Clinical Significance of Adjuvant Surgery Following Chemotherapy for Patients with Initially Unresectable Stage IV Gastric Cancer

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Abstract. *Background: More effective treatment is necessary to improve the poor prognosis for patients with unresectable gastric cancer. We investigated the efficacy and feasibility of adjuvant surgery following chemotherapy. Patients and Methods: Records of 70 patients with unresectable stage IV gastric cancer who underwent induction chemotherapy were reviewed retrospectively. Patients who developed an absence of non-curative clinical factors during chemotherapy underwent gastrectomy [adjuvant surgery (AS) group]; the others continued chemotherapy [non-AS group]. Results: Non-AS and AS groups contained 56 (80%) and 14 (20%) patients, respectively. In the AS group, 92.9% of patients had one non-curative clinical factor, while 48.2% of patients in the non-AS group had two or more non-curative clinical factors (p=0.0386). In the AS group, operative outcomes, including the postoperative complication rate (21.4%), were acceptable. The 3-year overall survival rate in the AS group was 65.6% versus 7.7% in the non-AS group (p<0.0001). In patients with one non-curative clinical factor of peritoneal dissemination, the median survival of the AS group was 29.5 months versus 11.4 months in the non-AS group (p=0.0230). Conclusion: Adjuvant surgery for initially unresectable stage IV gastric cancer was safe and feasible, and may improve the prognosis for patients with one non-curative clinical factor, such as peritoneal dissemination.*

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Gastric cancer is the second leading cause of cancer death worldwide. Despite development of chemotherapy, the prognosis of patients with stage IV gastric cancer remains poor. The median survival time (MST) for patients with unresectable or metastatic gastric cancer is three months with best supportive care (1), and this is extended to 13 months with chemotherapy (2). In Japan, 15.1% of patients with resected cancer had stage IV disease by the Japanese staging system, with a poor 5-year survival rate of 9.0% (3). Therefore, novel therapeutic strategies for advanced gastric cancer are required.

Surgery is not a treatment option for patients with unresectable gastric cancer, except for those who need palliative surgery for bleeding, obstruction or perforation caused by the tumor. The standard therapy for these patients is systemic chemotherapy. Recently, several combined chemotherapy regimens containing S-1, capecitabine, platinum agents (cisplatin and oxaliplatin), taxanes (paclitaxel and docetaxel), irinotecan and trastuzumab (2, 4-10) have shown potent effects for gastric cancer. The development of chemotherapeutic agents for gastric cancer encouraged us to perform adjuvant surgery for patients with initially unresectable gastric cancer who were converted to resectable status following their response to the chemotherapy. In initially unresectable colorectal cancer, this strategy is considered to be "conversion therapy" (11). Although there have been a few reports of adjuvant surgery (12-16) for unresectable gastric cancer, its role in multimodal treatment, candidate for adjuvant surgery remains unclear.

The purpose of this study was to evaluate the efficacy and feasibility of adjuvant surgery in patients with unresectable advanced gastric cancer who were converted to resectable status following chemotherapy.

Table I. *Clinicopathological features in patients with initially unresectable advanced gastric cancer.*

