22 Adjuvant and Neoadjuvant Treatment: Standard Treatment and Clinical Trials in the East

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Actual Standard of Adjuvant Therapy in the East

Principles

Due to results of several clinical trials [1–3], it is widely accepted that good local control by either radiation therapy or surgery is essential to cure gastric cancer. D2 dissection provides better local control of gastric cancer than D1 or D1 + radiation [4, 5]. High incidence of nodal disease in gastric cancer occurs in relatively early stage tumor as well, which justifies prophylactic application of D2 lymphadenectomy for stage IB or more advanced tumors [6].

Standard of Care in the Eastern Asian Countries

D2 dissection is widely accepted as common practice without serious increase of mortality with limited increase of morbidity in the East, due to high volume of patients with gastric cancer in each institution. Based on this surgical practice, adjuvant treatment does not include radiation therapy. Based on the results of two pivotal studies in this area [7, 8], postoperative adjuvant chemotherapy is the standard of care.

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The advantage of postoperative setting of adjuvant treatment is that unnecessary toxic treatment can be avoided for patients who do not need any adjuvant treatment (stage I). This was a weak point of pre- or perioperative adjuvant treatment. In the MAGIC study of perioperative chemotherapy, 8.3 % of patients in surgery alone arm had T1 tumor, suggesting that similar proportion of patients in the peri-operative chemotherapy group were overtreated by unnecessary toxic agents [9]. Good prognosis of stage I patients after surgery alone means probability of occult residual cancer cells, which are target of adjuvant treatment, is very low (less than 10 %) in these patients [10]. Unlike Western countries, proportion of stage I patients in Korea and Japan is more than 50 %, thus this concept is quite important for patients and medical economy [11, 12].

Standard Regimen of Postoperative Chemotherapy

The adjuvant chemotherapy trial of TS-1 for gastric cancer (ACTS-GC) study showed significantly better overall survival (OS) and relapse-free survival (RFS) of the patients with stage II and III (Japanese classification [13]) gastric cancer using TS-1 monotherapy than surgery alone. Hazard ratio (HR) was 0.669 (95 % CI:0.540–0.828) for whole patients and that was 0.509, 0.708, 0.791 for stage II, IIIA, IIIB patients, respectively [8]. This monotherapy reduced mainly peritoneal (HR: 0.687) and nodal + local

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recurrence (0.505) but not remarkably distant metastasis (HR: 0.86). Based on these results, S-1 monotherapy is widely accepted in East Asian countries as one of the standard adjuvant treatment.

CLASSIC study showed significantly better disease-free survival (DFS) and OS for stage II and III (UICC TNM classification [14]) using XELODA + oxaliplatin (XELOX). HR of DFS was 0.56 (95% CI: 0.44–0.72) for whole patients and that was 0.55, 0.57, 0.57 for stage II, IIIA, IIIB patients, respectively [7]. These results were confirmed after 5-year follow up [15]. The HR of OS was 0.66 (95CI: 0.51–0.85) for whole population and 0.54, 0.75, and 0.67 for stage II, IIIA, IIIB, respectively. The HR of DFS was 0.58 (95% CI: 0.48–0.72). This doublet chemotherapy reduced mainly hematogenous (HR: 0.61) and nodal + local (HR: 0.51) but not peritoneal recurrence (HR: 0.87), which makes clear contrast with TS-1 monotherapy. Based on these results, XELOX is one of the standard treatments in Korea, China, and Taiwan. This study has two weak points: First, high proportion of patients did not receive allocated treatment (11% in surgery alone arm and 19% in chemotherapy arm) and secondly unusually large number of censored cases are seen in survival curves (both OS and DFS), suggesting lack of robustness of the statistical analyses.

Remaining Clinical Questions

1. Is stronger or more intensive adjuvant treatment more efficient?
   Since there was a tendency of worse HR with more advanced stage in the ACTS-GC study, more intensive treatment is searched for stage III patients. Theoretically, more intensive and therefore stronger chemotherapy might be better than single agent therapy, but expected worse feasibility (tolerance) of such treatment after D2 gastrectomy might ruin chemotherapeutic effect.
2. Can OS be improved by adding preoperative chemotherapy to postoperative chemotherapy?
   Advantage and disadvantage of preoperative chemotherapy (neoadjuvant chemotherapy (NAC)) is shown in Table 22.1. Unlike colon cancer, disturbance of oral intake is prominent after surgery in gastric cancer patients. Therefore, the most important benefit of NAC is high tolerability of rather intensive treatment, using multiple drugs. Another important benefit of NAC in gastric cancer is related with higher incidence of surgical complications

