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Advanced gastric cancer: is chemotherapy needed after surgery?

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"The positive results of these two large-scale randomized controlled trials, ACTS-GC and CLASSIC remove all doubts on the necessity of adjuvant chemotherapy for advanced gastric cancer. However, the question remains of whether adjuvant chemotherapy can be adopted worldwide."

Over the last few decades, many clinical trials have tried to demonstrate the value of adjuvant chemotherapy after surgery for gastric cancer, but most have failed to provide evidence of any clinical benefit. However, these studies did demonstrate that it is important to select appropriate target patients for adjuvant chemotherapy [1].

Recently, two monumental Phase III, large-scale, prospective, multicenter randomized controlled trials (RCTs), the Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) [2] and the Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer (CLASSIC) [3], validated the benefit of adjuvant chemotherapy following standardized surgery.

The results of the ACTS-GC trial conducted in Japan provide concrete evidence of a 5-year overall survival (OS) gain for adjuvant chemotherapy after D2 gastrectomy for advanced gastric cancer (AGC). A total of 1059 patients with Stage II (excluding T1) and III gastric cancer [4] were randomized into two groups: administration of S-1, a 5-fluorouracil-based oral anticancer drug (40 mg/m^2 oral S-1 twice daily for 4 weeks plus 2 weeks of rest, repeated every 6 weeks for 1 year) after D2 gastrectomy compared with surgery alone. The results showed that adjuvant S-1 chemotherapy provided a 5-year OS benefit of 10.6 percentage points (from 61.1 to 71.7%) and an improvement in 5-year relapse-free survival (RFS) of 12.3 percentage points (from 53.1 to 65.4%). The hazard ratio (HR) for 5-year OS was 0.67 (95% CI: 0.54–0.83) and the HR for 5-year RFS was 0.65 (95% CI: 0.54–0.79). Based on this result, adjuvant chemotherapy with S-1 after D2 gastrectomy is now applied as a standard treatment for resectable AGC in many Eastern countries.

The more recent CLASSIC trial, which was conducted in Korea, China and Taiwan, evaluated the effects of adjuvant XELOX after D2 gastrectomy. Eight 3-week cycles of XELOX (oral capecitabine 1000 mg/m^2 twice daily for 2 weeks and oxaliplatin 130 mg/m^2 on Day 1 of each cycle) were given to patients with Stage II and III gastric cancer [5] and the results compared with those of surgery alone. The 3-year disease-free survival (DFS), which was the primary end point of this study, was better in the XELOX (74%) than the surgery alone (59%) with a HR of 0.56 (95% CI: 0.44–0.72; $p < 0.001$) for XELOX compared to surgery alone. The final 5-year follow-up results of the CLASSIC trial presented at the European society for Medical Oncology 15th World Congress on Gastrointestinal Cancer showed that not only the DFS but also the 5-year OS, were significantly better after adjuvant XELOX plus D2 gastrectomy than after surgery alone. The CLASSIC trial offered decisive evidence of the necessity for adjuvant chemotherapy after D2 gastrectomy and the National Comprehensive Cancer Network now recommends the use of XELOX for adjuvant chemotherapy after D2 gastrectomy [6].

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The positive results of these two large-scale RCTs, ACTS-GC and CLASSIC remove all doubts on the necessity of adjuvant chemotherapy for AGC. However, the question remains of whether adjuvant chemotherapy can be adopted worldwide. D2 gastrectomy has been a standard surgical procedure in Korea and Japan for a long time. In contrast, due to its unacceptably high surgery-related mortality and morbidity without survival benefit, D2 gastrectomy has not typically been recommended in western countries [7]. However, long-term follow-up studies (median 15.2 years) have revealed that D2 gastrectomy is associated with reduced gastric cancer-related death compared with D1 gastrectomy (gastrectomy with limited lymph node dissection) [8], and D2 gastrectomy is now recommended as a standard procedure for gastric cancer in western countries but with a prerequisite: D2 gastrectomy should be performed only by experienced surgeons who can conduct it safely in specialized centers [6,9]. The clinical benefit of adjuvant S-1 or XELOX is primarily derived following D2 gastrectomy; therefore, the effect of those chemotherapy after limited lymph node dissection less than D2 gastrectomy has not been established. In practice, perioperative chemotherapy or a combination of chemotherapy with radiation therapy after limited surgery is popular in the western hemisphere, where D2 gastrectomy is not widely performed.

> "If D2 gastrectomy cannot be performed safely, perioperative chemotherapy or postoperative chemoradiation therapy would be an alternative treatment strategy for advanced gastric cancer."