Variables	All patients (n=70)	Non-AS group (n=56)	AS group (n=14)	*p*-Value[a]
Age (years)[b]	64.4±11.6	65.3±11.6	60.8±11.5	0.1959
Gender				
Male	46 (65.7%)	38 (67.9%)	8 (57.1%)	
Female	24 (34.3%)	18 (32.1%)	6 (42.9%)	0.5336
Histology[c]				
Well	2 (2.9%)	2 (3.4%)	0	
Moderate	13 (18.6%)	10 (17.9%)	3 (21.4%)	
Poorly	46 (65.7%)	35 (62.5%)	11 (78.6%)	
Other	2 (2.9%)	2 (3.6%)	0	1.0000
Staging laparoscopy or exploratory laparotomy (before chemotherapy)				
Yes	15 (21.4%)	8 (14.3%)	7 (50.0%)	
No	55 (78.6%)	48 (85.7%)	7 (50.0%)	0.0078
Chemotherapy regimen (first-line)				
S-1	15 (21.4%)	14 (25.0%)	1 (7.1%)	
S-1/cisplatin	25 (35.7%)	19 (33.9%)	6 (42.9%)	
S-1/docetaxel	17 (24.3%)	12 (21.4%)	5 (35.7%)	
XP (HXP)	6 (1) (8.6%)	4 (0) (7.1%)	2 (1) (14.3%)	
Paclitaxel	6 (8.6%)	6 (10.7%)	0	
UFT/PSK	1 (1.4%)	1 (1.8%)	0	0.3870
Non-curative clinical factor[d]				
N factor	25 (35.7%)	23 (41.1%)	2 (14.3%)	
M factor	30 (42.9%)	29 (51.8%)	1 (7.1%)	
P factor	42 (60.0%)	30 (53.6%)	12 (85.7%)	0.0086
No. of non-curative clinical factors				
1	42 (60.0%)	29 (51.8%)	13 (92.9%)	
2	19 (27.1%)	18 (32.1%)	1 (7.1%)	
3	8 (11.4%)	8 (14.3%)	0	
4	1 (1.4%)	1 (1.8%)	0	0.0386

Non-AS group: Non-adjuvant surgery group, AS group: adjuvant surgery group, Well: well-differentiated adenocarcioma, Moderate: moderately differentiated adenocarcinoma, Poor: poorly differentiated adenocarcinoma, XP: capecitabine plus cisplatin, HXP: capecitabine plus cisplatin with trastuzumab, UFT/PSK: tegafur/uracil plus protein-bound polysaccharide kureha. [a]Fisher's exact test or Student *t*-test. [b]Mean±SD. [c]Data for seven cases of the non-AS group were not available. [d]Some cases overlapped.

Patients and Methods

Patients characteristics. The records of 70 patients with unresectable stage IV gastric cancer and remnant gastric cancer who were treated at the Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University between April 2005 and September 2013 were reviewed retrospectively (Table I). All 70 patients were considered to have unresectable disease based on image evaluation with or without staging laparoscopy or exploratory laparotomy due to non-curative clinical factors, such as N factor (lymph node metastasis beyond the regional lymph nodes), M factor (distant metastasis, such as to liver, lung, bone and skin) and P factor (positive peritoneal cytology with/without peritoneal dissemination). Stage classification and assessment of resected specimens were carried out in accordance with the guidelines of the Japanese Gastric Cancer Association (17).

Treatment strategy. Figure 1 shows the treatment strategy. Initially, all 70 patients underwent induction therapy with systemic chemotherapy. The indication for adjuvant surgery included the development of an absence of non-curative clinical factors during chemotherapy based on image evaluation and preoperative observation in the abdominal cavity by staging laparoscopy or laparotomy. In patients anticipated to be able to undergo curative resection from these examinations following the response to chemotherapy, gastrectomy with lymph node dissection was performed with the aim of R0 resection [adjuvant surgery (AS) group]. On the other hand, patients with persistent non-curative clinical factors continued to receive systemic chemotherapy [non-AS group]. Operative complications were graded according to the Clavien-Dindo classification of surgical complications (18).

Chemotherapy. For first-line chemotherapy, S-1 alone, S-1 plus cisplatin (SP), S-1 plus docetaxel, capecitabine plus cisplatin with or without trastuzumab (HXP, XP), paclitaxel alone, and tegafur/uracil plus protein-bound polysaccharide kureha (UFT/PSK) were administered. For the regimen of S-1 alone, S-1 was given orally twice daily for the first four weeks of a 6-week cycle. The dose of S-1 administered each time was as follows: for those with body surface area less than 1.25 m^2, 40 mg; for 1.25-1.5 m^2, 50 mg; and for greater

