The first step on earth: A small step for a trial, a giant leap for mankind

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Gastric cancer is the second leading cause of cancer-related deaths worldwide (1). The 5-year survival rate is about 75% in resected patients with the early stage of the disease. However, the prognosis worsens with lymph node involvement, which predicts an increase in the probability of loco-regional and distant recurrences. As a result, there is a great interest in adjuvant therapies for resected gastric cancer patients over the last 40 years.

As a result of the INT0116 trial, a postoperative chemoradiotherapy became the standard treatment for stages II-IV in gastric cancer patients who underwent D0/D1 resections in the United States (2). The INT0116 trial found that postoperative chemoradiotherapy improved the 3-year survival from 41% to 50%, compared to surgery alone. In Europe, following the results of the MAGIC trial, perioperative chemotherapy has been accepted as standard care for gastric cancer with an improved 5-year survival from 23% to 36%, compared to surgery alone (3). Most of the patients in both the INT0116 and MAGIC trials underwent D0/D1 resections since the two large European trials that compared D1 and D2 resections failed to demonstrate any survival benefit of D2 over D1 resections (4,5). However, 15-year follow-up results of a Dutch trial showed a gastric cancer-specific survival improvement with a D2 resection (6). In Asia, a single-center Taiwanese trial found that a D2 resection led to better survival outcomes than a D1 dissection (7). As a result, the D2 resection is now recommended for gastric cancer not only in Asia but in Europe and the US as well.

The ACTS-GC trial was the first multicenter prospective randomized study that showed the benefit of adjuvant chemotherapy for gastric cancer patients who underwent D2/D3 resections. A total of 1,034 Japanese patients were randomly assigned to undergo surgery followed by adjuvant therapy with S-1 (517 patients) or surgery alone (526 patients). The three-year survival rates were 80.1% and 70.1% in the S-1 and control group, respectively (P=0.003). The 5-year follow-up results of the ACTS-GC trial reconfirmed that 1 year of treatment with S-1 improved the OS and RFS compared to the surgery alone (8).

Moreover, the ACTS-GC trial showed the clinical significance in terms of demonstrating natural survival outcomes and a pattern of recurrence after D2/D3 resection in gastric cancer patients. However, there were some limitations in this trial. First, the ACTS-GC trial was performed only in Japan. Recently, the CLASSIC trial was performed in Asian (Korea, China, and Taiwan) (9). It is the second largest randomized trial for adjuvant chemotherapy in gastric cancer patients. It demonstrated that combination chemotherapy with capecitabine and oxaliplatin after a D2 gastrectomy improved the 3-year DFS compared to the surgery alone. The ACTS-GC and CLASSIC trial used the D2/D3 and D2 resections, respectively, for all patients since the D2 resection is the standard method of surgery in East Asia. Unfortunately, the benefits of the adjuvant chemotherapy in these trials might not be easily extrapolated to populations who commonly received D1 resections in Western countries. Second, in the subgroup analysis of the ACTS-GC trial, the more advanced stages showed a trend of decreasing benefits for adjuvant S-1 monotherapy. We therefore need to investigate more potent adjuvant regimens for advance stage gastric cancer patients, especially considering the disappointing survival outcomes in stage IIIB patients (disease-free survival rate of 37.6% at 5 years). Third, we also should consider the treatment duration and dose intensity in the ACTS-GC trial to choose a better regimen for future adjuvant trials. Only two thirds of all patients completed the 1-year treatment in the ACTS-GC, while the CLASSIC trial had a shorter duration of treatment with a

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Table 1. Survival Rates.

Study	3-year Survival Rates		5-year Survival Rates	
	Surgery only (%)	Adjuvant therapy (%)	Surgery (%)	Adjuvant therapy (%)
INT0116	41	50	28	43
MAGIC[‡]	31	44	23	36
ACTS-GC	70	80	61	72
CLASSIC	78	83	N/A	N/A

[‡]The patients of the MAGIC trial received perioperative therapy rather than adjuvant therapy.

higher dose intensity using doublets. Fourth, it should also be noted that the peritoneum was the most frequent recurrence site although patients with positive peritoneal fluid cytology were excluded. Previous Japanese studies have reported a treatment effect of S-1 for peritoneal metastasis, which was not definitely shown in the ACTS-GC study. S-1 adjuvant chemotherapy reduced the incidence of recurrence, but the pattern of recurrence did not change at all. It emphasizes the necessity of a new treatment strategy again for resected advanced gastric cancer. Fifth, there are some limitations of the data quality with different patient follow-up schedules between the adjuvant chemotherapy and surgery alone groups. Finally, the follow-up loss rate was relatively high (12.4%) probably due to too many participating centers.

All of the four trials (INT0116, MAGIC, ACTS-GC, and CLASSIC) demonstrated the clinical significance of adjuvant chemotherapy for gastric cancer. But overall, the survival rates of the ACTS-GC and CLASSIC trials were quite better than those of the INT0116 and MAGIC trials (Table 1), which mean that curative D2 surgery is the most important factor for gastric cancer.

In summary, the ACTS-GC was the first randomized prospective trial showing the benefits of adjuvant chemotherapy after D2/D3 resections in gastric cancer patients. However, it is necessary to investigate the proper adjuvant regimen for patients with more advanced stages and those who underwent D1 resection (high remaining tumor burden from non-curative surgery compared to the D2 resection) based on the limitation of the S-1 monotherapy efficacy in the ACTS-GC trial.

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