Table 22.1 Neoadjuvant versus postop adjuvant

	NAC	Postop adjuvant
Primary lesion	Expecting shrinkage	Resected
	Delayed resection	Early resection
	Minimal spillage	Spillage of tumor cells
Micrometastasis	Early treatment	Delayed treatment
	Less influence by surgery	Growth stimulation by surgery?
Macroscopic metastasis	M1 possible	Only micrometastasis
Tumor burden	Large tumor burden	Minimum tumor burden
Drug delivery	Better	Reduced
Judgment of efficacy	Always evaluable	Impossible
Selection of pts	Less information	Maximum information
Compliance of CTX	High	Low
Influence to surgery	Growth during CTX	No influence
	Toxicity may cancel surgery	
	Toxicity may delay surgery	
	Potential increase of morbidity	
	Potential increase of mortality	

which may hamper early start of adjuvant chemotherapy than in colorectal cancer.

3. Is there any role of radiation therapy added to chemotherapy after D2 surgery?
   The update analysis of INT0116 study showed that chemoradiotherapy in this trial reduced mainly local regional recurrence but not systemic recurrence. These data support the finding that this treatment is effective after D0/1 surgery but not after D2 surgery [16]. After the results of INT0116 study were published, a Korean group performed a phase III study to compare adjuvant chemoradiation with surgery with chemotherapy (XELOX) alone (ARTIST trial) [17]. Although there was a subgroup in which borderline benefit of this treatment was suggested, primary endpoints did not meet [17]. Chemoradiation after D2 surgery was not accepted as efficient adjuvant treatment for gastric cancer but there remains a question about role of radiation therapy after D2 surgery in advanced stage.

Ongoing Phase III Clinical Trials in Asia to Solve these Questions (Table 22.2)

1. Comparing two adjuvant chemotherapy after D2 surgery
   a. S-1 + oxaliplatin (SOX) versus S-1 (POTENT study)
   b. Capecitabine + oxaliplatin (XELOX) versus XELOX + docetaxel
   c. S-1 versus S-1 + docetaxel
2. Evaluation of additional effect of NAC
   a. NAC by docetaxel + SOX followed by adjuvant S-1 after D2 surgery versus S-1 adjuvant after D2 surgery
   b. NAC by SOX followed by SOX after D2 versus SOX after D2

Table 22.2 Recent randomized trials for neoadjuvant and adjuvant chemotherapy

Number in the text	Trial registration number	Control arm	Test arm 1	Test arm 2	Country	Sponsor
1-a) POTENT	NCT01795027	S-1	SOX		China	University
1-b)	NCT01935778	XELOX	XELOX + Doc		Korea	Hospital
1-c) START-2	UMIN000010337	S-1	S-1 + Doc		Japan	Cooperative Group
2-a) PRODIDY	NCT01515748	S-1	NAC by DSOX + surgery + S-1 (post)		Korea	Drug company
2-b) RESONANCE	NCT01583361	SOX	NAC by SOX + surgery + SOX		China	Hospital
2-c)	NCT01534546	XELOX	SOX	NAC by SOX + surgery + SOX + S-1	China	University
2-d)	NCT01665274	XELOX	NAC by XELOX + surgery + XELOX		China	University
3-a) ARTIST II	NCT01761461	SOX	S-1	SOX + S-1 with radiation + SOX	Korea	Hospital
3-b)	NCT01815853	Periop XELOX	Preop CRT (XELOX) + surgery + XELOX		China	University
3-c)	NCT01711242	XELOX	XELOX with radiation		China	University

CRT chemoradiation therapy

   c. NAC by SOX followed by SOX after D2 followed by S-1 versus SOX after D2 versus XELOX after D2
   d. NAC by XELOX followed by XELOX after D2 versus XELOX after D2
3. Role of radiation therapy added to adjuvant chemotherapy
   a. Surgery + S-1 versus surgery + SOX versus surgery + SOX + radiation (ARTIST II trial)
   b. NAC by XELOX + surgery followed by XELOX with or without concurrent preoperative radiotherapy
   c. Surgery + XELOX with radiation versus XELOX

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