer (%) | Patients who underwent D2 surgery (%) | Hazard ratio for OS (95% CI) | p value | Ref. |
|---|---|---|---|---|---|---|---|
| Intergroup-0116 (USA) | Surgery alone vs postoperative chemoradiation | 556 | 20 | 10 | 1.35 (1.09–1.66)† | 0.005 | [5] |
| MAGIC (UK) | Surgery alone vs perioperative chemotherapy | 503 | 26 | 38 | 0.75 (0.60–0.93) | 0.009 | [7] |
| ACTS-GC (Japan) | Surgery alone vs postoperative S-1 | 1059 | 0 | 100 | 0.68 (0.52–0.87) | 0.003 | [9] |
| CLASSIC (East Asia) | Surgery alone vs postoperative capecitabine and oxaliplatin | 1035 | 0 | 100 | 0.72 (0.52–1.00)‡ | 0.0493 | [10] |

†Hazard ratio of surgery-only group.

‡Overall survival data are not yet mature; a primary end point of this study was disease-free survival.

EGJ: Esophagogastric junction; OS: Overall survival.

post-operative chemotherapy (Table 1).

### Postoperative chemoradiation

Based on the results of the Intergroup-0116 study, adjuvant chemoradiotherapy has been adopted as the standard adjuvant treatment for curatively resected gastric cancer in North America [5]. This study randomized 556 patients with localized gastric or esophagogastric junctional cancer (stage 1B-IV), who underwent curative resection, into a surgery-plus-postoperative-chemoradiotherapy arm and a surgery-alone arm. The adjuvant treatment consisted of bolus 5-fluorouracil (FU) and leucovorin (LV) for 5 days, followed by concurrent chemoradiation (4500 cGy) for 5 weeks. Following completion of radiotherapy, monthly chemotherapy with 5-FU and LV was administered twice. With a median follow-up period of 5 years, chemoradiotherapy significantly prolonged overall survival (median 36 vs 27 months; hazard ratio [HR]: 1.35; 95% CI: 1.09–1.66; p = 0.005) as well as relapse-free survival (median 30 vs 19 months; HR: 1.52; 95% CI: 1.23–1.86; p <0.001). In this study, postoperative chemoradiation was associated with high rates of toxicity (54% of grade 3 or higher hematologic toxicity), and this led to a relatively low compliance for treatment (64% of completion rates for preplanned therapy). An update analysis, with more than a 10-year median follow-up period, indicated significant survival benefits of chemoradiation in terms of both overall survival (HR: 1.32; 95% CI: 1.10–1.60; p = 0.0046), and disease-free survival (HR: 1.51; 95% CI: 1.25–1.83; p < 0.001) [6]. However, this trial has been heavily criticized for the inadequacy of standard surgery used: only 10% of the patients underwent D2 lymph node dissection and, D1 resection, generally considered as the minimum lymphadenectomy for gastric cancer, was not performed in 54% of patients.

### Perioperative chemotherapy

Perioperative chemotherapy is currently the standard practice across Europe for patients with resectable gastric cancer. This treatment is based on the results of the MAGIC trial in the UK [7]. In the MAGIC study, perioperative chemotherapy consisted of three preoperative and three postoperative cycles of epirubicin, cisplatin, and 5-FU (ECF). Outcomes of this treatment were compared with those of surgery alone in 503 patients with resectable adenocarcinoma of the stomach, esophagogastric junction, or lower esophagus. The MAGIC study demonstrated that the perioperative-chemotherapy group had significantly improved overall survival (HR: 0.74–0.75; 95% CI: 0.60–0.93; p = 0.009) and progression-free survival (HR: 0.66; 95% CI: 0.53–0.81; p < 0.001). Surgical morbidity and mortality were similar between both arms. This study showed the difficulties associated with delivering postoperative chemotherapy. Only 65% of patients who had surgery were able to start postoperative phase of treatment, and planned chemotherapy could be completed in only 50%.

