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Update of Adjuvant Chemotherapy for Resected Gastric Cancer

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Gastric cancer is the second cause of cancer that is related to death and the fourth most common cancer, worldwide. Complete resection of cancer is the only curative treatment for gastric cancer. However, even if complete resection is possible, recurrence is frequently observed in Gastric patients. Therefore, adjuvant treatment modality for resectable gastric cancer is needed to increase the survival of patients. This study wants to describe the role of adjuvant chemotherapy for resectable gastric cancer, with updated data of recent studies. Several meta-analysis studies demonstrated a benefit of adjuvant chemotherapy for resectable gastric cancer. Due to the heterogeneity of the population and regimens, there is no consensus regarding the adjuvant chemotherapy. Recently published, well designed phase III studies demonstrated the statistically significance of adjuvant chemotherapy for the resectable gastric cancer, with the extended lymph node dissection. Further phase III trials, to determine the best regimen and schedule of adjuvant chemotherapy, was suggested to use the fluoropyrimidine based regimen as control group.

Key Words: Gastric cancer; Adjuvant chemotherapy; Review

Introduction

Gastric cancer is the second cause of cancer related death worldwide, with 988,000 new cases and 736,000 deaths per year.(1) Despite decreasing frequency of worldwide, the high incidence of gastric cancer is a still major health concern in Eastern countries such as Korea and Japan. Complete resection of cancer is the only curative treatment for gastric cancer. However, even if complete resection is possible, recurrence is so frequent at later.(2) So adjuvant treatment for resectable gastric cancer is needed to increase the survival of patients. So many phase II or phase III trials were undertaken to detect the role of adjuvant chemotherapy for resectable gastric cancer. However until recently published, well designed phase III studies,(1,3) there is no consensus about adjuvant chemotherapy for gastric cancer. And the clinical practice of the management for gastric cancer is so diverse according to countries such as the extent of resection of gastric cancer, whether inclusion of radiotherapy or not, and timing of adjuvant chemotherapy. The D2 dissection is traditionally considered as standard treatment in Eastern countries. However western countries usually prefer to do dissection of lymph nodes with less than D2 dissection due to result of early Dutch trial that showed no benefit of D2 dissection.(3) However, long term follow up Dutch trials showed a reduction of cancer related death with surgery with D2 dissection.(4) Taiwanese study also supported benefit of D2 lymph node dissection for gastric cancer.(5) These studies supported rationale for the D2 dissection of gastric cancer worldwide when D2 surgery is done by experienced surgeons.(6) With recently published, well designed phase III trials for D2 dissection for gastric cancer and large scaled, patient's data driven. This study wants to describe the role of adjuvant chemotherapy for resectable gastric cancer with updated data of recent studies not the

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radiotherapy or perioperative chemotherapy.

Meta-Analysis of Adjuvant Chemotherapy

Several groups published the meta-analysis of data of adjuvant chemotherapy for gastric cancer for decades.(3,4,7-12) Hermans et al.(13) did not demonstrate the significant benefit of adjuvant chemotherapy versus surgery alone (odd ratio [OR] 0.88, 95% confidence interval [CI] 0.72~1.08),(14) However authors re-analysis the data including two important studies and demonstrated the significance (OR 0.82, 95% CI 0.68~0.97). Earle and Maroun(7) investigated using only western population the benefit of adjuvant chemotherapy for the gastric cancer, they demonstrated the significant benefit of survival of adjuvant chemotherapy versus surgery alone (OR 0.8, 95% CI 0.66~0.97). The Global Advanced/Adjuvant Stomach Tumor Research International Collaboration (GASTRIC) group published result of meta-analysis of individual patient data from 17 trials (3,838 patients) with median follow up exceeding 7 years.(3) They collected the data of patients from 17 trials and updated the survival status and date of last follow-up. They demonstrated that adjuvant chemotherapy was associated with a statistically significant benefit with overall survival (hazard ratio [HR] 0.82, 95% CI 0.76~0.90) and disease free survival (HR 0.82, 95% CI 0.75~0.90), In terms of analysis of regimens, they showed a statistically significant benefit of adjuvant monochemotherapy over surgery alone (HR 0.60, 95% CI 0.42~0.84; P=0.03). With polychemotherapies of fluorouracil, mitomycin C, and others without anthracyclines, the statistically significant benefit for overall survival was observed (HR 0.74, 95% CI 0.58~0.95; P=0.03). Polychemotherapies with fluorouracil, Mitomycin C, and anthracyclines demonstrated a significant HR reduction of overall survival (HR 0.82, 95% CI, 0.71~0.96; P=0.01), however other polychemotherapies group did not detecte a significant effect of adjuvant regimens versus surgery alone (HR 0.89, 95% CI 0.78~1.02; P=0.09). Based on these data, they suggested the fluoropyrimidines based regimen seems reasonable regimen options.(3)

The recently published meta-analysis studies suggest the benefit of adjuvant chemotherapy for gastric cancer, however they did not demonstrate consensus of chemotherapeutic regimen, schedule, and duration of treatment for adjuvant chemotherapy for gastric cancer.