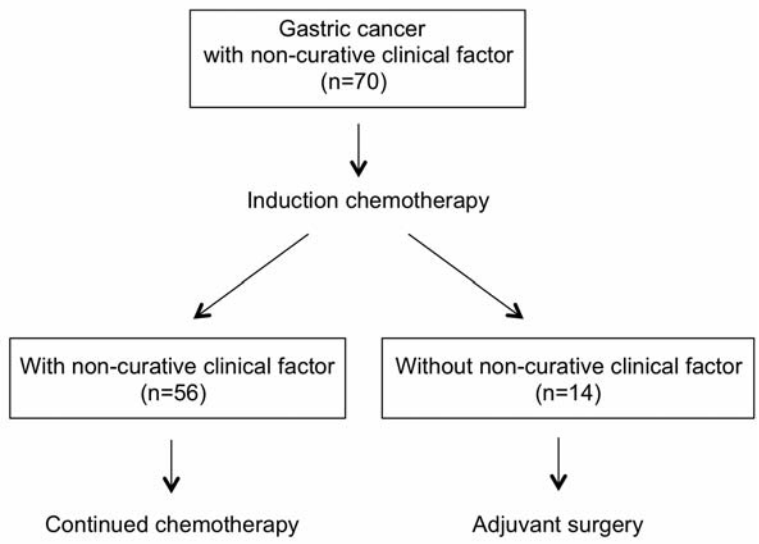

Figure 1. *Flow of patients through the study.*

Table II. *Operative outcomes of adjuvant surgery in 14 patients following the response to chemotherapy.*

Variables	AS group (n=14)
Period from induction of chemotherapy to adjuvant surgery (days)	100 (59-212)[a]
Interval between the days of last administration of chemotherapy and adjuvant surgery (days)	28 (13-72)[a]
Operation time (min)	301 (209-536)[a]
Blood loss (g)	274 (48-1665)[a]
Postoperative hospital stay (days)	13 (8-24)[a]
Operative procedure	
Open total gastrectomy	5 (with splenectomy: 1, with hepatectomy: 1)
Open distal gastrectomy	1
TLTG	5
TLDG	3
Postoperative complication	
None	11
Ileus (grade I)	1
Liver dysfunction (grade I)	1
Stenosis of esophagojejunal anastomotic site (grade IIIb)	1
Resectability	
pR0 resection	14
Histrogical therapeutic effect (primary lesion)	
Grade 1a	6
Grade 1b	2
Grade 2	6

TLTG: Totally laparascopic total gastrectomy, TLDG: totally laparscopic distal gastrectomy. [a]Data are expressed as median and range.

than 1.5 m2, 60 mg. For the SP regimen, S-1 (80 mg/m^2) was administered orally for three weeks, followed by a drug-free interval of two weeks. Cisplatin (60 mg/m^2) was administered on day 8 of each cycle (*i.e.*, every five weeks). For the docetaxel plus S-1 regimen, S-1 (80 mg/m^2) was administered orally for two weeks, followed by a drug-free interval of one week. Docetaxel (40 mg/m^2) was administered on day 1 of each cycle (*i.e.* every three weeks). For the XP regimen, cisplatin (80 mg/m^2) was given on day 1 of each 3-week cycle. Capecitabine (1,000 mg/m^2) was given orally twice a day for the first two weeks of the cycle followed by a 1-week rest period. Tumors were tested for human epidermal growth factor receptor 2 (HER2) status with immunohistochemistry and fluorescence *in situ* hybridization (FISH). Trastuzumab (8 mg/kg) was given on day 1 for patients whose tumor samples were scored as 3+