The efficacy of the perioperative strategy was subsequently demonstrated by an National Federation of French Cancer Centres and French Federation of Digestive Cancer multicenter Phase III study [8]. In this French study, 224 patients with resectable adenocarcinoma of the stomach, esophagogastric

junction, and lower esophagus were randomly assigned to groups that either received surgery alone or perioperative chemotherapy, consisted of two or three preoperative cycles and three or four postoperative cycles of infused 5-FU and cisplatin. Perioperative chemotherapy was significantly associated with improved overall survival (HR: 0.69; 95% CI: 0.50–0.95; p = 0.02) and disease-free survival (HR: 0.65; 95% CI: 0.48–0.89; p = 0.003).

One of major concerns for these trials was the accuracy of baseline clinical staging. Although accurate clinical staging should be emphasized to avoid unnecessary chemotherapy or following nontherapeutic surgery in perioperative chemotherapy, which includes preoperative therapy, staging endoscopic ultrasonography or laparoscopy was not mandatory in these studies. This may lead to the high rates of incurable resection (~20–30%) in both perioperative and surgery-only groups of these trials.

### Postoperative chemotherapy

In East Asia, postoperative chemotherapy with oral fluoropyrimidine-based regimens has been adopted as a standard adjuvant therapy. This can be attributed largely to the results of the ACTS-GC trial [9] and the recent CLASSIC trials [10]. The ACTS-GC study, conducted in Japan, included 1059 patients with stage II–III gastric cancer who underwent D2 gastrectomy, and postoperative S-1, oral fluoropyrimidine, for 1 year was compared with surgery alone. This study was interrupted following interim analysis because the efficacy of S-1 was strongly suggested. With a median follow up of approximately 3 years, the S-1 group had improved both overall survival (HR: 0.68; 95% CI: 0.52–0.87; p = 0.003) and relapse-free survival (HR: 0.62; 95% CI: 0.50–0.77; p <0.001) compared with the group that received surgery alone. The 5-year follow-up analyses confirmed the prolonged overall survival (HR: 0.67; 95% CI: 0.54–0.83) and relapse-free survival (HR: 0.65; 95% CI: 0.54–0.79) in the postoperative S-1 group [11].

The CLASSIC study tested the combination of capecitabine and oxaliplatin in patients with stage II–IIIB gastric cancer who underwent D2 surgery. This trial was performed in South Korea, China and Taiwan, with 1035 patients randomly assigned to eight cycles of postoperative chemotherapy or surgery alone. After a median follow-up period of approximately 3 years, this study was terminated early when interim analysis indicated improved disease-free survival in the chemotherapy group (HR: 0.56; 95% CI: 0.44–0.72; p <0.0001). Although the data regarding overall survival were not mature, a significant survival benefit was observed for the patients who received the adjuvant capecitabine and oxaliplatin (HR: 0.72; 95% CI: 0.52–1.00; p = 0.0493).

### Reasons for the discrepancies between standard treatments among geographic regions

Geographic differences in the standard adjuvant therapy for resectable gastric cancer can be explained primarily by regional differences in the standard surgery used. The optimal extent of lymphadenectomy for curative resection of gastric cancer has been an issue of debate for several decades. D1 lymphadenectomy is defined as the removal of perigastric nodes 'en bloc' with the specimen, and D2 resection as the removal of the first- and second-tier nodes along with the lymph nodes of the left side of the hepatoduodenal ligament. Extended (D2) lymph node dissection has been well established as the standard of care in East Asia. However, Western surgeons have been skeptical of the benefit of D2 resection over limited (D1) lymphadenectomy, based on the conflicting results reported by previous trials. Two large randomized trials in Europe – the Dutch Gastric Cancer Trial [12] and the UK Medical Research Council trial [13] – have compared D2 and D1 surgery without adjuvant treatment. In these trials, D2 surgery did not improve the 5-year overall survival and was associated with significantly increased postoperative morbidity and mortality compared with D1 surgery. Higher complication rates following D2 surgery resulted primarily from pancreaticosplenectomy, which was an integral part of D2 surgery in these European trials [12,13]. With preservation of the pancreas and/or spleen, however, D2 surgery could be safely performed in Western countries [14,15]. Furthermore, pancreas-preserving D2 surgery showed potential advantages in terms of survival as well as safety in a large Japanese case series [16]. More recently, a Taiwanese single-center randomized prospective trial showed that extended lymph node dissection offers a survival benefit compared with D1 dissection [17]. In addition, the 15-year follow-up results of the Dutch Gastric Cancer Trial study showed that D2 surgery is associated with a lower rate of disease-related death than D1 surgery in Western patients [18]. These data demonstrated that D2 surgery can be performed safely in Western patients and is superior to D0/1 resection in terms of survival as well as locoregional control of disease.

