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# Adjuvant Chemotherapy of Gastric Cancer

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## Abstract

Adjuvant chemotherapy is a standard treatment for operable gastric cancer. However, the preferred treatment varies by geographical region. Southwestern Oncology Group (SWOG) conducted a randomized trial of adjuvant chemotherapy for patients with surgically resected gastric cancer. The 3-year survival rates were 50% in the chemoradiotherapy group and 41% in the surgery group. The Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial that compared perioperative chemotherapy with the ECF regimen (epirubicin, cisplatin, and 5-fluorouracil) and patients with surgery alone had a 5-year survival rate of 36 and 23%. The Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) showed that the 3-year overall survival rate was 80.1% in the S-1 group and 70.1% in the surgery-only group in stage II or III gastric cancer patients who underwent a D2 gastrectomy. An analysis of the Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer (CLASSIC) study showed 3-year disease-free survival, 74% in the chemotherapy and surgery group and 59% in the surgery-only group in the patients with stage II–IIIB gastric cancer who had D2 gastrectomy. In conclusion, for all patients with stage II and III gastric cancer, standard D2 gastrectomy and adjuvant chemotherapy are strongly recommended for improved survival rates.

**Keywords:** gastric cancer, D2 lymph node dissection, chemotherapy

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## 1. Introduction

Gastric cancer is the second most common cause of cancer-related death worldwide [1]. Radical operation is the main treatment for gastric cancer, but the recurrence rate following surgery is high due to the early dissemination of cancer cells via the lymphatic system (about 40–80% in advanced gastric cancer) [1, 2]. In East Asia, especially Japan and Korea, D2 lymph node dissection is the standard treatment for operable gastric cancer [3, 4].

However, in the Western world, D2 gastrectomy is not as widely performed as in Japan and Korea [5]. Western surgical studies have shown that most patients present with tumors that penetrated the submucosa; they have a 5-year survival rate of 20–30% [6]. Postoperative chemotherapy is a standard treatment component of resectable gastric cancer and has improved patient outcomes [3, 4]. Treatment results of adjuvant chemotherapy may depend on the interaction between residual cancers and anticancer drugs. The Japanese recommendation for adjuvant chemotherapy is based on the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) study, which showed a survival benefit with adjuvant chemotherapy after D2 gastrectomy compared with surgery alone [4]. This study showed a survival benefit for stage II and IIIA gastric cancer [4]. However, the FLAGS trial for advanced gastric cancer or gastroesophageal cancer that compared cisplatin and S-1 versus cisplatin and fluorouracil in non-Asian countries did not prolong overall survival [7]. In Korea, adjuvant immunochemotherapy in advanced gastric cancer patients, who had undergone radical subtotal gastrectomy for stage III gastric cancer has been performed. For immunotherapy, a *Streptococcus pyogenes* preparation (picibanil) was followed by MF (mitomycin C and 5-FU) in the late 1990s and early 2000s [3, 8]. The Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer (CLASSIC) study was designed to compare the effect of adjuvant capecitabine plus oxaliplatin after D-2 gastrectomy with stage II or III gastric cancer [1]. Although adjuvant chemotherapy is a standard treatment option for operable gastric cancer, there have been some differences concerning methods of chemotherapy and survival data between the Western world (Europe and North America) and East Asia (Korea and Japan). Therefore, this article summarizes the adjuvant chemotherapy for resectable gastric cancer using a medical literature review.

## 2. Treatment results with adjuvant chemotherapy

Treatment results of adjuvant chemotherapy may depend on the interaction between residual tumor and anticancer drugs. The tumor burden should be reduced as much as possible to obtain the most optimal survival benefit of adjuvant chemotherapy [10]. As compared to Western countries, the high survival rate in East Asia might have resulted from a selection of early-stage patients and radical operations, including systematic lymph node dissection [10]. The Southwestern Oncology Group (SWOG) conducted a two-armed prospective, randomized trial of adjuvant chemotherapy for patients with gastric adenocarcinoma surgically resected to negative margins (**Table 1**). Most patients (54%) had undergone a D0 dissection, which is less than a complete dissection of the N1 nodes. The chemotherapy regimen included fluorouracil, 425 mg/m<sup>2</sup> of body-surface area per day, and leucovorin, 20 mg, followed by radiotherapy of 4500 cGy of radiation at 180 cGy/day. The median survival time in the surgery group was 27 months as compared with 36 months in the chemoradiotherapy group [5]. The 3-year survival rates were 50% in the chemoradiotherapy group and 41% in the surgery-only group [5, 11]. The 503-patient United Kingdom National Cancer Research Institute (NCRI) Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial was the first randomized trial to demonstrate the survival benefit from the use of perioperative chemotherapy for patients with resectable gastric cancer compared with surgery alone.

Study	Regimen (surgery + chemotherapy surgery alone)	No. of patients	3-YSR (%)	5-YSR (%)
Macdonald et al. [5]	5FU + leucovorin + radiotherapy	281	50	40
	Control	275	41	30
Cunningham et al. [6]	Epirubicin + cisplatin +5FU	250	45	36
	Control	253	30	23
Sakuramoto et al. [4, 9]	S-1	529	80	71
	Control	530	61	70
Bang et al. [1, 2]	Capecitabine + oxaliplatin	520	83	78
	Control	515	78	69

YSR, year survival rate.