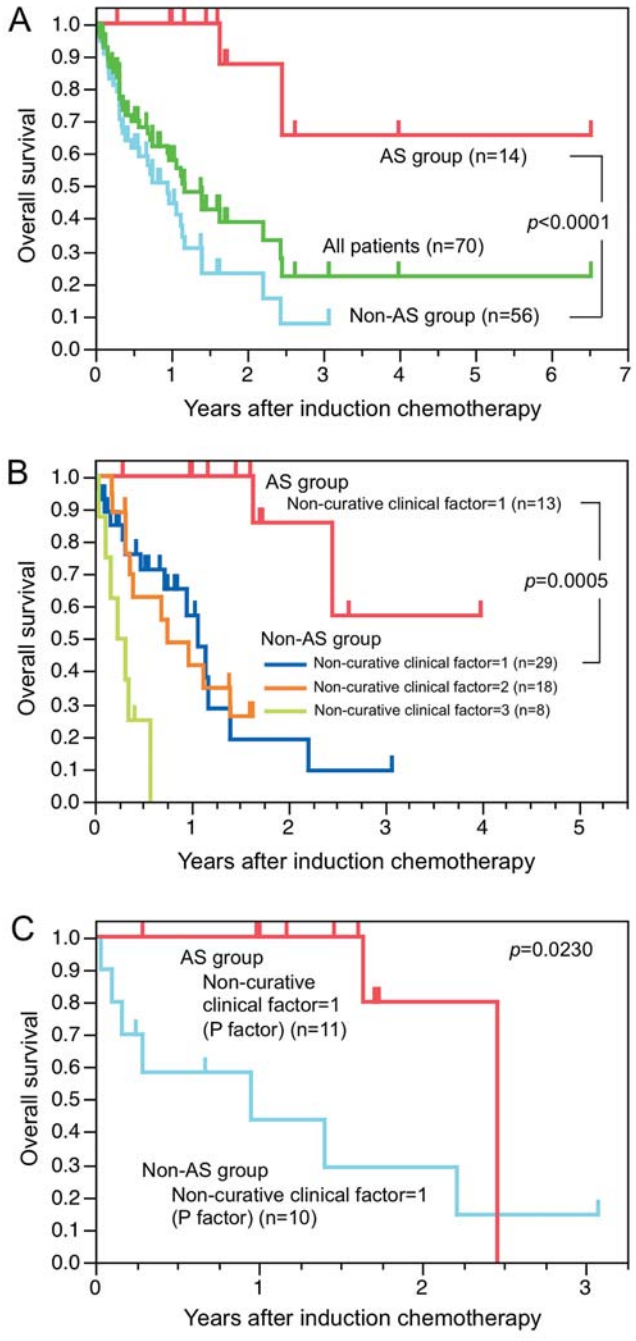

Figure 2. *A: Overall survival of all patients, adjuvant surgery (AS) group and non-AS group analyzed in this study. B: Overall survival of each group according to the number of non-curative clinical factors. C: Overall survival of each group with one non-curative clinical factor of peritoneal dissemination.*

on immunohistochemistry or were FISH-positive (HER2/CEP17 ratio ≥2) for the HXP regimen. For the regimen of paclitaxel alone, paclitaxel (80 mg/m^2) was administered, and this was repeated weekly for three out of four weeks. For the UFT/PSK regimen, UFT (300 mg) plus PSK (3 g) was given orally each day.

Statistical analysis. Associations between variables were tested with Fisher's exact test or Student's *t*-test. The survival rates of each group were compared with the log-rank test. A level of $p<0.05$ was considered significant.

Results

Patients' characteristics. The clinicopathological characteristics of the 70 patients (46 males and 24 females) analyzed are summarized in Table I. The non-AS and AS groups contained 56 (80%) and 14 (20%) patients, respectively. Histopathologically, poorly-differentiated adenocarcinoma was dominant in both groups (62.5% in the non-AS group and 78.6% in the AS group). Staging laparoscopy or exploratory laparotomy was performed before induction chemotherapy in 50% of patients in the AS group and in 14.3% of patients in the non-AS group ($p=0.0078$). The majority of first-line chemotherapy was the S-1-based regimen (80.3% in the non-AS group and 85.7% in the AS group), particularly the S-1/cisplatin regimen.

Non-curative clinical factors. The predominant non-curative clinical factor of the AS group was the P factor (85.7%), while for many of those of the non-AS group the M and P factors predominated (51.8% and 53.6%) ($p=0.0086$). In the AS group, the number of non-curative clinical factors was mainly one (92.9%), while approximately half of the patients (48.2%) in the non-AS group were diagnosed with more than two non-curative clinical factors ($p=0.0386$).

Adjuvant surgery. The operative outcomes of adjuvant surgery are shown in Table II. No patient encountered major intraoperative complications. The median postoperative hospital stay was 13 days. In terms of the operative procedure, open gastrectomy was performed on five patients from 2005 to 2011 and one patient in 2012 who required conversion to open surgery because of bleeding from the spleen. Laparoscopic gastrectomy was performed on eight patients from 2012. The postoperative complication rate was 21.4% (3/14), including ileus (grade I) and liver dysfunction (grade I) each in one patient. One patient underwent re-operation for stenosis of the esophagojejunal anastomotic site due to compression by the crus of the diaphragm one year after open total gastrectomy (grade IIIb). No direct operative mortality or postoperative hospital mortality was observed. With regard to resectability, R0 resection was achieved in all patients (100%). For the histological therapeutic effect assessed from the resected specimen, all of the patients were grade 1a-2, while no patient was evaluated as grade 0 or grade 3.