In Intergroup-0116 and MAGIC trials, D2 gastrectomy was performed in only 10 and 38% of patients, respectively. This suggests that patients in the Western trials have been surgically undertreated compared with those in Eastern trials. This may explain why the additional local therapy using radiation (in

North America) and intensive perioperative triplet chemotherapy (in Europe) have improved survival outcomes in Western countries. A recent retrospective study in the Netherlands supports this point of view, as the survival benefit of postoperative chemoradiation compared with surgery alone was seen in patients who underwent D1 resection, but not D2 resection [19]. Furthermore, even when additional radiation or intensive perioperative chemotherapy was given, the survival outcomes of patients treated with adjuvant therapy in Western trials were inferior to those who received surgery alone as part of the Korean and Japanese trials [5,7, 9,10]. Although stage migration caused by differences in the number of dissecting lymph nodes may account for this phenomenon, at least in part [20], this suggests that these strategies cannot compensate for the inferior efficacy of suboptimal surgery (D0/1).

The standard adjuvant therapies currently used in the West were established before D2 gastrectomy was adopted as optimal surgery. Now, Western investigators recognize that D2 surgery is superior to D0/1 surgery and safe when performed by experienced surgeons. Considering that Western patients generally have negative prognostic factors, such as older age, higher BMI, and more proximal tumors compared with Eastern patients, it remains controversial whether the prognosis of Western patients who underwent D2 surgery differs substantially from that of Eastern patients before the upcoming results of a well-conducted prospective trial [15]. However, a retrospective analysis conducted at the Memorial Sloan-Kettering Cancer Center (New York, NY, USA), which involved D2 gastrectomy in approximately 80% of the study population, showed that the survival outcomes by stage were close to those in Korea and Japan [1,21].

Despite compelling evidence of the benefits of D2 surgery, it will take considerable time and effort before D2 surgery is widely performed in the West. This can be attributed primarily to the lack of expertise in this procedure, and an insufficient number of patients to implement the new surgical technique [22]. Nevertheless, we argue that the standard adjuvant treatments used in the West need to be reconsidered, because D2 gastrectomy has finally been recognized as optimal surgery and is often performed in the West, particularly in high-volume centers, and its outcomes in the West seem to be approaching those reported in the East. Considering that the ability of locoregional disease control by surgery is one of the most important factors to determine the adjuvant therapeutic strategies, questions surrounding the adequacy of current standard adjuvant therapies in Western patients who received D2 surgery will become increasingly important with the growing use of D2 surgery in the West. Dedicated investigations may be necessary to address this issue.

Another potential reason for regional differences in the standard adjuvant therapy is the heterogeneity of study populations in previous clinical trials for gastric cancer. The ACTS-GC and CLASSIC trials, which were conducted in East Asia, included only patients with gastric cancer. However, Western trials, especially those conducted in the UK, developed therapeutic strategies for localized gastric cancer by including considerable numbers of patients with adenocarcinoma of the esophagogastric junction or lower esophagus, primarily because of the increasing incidence of these cancers and decreasing incidence of gastric cancer. However, unlike gastric cancer, esophageal cancer tends to easily invade surrounding tissue and regional lymph nodes because of the lack of serosa and abundance of lymphatics in the esophagus. As a consequence, long-term survival rates for esophageal cancer rarely exceed 20%, even after successful resection in advanced disease. For this reason, multimodality therapies, including chemotherapy, radiotherapy and surgery, have been widely investigated for esophageal cancer. Western trials have also evaluated this strategy for gastric cancer. Given the significant differences between esophageal cancer and gastric cancer in terms of etiology, biology and clinical characteristics, the inclusion of patients with adenocarcinoma of the esophagogastric junction or lower esophagus in clinical trials for gastric cancer does not seem appropriate.