The Medical Research Council Adjuvant Gastric Infusional Chemotherapy trial conducted in the UK investigated the benefit of combination chemotherapy with intravenous (iv.) epirubicin (50 mg/m^2) and cisplatin (60 mg/m^2) on Day 1, and infusional iv. fluorouracil (200 mg/m^2) for 21 days (ECF), for three cycles before and after surgery for patients with resectable lower esophageal cancer and gastric cancer [10]. In this study, 503 patients were randomized into a perioperative chemotherapy group and surgery alone group. The results showed no difference in postoperative complications and mortality between the groups; however, perioperative chemotherapy improved 5-year OS from 23 to 36% with a HR of 0.75 (95% CI: 0.60–0.93, p = 0.009). Even though the patient group was contaminated by lower esophageal cancer and fewer than half of the patients underwent D2 gastrectomy, this result provided evidence that perioperative ECF chemotherapy can be a viable alternative for prolonging the survival of patients with gastric cancer.

In the USA, the Intergroup 0116 trial investigated the role of postoperative chemoradiation therapy for cancer of the stomach and esophagogastric junction [11]. A total of 556 patients were randomly assigned to two groups: a postoperative chemoradiation group (fluorouracil and leucovorin combined with 4500 cGy of radiation for 25 fractions, n = 281) and a surgery alone group (n = 275). The results showed that the risk of death was higher in the surgery alone group (HR: 1.35, 95% CI: 1.09–1.66, p = 0.0005), with a median OS of 27 months in the surgery alone group compared with 36 months in chemoradiation group. Although most of the patients underwent gastrectomy with limited lymph node dissection (D0 gastrectomy; 54%), and only 10% of patients underwent D2 gastrectomy; chemoradiation was associated with a survival gain.

Thus, the results of two major RCTs based on western populations suggest that chemotherapy or chemoradiation can provide a survival benefit when oncologically sufficient surgery cannot be performed.

Comparing the results of RCTs in eastern and western populations raise some intriguing issues. The survival rate for surgery alone in the East is much better than those of perioperative chemotherapy or postoperative chemoradiation therapy in the West. It has been suggested that this difference reflects different baseline clinicopathologic characteristics between East and West because the incidences of proximal tumor, diffuse type of histology and obesity are higher in western than eastern patients with gastric cancer [12]. However, a study that compared the survival outcomes between patients in the USA and Korea reported that survival of gastric cancer patients was better in the East than the West even after correction for confounding factors by multivariable analysis [13]. In addition, a multicenter, Phase II clinical trial conducted by the Italian Gastric Cancer Study Group reported that the survival outcomes of pancreas-preserving D2 gastrectomy in experienced centers were similar to those in Japan [14]. Thus, we believe that D2 gastrectomy can provide similar survival benefits in western countries if it is adequately performed.

Combined, these results indicate that adjuvant chemotherapy with S-1 (The recommendation dose of S-1 is different between East, 80 mg/m^2/day, and in West, 60 mg/m^2/day, respectively [2,15]) or XELOX after D2 gastrectomy is currently the best option for AGC. However, D2 gastrectomy is technically difficult and can increase the surgery-related morbidity and mortality rates if performed by inexperienced hands. Thus, it is not wise to insist on D2 gastrectomy without thorough consideration of the experience level of the surgeon or the hospital volume. If D2 gastrectomy cannot be performed safely, perioperative chemotherapy or postoperative chemoradiation therapy would be an alternative treatment strategy for AGC.

> "…from now on, we need to explore and develop clinically usable biomarkers that can identify a certain molecularly defined group of patients who need chemotherapy after D2 gastrectomy."

Now the emerging question is whether all patients after D2 gastrectomy require chemotherapy. Taking advantage of the recent state-of-the-art genomic technology, from now on, we need to explore and develop clinically usable biomarkers that can identify a certain molecularly defined group of patients who need chemotherapy after D2 gastrectomy. Up to now, only a few biomarkers such as dihydropyrimidine dehydrogenase, orotate phosphoribosyltransferase, thymidylate synthase, which are the genes of 5-fluorouracil metabolic pathway [16] were suggested as predictive markers for S-1 in gastric cancer treatment. Yet, these biomarkers are not conclusive and need further validation for clinical use because there has been no systematic evaluation of the clinical value of these markers in randomized prospective setting or alternative appropriately designed studies [17]. We need to discover markers such as ras mutation in colorectal cancer, which is indicative of cetuximab resistance [18] or Oncotype Dx (21-gene recurrence score assay) in breast cancer that can predict the prognosis and guide the necessity of additional chemotherapy [19]. Although daunting, this effort will spare many patients who do not require chemotherapy after D2 gastrectomy. In the meantime, we should double the effort to propagate D2 surgery to countries where gastric cancer surgery has yet to be standardized. More than a million patients are newly diagnosed every year and most of those have advanced stage disease. Without doubt, surgery will remain an important and irreplaceable treatment for AGC, even in the era of molecularly targeted cancer therapeutics.

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