Previous large scaled phase III Japanese trial with mitomycin C, fluorouracil, and followed oral UFT, a combination of tegafur, a prodrug of 5-fluorouracil (5-FU) and uracil treatment did not show significant difference between two groups.(15) They considered that negative result was from high proportion of T1 patients in their patients, because at these staged patients, the surgery alone yields a very good survival rate and there seemed no need for adjuvant therapy. The authors concluded that patients with T1 staged patients with gastric cancer should be excluded from further adjuvant chemotherapy trial, after that, following trials usually excluded these stage patients.

Adjuvant Chemotherapy for Extended Surgery Using D2 Lymph Node Dissection

The role of adjuvant chemotherapy for resectable gastric cancer was still remained to be answer to question, because so many previous phase III studies did not clearly show the benefit of adjuvant chemotherapy in case of D2 lymph node dissection setting. Previous studies usually did not enroll enough number of patients and included early stage patients.(16)

In Japan and Korea, D2 lymph node dissection was considered as standard treatment for early gastric cancer. Until the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) study, there were no well designed, large number patients enrolled phase III studies that show a significant benefit of adjuvant chemotherapy for gastric patients with D2 lymph node dissection.(17) The ACTS-GC study group demonstrated that adjuvant chemotherapy with 1 year treatment of S-1, oral fluoropyrimidine showed a significant benefit for gastric cancer with stage II and III who underwent gastrectomy with extended (D2) lymph node dissection.(17) The HR for death the S-1 treatment group, as compared with the surgery

Table 1. Meta-analysis of adjuvant chemotherapy for resectable gastric cancer

Author	Year	Number of trials	Number of patients	HR for overall survival (95% CI)
Mari et al.(10)	2000	20	3,658	0.82 (0.75~0.89)
Zhao and Fang(11)	2008	15	3,212	0.90 (0.84~0.96)
Liu et al.(12)	2008	19	4,599	0.85 (0.80~0.90)
GASTRIC group(3)	2010	17	3,838	0.82 (0.76~0.90)

HR = hazard ratio; CI = confidence interval.

alone group, was 0.68 (95% CI 0.52~0.87, P=0.003), the primary end point was overall survival, the 3 year overall survival rate was 80% in the S-1 group (95% CI 76.1~84.0) and 70.1% in the surgery only group (95% CI 0.50~0.77; P< 0.001). This study showed significant difference at 3 year overall survival. This study was first well designed, large scale study to demonstrate a benefit of adjuvant chemotherapy for gastric cancer with extended resection. However there is still issue about the regimen for adjuvant chemotherapy. Because S-1 monotherapy has not shown satisfied activity againist advanced gastic cancer. The reason that S-1 monotherapy showed effectiveness at adjuvant chemotherapy againist gastric cancer should be defined with further treatment. There are some opportunities to use recently introduced drug regimens that showed high activity to advanced gastric cancer as adjuvant chemotherapeutic drug. The duration of adjuvant treatment should be confirmed with further trials, because only 65% of patients who allocated on adjuvant chemotherapy remained on drug treatment.

In Korea, clinical trial with using a different regimen for adjuvant chemotherapy for the patients with gastric cancer was tried and recently published; Bang et al.(1) studied role of adjuvant chemotherapy against patients with gastric cancer who underwent D2 extended lymph node dissection using capecitabine and oxaliplatin combination treatment compared with surgery alone. This study demonstrated adjuvant chemotherapy was effective to at adjuvant setting against patients with gastric cancer. They enrolled patients with stage II~IIIB gastric cancer who had curative D2 resection. The primary endpoint was 3 year disease free survival, there is controversy about 3 year disease free survival as primary endpoints of resectable gastric cancer that used at The capecitabine and oxaliplatin adjuvant study in stomach cancer (CLASSIC) study, was not yet formally validated. However recently using GASTRIC data, Rougier and Sakamoto(18) showed that 3 year disease free survival was strongly correlated with 5 year overall survival and disease free survival was shown to be a relevant surrogate of overall survival. They collected 1,035 patients who were randomly assigned to receive either oxaliplatin/capecitabine combination group (n=520) or surgery (n=515). 3 year disease free survival was higher in the chemotherapy group than in the surgery alone group (HR 0.56, 95% CI 0.44~0.72; P< 0.0001),(1) 3 year disease free survival was 74% (95% CI 67~79) in the chemotherapy group and 59% (95% CI 53~64) in the surgery only group. In subgroup analysis, they showed the significant benefit through at all disease stage (II, III, and IIIB) that was not demonstrated at ACTS-GC study and patients with further nodal involvement could be more benefit (N2> N1> N0). The result of 3 year survival was not significant different with HR 0.72 (95% CI 0.52~1.00; P=0.0493), longer follow-up are need to show the significant benefit. In terms of safety profile, frequency of grade 3~4 adverse events was high compared with that of ACTS-GC but comparable to that of colon cancer studies,(19) most common were neutropenia (22%), thrombocytopenia (8%), and vomiting (7%). However 56% of patients experienced at least one grade 3~4 adverse events and 10% of patients discontinued chemotherapy due to adverse events in the chemotherapy group. Close monitoring of patient's status should be warranted.

Conclusions

Recently published studies supported that adjuvant chemotherapy could be benefit for resectable gastric cancer with extended lymph node dissection. However further clinical trials should be undertaken to make a consensus which regimen is better than others, time duration of adjuvant chemotherapy, and how to apply with multimodal treatment options. Further phase III trials to determine the best regimen and schedule of adjuvant chemotherapy was suggested to use the fluoropyrimidine based regimen as a control group.

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