Although there is a lack of clear evidence, global differences in treatment outcomes and adjuvant therapy for localized advanced gastric cancer may be, in part, influenced by different tumor biology between the Western and Eastern patients. A recently published study compared the survival of patients with gastric cancer who performed R0 resection between each high-volume center in the USA and Korea. Interestingly, even after adjustments of differences in age, sex, tumor location, Lauren's classification, number of lymph nodes resected and depth of invasion, disease-specific survival was superior in Korean patients compared with US patients [23]. This may suggest the likelihood of favorable inherent tumor biology in Asian patients compared to Western patients. However, because this study was performed retrospectively, prospective validation is required and supporting data should be followed to draw a clear conclusion on this issue.

**Table 2. Phase III trials comparing adjuvant therapeutic strategies for gastric cancer.**

| Study name | Treatment arms | Strategies investigated in the experimental arm | Total patients | Hazard ratio for DFS (95% CI) | Hazard ratio for OS (95% CI) | Ref. |
|---|---|---|---|---|---|---|
| AMC 0101 (Korea) | Mf vs iceMFP | Early systemic chemotherapy, prolonged treatment period, addition of cisplatin, intraperitoneal chemotherapy | 521 | 0.70 (0.54–0.90) p = 0.006 | 0.71 (0.53–0.95) p = 0.02 | [28] |
| AMC 0201 (Korea) | Mf vs MFP | Addition of cisplatin, prolonged treatment period | 855 | 1.07 (0.85–1.35) p = 0.59 | 1.10 (0.84–1.44) p = 0.48 | [25] |
| CALGB 80101 (USA) | 5-FU/LV plus radiation vs ECF plus radiation | Addition of epirubicin and cisplatin | 540 | 1.00 (0.79–1.27) p = 0.99 | 1.03 (0.80–1.34) p = 0.80 | [24] |
| ARTIST (Korea) | XP vs XP plus radiation | Addition of radiation | 458 | p = 0.09 | N/A | [31] |
| ITACA-S (Italy) | 5-FU/LV vs 5-FU/LV/ irinotecan followed by docetaxel/cisplatin | Addition of irinotecan, docetaxel and cisplatin | 1106 | 0.98 (0.83–1.16) p = 0.83 | (0.83–1.20) p = 0.99 | [27] |

5-FU/LV: 5-fluorouracil and leucovorin; DFS: Disease-free survival; ECF: Epirubicin, cisplatin and 5-fluorouracil; iceMFP: Intra-operative intraperitoneal cisplatin, early (day after surgery) mitomycin, long-term oral fluoropyrimidine, and cisplatin; Mf: Mitomycin and short-term (3 months) oral fluoropyrimidine; MFP: Mitomycin, long-term (1 year) oral fluoropyrimidine, and cisplatin; OS: Overall survival; XP: Capecitabine and cisplatin.

