



Now and Near Future of Adjuvant Therapy for Gastric Cancer

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Perspective

Adjuvant chemotherapy following R0 resection of advanced gastric cancer has been performed in Japan since the 1950 [1]. Many phase III studies have been conducted to evaluate the role of adjuvant chemotherapy compared to surgery alone. However, the efficacy of adjuvant chemotherapy was not demonstrated for some time for several reasons, including small sample sizes, study population heterogeneity, use of various chemotherapy regimens, and differences in surgical quality.

In 2010, a meta-analysis conducted by the Global Advanced/Adjuvant Stomach Tumor Research International Collaboration (GASTRIC) group analyzed 17 trials [2] that included: 3,838 cases, and demonstrated a significant benefit of postoperative adjuvant chemotherapy with fluorouracil-based regimens compared to surgery alone with respect to both overall survival (OS) (HR: 0.82, 95%CI, 0.76-0.90, $p < 0.001$) and disease-free survival (DFS) (HR: 0.82, 95%CI, 0.75-0.90, $p < 0.001$). Furthermore, 5-year OS rates increased from 49.6% to 55.3% with adjuvant chemotherapy. Four major randomized phase III studies of adjuvant therapy performed in western countries and East Asia [3-6], also demonstrated incontrovertible survival benefits associated with adjuvant therapy (Table 1).

Therefore, adjuvant therapy is considered to be effective in improving DFS and OS following complete surgical resection (R0) of locally advanced gastric cancer by eradicating micro-metastases in both loco-regional and distant sites. However, no global consensus regarding the best strategy following curative surgery for loco-regional resectable advanced gastric cancer currently exists.

In eastern countries such as Japan and Korea, D2 gastrectomy (lymphadenectomy of the perigastric artery [D1] plus the celiac artery and its branches) is considered to be imperative for the treatment of advanced cases; D2 dissection was performed in the ACTS-GC and CLASSIC studies in almost all cases. In contrast, in the MAGIC study, D2 gastrectomy was performed in fewer than half of all cases, and only 9.6% of cases underwent this procedure in the INT0116 study. The survival benefit provided by chemoradiation in the INT0116 study was suggested to improve local control of microscopic disease remaining in the surgical bed in the case of inadequate surgery. An analysis of failure patterns supports this hypothesis: chemoradiation decreased local recurrence (8% vs 2%) and regional failure (39% vs 22%) but the percentages of distant failures in the two treatment arms were almost equivalent (18% in the surgery alone arm vs. 16% in the chemoradiation arm). The extent of surgery obviously influences loco-regional control. However, D2 lymphadenectomy, particularly when combined with splenectomy or pancreaticosplenectomy, has been reported to increase both morbidity and mortality. In western countries, it was widely accepted that D2 gastrectomy does not improve survival compared to D1 gastrectomy and is associated with increased postoperative morbidity and mortality based on the results of two large European randomized trials [7,8]. However, the 15-year follow-up results of a Dutch trial reported in 2010 [9], demonstrated a lower rate of local recurrence and cancer-related mortality in the D2 group compared to the D1 group. Furthermore, in the last decade, D2 dissections with safer, spleen- and pancreas- preserving D2 resection techniques have become increasingly popular in western countries and are recommended in high-volume hospitals with experienced surgeons [10]. Therefore, the discrepancy between the utility of R0 operations in the east and west is expected to be reduced in the future, and differences in adjuvant chemotherapy use in the east and west are expected to decline in the nearly future, as well.

In a subgroup analysis of the ACTS-GC and CLASSIC studies, adjuvant chemotherapy significantly improved 5-year OS of stage II gastric cancer (ACTS-GC: HR 0.509, 95%CI, 0.338-0.765, CLASSIC: HR, 0.66, 95%CI, 0.51-0.85), but for stage IIIB gastric cancer, no significant effects were observed (ACTS-GC: HR, 0.791, 95%CI, 0.520-1.205, CLASSIC: HR, 0.67, 95%CI, 0.39-1.13).

Therefore, more intensive strategies have been evaluated for stage III advanced gastric cancer.

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Table 1: Major randomised phase III studies of adjuvant therapy for localized gastric cancer.

Study	Stage	Treatment	No.	D2 dissection (%)	5-Year DFS (%)	5-Year OS (%)	The ratio of the completed (%)	P Value
Western								
Macdonald et al. [3]	IB-IV(MO)	post-operative FL+RT	281	9.6	48*	50*	63	0.005
(INT016)		Surgery alone	275		31*	41*		
Cunningham et al. [4]	II-IV(MO)	Pre & post operative ECF	250	42.5	NA	36.3	49.5	0.009
(MAGIC)		Surgery alone	253	40.3	NA	23		
Eastern								
Sasako et al. [5]	II-III	Adjuvant S-1	529	100	65.4	71.7	65.8	<0.05
(ACTS-GC)		Surgery alone	530	99.8	53.1	61.1		
Noh et al. [6]	II-III	Adjuvant XELOX	520	100	68	78	66.5	0.0015
(CLASSIC)		Surgery alone	515	100	53	69		

*: 3 year survival; FL: 5 fluorouracil+leucovorin; RT: Radiotherapy; ECF: epirubicin+cisplatin+5FU; XELOX: capecitabin+oxaliplatin

In Japan, S-1+cisplatin (SC) [11], S-1+oxaliplatin (SOX) [12,13], and docetaxel+S-1 (DS) [14] were effective in improving survival in patients with unresectable or recurrent gastric cancer, and are regarded as candidate postoperative adjuvant chemotherapy regimens. The SC regimen was confirmed to be feasible in the postoperative setting in a phase II study, which reported a promising 3-year OS rate of 84.5%. The SOX regimen was also reported to be as effective and less toxic than SC for advanced gastric cancer, therefore, SOX appears to be more suitable for adjuvant chemotherapy than SC. A phase III study comparing adjuvant DS to S-1 (JACCRO GC-07) in stage III gastric cancer was initiated in 2013 and is currently on-going.

Another area of research involves the use of molecularly targeted agents. Both trastuzumab (an antibody directed against human epidermal growth factor receptor 2 [HER2]) [15] and ramucirumab (an antibody directed against vascular endothelial growth factor receptor 2) [16] demonstrated efficacy in phase III clinical trials combined with other chemotherapeutic agents. In the ToGA (Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer) study, trastuzumab combined with cisplatin and either fluorouracil or capecitabine significantly prolonged OS in patients with HER2-positive gastric cancer; these regimens are also being investigated as neoadjuvant and/or adjuvant therapies in HER2-positive gastric cancer [17].

In conclusion, adjuvant chemotherapy for advanced gastric cancer following R0 operation by D2 gastrectomy is associated with improvement in OS, but more effective regimens are required for the treatment of stage III gastric cancer.

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