**Table 1.** Adjuvant chemotherapy compared to the surgical control of curative resection of stomach cancer.

The patients who received perioperative chemotherapy with the ECF regimen (epirubicin, cisplatin, and 5-fluorouracil, 5FU) had a 5-year survival of 36%, compared with 23% in patients treated with surgery alone [12] (**Table 1**). Kim et al. evaluated 10,783 consecutive patients who underwent operation for gastric cancer [3]. The prognostic significance of treatment modality (surgery alone, surgery + chemotherapy, surgery + immunotherapy + chemotherapy <immunochemotherapeutic treatment>) was evaluated for stage III gastric cancer. The protocol for immunochemotherapy was as follows: Picibanil (a *Streptococcus pyogenes* preparation; Tokyo, Japan), mitomycin C 4 mg/50 kg, and 5-FU 500 mg/50 kg. They concluded that radical lymph node dissection, with more than 25 resected lymph nodes, improved survival in patients with stage II and IIIC disease; as postoperative adjuvant therapy, immunochemotherapy was most effective in patients with stage III disease. There were significant differences in survival in stage III patients; the 5-year survival rates were 44.8% for the immunochemotherapy group, 36.8% for the surgery + chemotherapy group, 36.8% for the surgery + chemotherapy group, and 27.1% for the surgery-alone group [3]. In the meta-analysis, which assessed entitled adjuvant chemotherapy after curative resection for gastric cancer in Non-Asian patients, Earle et al. concluded adjuvant chemotherapy may produce a small survival benefit of borderline statistical significance in patients with curatively resected gastric carcinoma [13]. Sakuramoto et al. reported that patients with stage II or III gastric cancer who underwent gastrectomy with extended (D2) lymph node dissection were randomly assigned to undergo surgery followed by adjuvant chemotherapy with S-1 or to undergo surgery only. The analysis of the follow-up data showed that the 3-year overall survival rate was 80.1% in the S-1 group and 70.1% in the surgery-only group [4]. Consecutive results of the ACT-GC trial showed the overall survival rate at 5 years was 71.1% in the S-1 group and 61.1% in the surgery-only group (**Table 1**) [9]. In the Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer (CLASSIC) trial, the patients with stage II–IIIB gastric cancer who had curative D2 gastrectomy were randomly assigned to receive adjuvant chemotherapy of eight cycles of oral capecitabine (1000 mg/m<sup>2</sup> twice daily on days 1–14 of each cycle) plus intravenous oxaliplatin (130 mg/m<sup>2</sup> on day 1 of each cycle) for 6 months or surgery only. The 3-year disease-free survival was 74% in the

chemotherapy and surgery group and 59% in the surgery-only group. They concluded that adjuvant capecitabine plus oxaliplatin treatment after curative D2 gastrectomy should be considered as a treatment option for patients with operable gastric cancer [1].

### 3. Discussion

Adjuvant chemotherapy is a standard treatment option for operable gastric cancer and improves patient outcomes, but the preferred treatment differs by geographical region [10]. The recommended adjuvant treatment is chemoradiotherapy in the United States and perioperative chemotherapy in the United Kingdom and some parts of Europe [1, 5, 12]. The Japanese ACT-GC trial was the first large-scale randomized trial of adjuvant chemotherapy after curative resection with D2 gastrectomy [4]. In the Republic of Korea, the CLASSIC trial was the second large-scale randomized trial after D2 gastrectomy [1]. The survival rate of two Asian large-scale randomized trials was substantially higher than in the US Intergroup-0116 and UK MAGIC trials (78% in the CLASSIC trial, 80% in ACT-GC vs. 30–40% in the Intergroup-0116 and MAGIC trials) [1, 4, 5, 12]. Most recurrences after surgery of gastric cancer occurred within 3 years of surgery [14]. The duration of adjuvant chemotherapy differed from previous studies. Kim et al. had adjuvant chemotherapy for 24 months [3]. The ACT-GC trial had adjuvant chemotherapy for 12 months [4]. CLASSIC trial had adjuvant chemotherapy 6 months [1]. The duration of adjuvant chemotherapy after surgery was different, although similar survival results were present in two clinical trials. Kim et al. reported that radical lymph node dissection, with more than 25 resected lymph nodes, improved survival in patients with stage II and IIIa disease [3]. Postoperative immunochemotherapy was most effective in patients with stage II and III disease [3]. The favorable outcomes of Asian studies were a result of the consistent adoption of D2 gastrectomy and the quality control of surgery using video techniques [1, 4]. But postoperative chemoradiotherapy in the United States and perioperative chemotherapy in Europe is not based on D2 gastrectomy. In the Intergroup-0116 study, quality assessment was done for radiotherapy before the initiation of this treatment [5]. However quality control of surgery was not done, because patients were usually identified postoperatively, and they could not require specific surgical procedures. Only 10% of the patients underwent a D2 dissection, while 36% had a D1 dissection, and 54% had a D0 lymphadenectomy (a resection in which not all of the N1 nodes were removed) [5]. The low long-term survival rate of stomach cancer patients in Western studies might result from excessive residual tumor left behind during surgery. The high survival rate in countries such as South Korea and Japan might be the reflection of the small amount of residual tumor due to radical gastrectomy and extensive lymph node dissection [10]. Songun et al. [15] reported that after a median follow-up of 15 years, D2 lymphadenectomy with strict quality control is associated with lower locoregional recurrence and gastric cancer-related death rates in patients with stage II and IIIa disease than D1 surgery; they recommended D2 resection as the standard surgical approach to resectable gastric cancer [15]. The CLASSIC and ACT-GC trials showed the effectiveness of postoperative adjuvant chemotherapy with S-1 and XELOX for stage II and III gastric cancer patients who underwent D2 gastrectomy [1, 4]. Biological aspects may cause the different gastric cancer results between



East Asia and the Western world. However, no significant differences in prognostic factors were reported between these two regions of the world. In conclusion, for all patients with stage II and III gastric cancer worldwide, standard D2 gastrectomy and adjuvant chemotherapy are strongly recommended for a better rate of survival.

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