## Future perspective: improving standard adjuvant treatment

The most important issue in adjuvant therapy for localized gastric cancer relates to how to improve the clinical outcomes of current standard treatments. The results of the studies outlined in Table 2 offer some timely suggestions. Both the CALGB 80101 study in North America and the AMC 0201 study in Korea failed to demonstrate that intensification of adjuvant chemotherapy improves outcomes. The CALGB 80101 trial [24] intensified the regimen used in the Intergroup-0116 trial by adding two more drugs (epirubicin and cisplatin) to the bolus 5-FU and LV before and after 5-FU/radiotherapy for resected gastric or esophagogastric junction adenocarcinoma. In this study, in which a total of 546 patients were enrolled, more intensive systemic chemotherapy did not improve the overall survival (HR: 1.03; 95% CI: 0.80–1.34; p = 0.80) and disease-free survival (HR: 1.00; 95% CI: 0.79–1.27; p = 0.99) compared with 5-FU and LV. The AMC 0201 study increased the duration of oral fluoropyrimidine treatment to 12 months and added cisplatin to the combination of mitomycin-C and 3 months of oral fluoropyrimidine [25]. The control regimen in this study was based on prolonged survival of patients with resected stage III gastric cancer compared with surgery alone in a Spanish Phase III study [26]. This study also failed to show the benefit of intensive chemotherapy, with no differences in recurrence-free survival (HR: 1.07; 95% CI: 0.85–1.35; p = 0.59) and overall survival (HR: 1.10; 95% CI: 0.84–1.44; p = 0.48) between the two study arms. The recently presented ITACA-S trial, which included 1106 patients who underwent curative resection (D1 25% and D2/3 75%), did not show the differences in disease-free survival (HR: 0.98; 95% CI: 0.83–1.16; p = 0.83) and overall survival (HR: 1.0; 95% CI: 0.83–1.20; p = 0.97–0.99) between a group that received intensified chemotherapy (four cycles of 5-FU, LV and irinotecan, followed by three cycles of docetaxel and cisplatin) and control chemotherapy group (nine cycles of 5-FU and LV) [27]. Negative results of these Phase III trials suggest that simply intensifying the adjuvant chemotherapy (with or without radiation) by adding an agent or prolonging treatment duration does not always enhance its efficacy in patients with localized gastric cancer regardless of extent of surgery (D2 in AMC 0201, D1 or D2 in ITACA-S, and D0 or D1 in CALGB 80101) [24,25,27].

However, the AMC 0101 study, a companion trial of AMC 0201, evaluated the efficacy of two more strategies than were used in the AMC 0201 study in patients with D2-resected macroscopically serosa-invading gastric cancer with same control arm [28]. The two additional strategies were intraoperative intraperitoneal chemotherapy using cisplatin, and early initiation (day after surgery) of systemic chemotherapy. In this Phase III study, which included 521 patients, combined use of these strategies significantly improved recurrence-free survival (HR: 0.70; 95% CI: 0.54–0.90; p = 0.006) and overall survival (HR: 0.71; 95% CI: 0.53–0.95; p = 0.02) compared with the control regimen (mitomycin-C and 3 months of

oral fluoropyrimidine). This finding was verified by long-term follow-up results, with a median duration of 6.6 years [29]. In light of the negative results of AMC 0201, improved survival in AMC 0101 is attributable to early administration of chemotherapy and/or intraperitoneal cisplatin. These two strategies may enhance the efficacy of current standard regimens for gastric cancer, such as postoperative chemoradiation, perioperative chemotherapy, and postoperative chemotherapy. Regarding the potential benefits of early initiation of chemotherapy in localized gastric cancer, neoadjuvant chemotherapy is, in a sense, the earliest possible form of adjuvant chemotherapy. Despite poor compliance during the postoperative phase of the MAGIC trial, the successful outcome associated with perioperative chemotherapy also suggests the potential benefits of neoadjuvant chemotherapy. However, in the MAGIC trial, perioperative chemotherapy was compared with surgery alone [7]. Therefore, it is not clear whether improved survival could be attributed to preoperative chemotherapy, postoperative chemotherapy, or both. Furthermore, only 40% of the patients in the MAGIC trial underwent D2 surgery. Therefore, the efficacy of neoadjuvant chemotherapy in countries where D2 surgery and postoperative chemotherapy is the standard of care remains to be determined. The PRODIGY trial (preoperative docetaxel, oxaliplatin, and S-1 followed by postoperative S-1 vs postoperative S-1 for patients with D2 resection; NCT01515748 [101]) aims to answer this question.

In Europe and East Asia, where postoperative radiation has not been commonly used, the inclusion of postoperative radiation in standard therapeutic strategies has been considered to improve therapeutic efficacy. Despite the success of the Intergroup-0116 trial, the role of radiotherapy was seldom investigated in countries where D2 gastrectomy is the standard of surgery, because many investigators are reluctant to add another local therapy to an 'optimal' surgery. The results of a retrospective study that suggested potential benefits of adjuvant chemoradiation following D2 surgery [30] formed the basis of the ARTIST trial [31], which was conducted in Korea to evaluate adjuvant chemotherapy with or without radiation. By contrast to the Intergroup-0116 study, the control arm in the ARTIST trial underwent chemotherapy rather than observation, and D2 surgery was mandatory. However, this study failed to show that adding radiation to adjuvant chemotherapy improved outcomes for patients who underwent D2 gastrectomy. Although the inclusion of too many patients with early-stage cancer (~60% in stage IB or II) may have limited the power of the study, the negative results in the ARTIST trial bolstered the notion that radiation does not improve the efficacy of adjuvant chemotherapy following optimal surgery. The potential of combining postoperative radiotherapy with perioperative chemotherapy is currently being evaluated by the ongoing CRITICS trial (NCT00407186).

In the era of targeted therapy in oncology, biological agents have also been investigated for adjuvant treatment of gastric cancer. In the UK, the MAGIC-B is currently underway to determine the efficacy of adding bevacizumab to adjuvant therapy (perioperative epirubicin, capecitabine, and cisplatin with or without bevacizumab), and recently reported the feasibility of this regimen. In the recent AVAGAST trial [32], a combination of bevacizumab with standard chemotherapy failed to improve overall survival, the primary end point, in a global patient population with locally advanced and metastatic gastric cancer; although response rate and progression-free survival were both significantly increased. It will be interesting to see whether adding bevacizumab benefits Western patients in an adjuvant setting. With the success of the ToGA trial [33], the door to targeted therapy for gastric cancer has finally been opened. In locally advanced or metastatic gastric cancer with overexpressed HER-2, a combination of trastuzumab and chemotherapy significantly prolonged survival outcomes and is, therefore, considered the new standard of care. The efficacy of adjuvant trastuzumab in HER-2$^+$ breast cancer leads us to expect benefit from adjuvant trastuzumab in HER-2$^+$ gastric cancer. Nonetheless, by contrast with the strong prognostic value of HER-2 expression for breast cancer, the prognostic impact of HER-2 expression in resectable gastric cancer is weak [34]. Multiple biological agents are currently under investigation for use in gastric cancer, especially in metastatic or recurrent disease. If the results are promising, the role of these agents as adjuvant therapy should also be explored.

In summary, with the progress of adjuvant treatment, clinical outcomes of patients with localized advanced gastric cancer have been significantly improved. However, geographic discrepancies in standard adjuvant therapy still exist and these might be related to differences in standard surgical methods or heterogeneous study populations. Since D2 gastrectomy is recognized as the optimal surgery in the West, the standard adjuvant treatments used in the West may need to be reconsidered. Recent Phase III trials suggest that simple intensifications of chemotherapy regimens are not helpful to enhance the efficacy of adjuvant therapy. Instead, new strategies, such as early initiation of chemotherapy or intraperitoneal chemotherapy, may further

## Executive summary

- After much debate over the past few decades, adjuvant therapy has become the standard of care worldwide for resected localized gastric cancer.
- However, geographic differences exist in standard adjuvant treatments, with postoperative chemoradiation in North America, perioperative chemotherapy in the UK and postoperative chemotherapy in East Asia.
- Differences in the standard surgical procedures used and the patient populations selected for pivotal studies may account for geographic discrepancies in the adjuvant therapy.
- Now that D2 gastrectomy has finally become the standard surgery for localized gastric cancer in the West as well as in the East, standard adjuvant treatments in the West may need to be reconsidered.
- Results of the recent CALGB, AMC 0201, and ITACA-S studies suggest that simply intensifying chemotherapy by adding more cytotoxic agent or prolonging the duration of treatment are incapable of improving outcomes. Instead, the results of AMC0101 study suggest that new strategies, such as early initiation of chemotherapy and/or intraperitoneal chemotherapy, may further improve the current standard adjuvant therapy.
- The role of targeted agents in adjuvant treatment for localized gastric cancer should be investigated in future based on the experiences in recurrent or metastatic disease.

improve the efficacy of current standard treatments. In the era of personalized medicine, all patients should be treated based on multidisciplinary evaluation and discussion, and we have to work to improve our understanding of biology of locally advanced gastric cancer in order to provide optimized therapy for our patients.

### Financial & competing interests disclosure

*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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