Survival rates. Figure 2A shows the overall survival (OS) rate after induction chemotherapy in all patients (n=70), the non-AS group (n=56) and the AS group (n=14). The mean

follow-up time after induction chemotherapy was 8.1 months (range=0.04-36.9 months) in the non-AS group and 24.8 months (range=3.5-78.3 months) in the AS group. The MST was 14.1 months, and the 5-year OS rate was 22.3% in the whole patient group. Survival in the AS group was statistically more prolonged than in the non-AS group (3-year OS rates of 65.6% *versus* 7.7%, respectively; $p<0.0001$). Figure 2B shows the OS according to the number of non-curative clinical factors in each group. The MST of patients with one non-curative clinical factor in the AS group was more than 36 months, while in the non-AS group, that of patients with one, two and three non-curative clinical factors was 12.8, 9.0 and 3.8 months, respectively. In the patients who had one non-curative clinical factor, the OS of the AS group was significantly higher than that of the non-AS group ($p=0.0005$). Moreover, in patients who had one non-curative clinical factor (the P factor), the OS of those in the AS group (n=11) was significantly higher than that of those in the non-AS group (n=10) (MST of 29.5 months *versus* 11.4 months, respectively; $p=0.0230$) (Figure 2C).

Discussion

The rationale for induction chemotherapy in patients with initially unresectable advanced cancer is based on the impossibility of performing an R0 resection and a high risk of micrometastatic disease in addition to the presence of non-curative clinical factors. Although intensive chemotherapy is essential for increasing the R0 resection rate, patients with advanced cancer often do not have good performance status, and it is necessary to reduce the dose of the anticancer drug or to stop the protocol during chemotherapy. This is one of the reasons it is difficult to convert patients from an unresectable to a resectable status.

In spite of the development of new anticancer drugs, surgery remains the central element in the curative treatment of gastric cancer. Even with S-1 plus cisplatin, which is a standard regimen for unresectable and recurrent gastric cancer, the response rate was 54% and the MST was 13.0 months (2), which is similar to that for the non-AS group (11.4 months) in our study. In addition, only radical resection (R0 resection) is associated with long-term survival (19), while the prognosis of patients with noncurative tumor resection is extremely poor (20, 21). Therefore, adjuvant surgery with the aim of R0 resection should be performed before the tumor acquires refractoriness to anticancer drugs and begins to grow again, and before it becomes difficult to continue chemotherapy due to toxicity. In our series, pR0 resection was performed in all 14 patients who underwent gastrectomy, which is higher than in other studies (59-75%) (13-16).

The results of the present study suggest that adjuvant surgery following chemotherapy was safe and well tolerated, even by patients with unresectable gastric cancer, considering that advanced cancer and preoperative chemotherapy may increase morbidity and mortality due to depression of the immune system and malnutrition, such as cachexia (20-25). No operative or postoperative hospital mortality was observed. The operative time, blood loss, postoperative hospital stay and operative morbidity were acceptable compared with those for surgery without preoperative chemotherapy (26).

It is natural that patients in the AS group showed better survival than those in the non-AS group for several reasons. Firstly, the patients with initially unresectable gastric cancer analyzed in this study varied according to the severity of their non-curability, as indicated by the number of non-curative clinical factors. Most of the patients (92.9%) in the AS group had only one non-curative clinical factor, while half of the patients in the non-AS group (48.2%) had more than two non-curative clinical factors. Secondly, the patients in the AS group were chemotherapy responders, since they were converted to a resectable status. Thirdly, all patients (14/14) in the AS group underwent pR0 resection. Considering these biases, we analyzed the OS of the patients with one non-curative clinical factor in each group, which still showed there to be a better prognosis in the AS group (Figure 2B). Indeed, to examine the efficacy of adjuvant surgery for initially unresectable gastric cancer, a randomized control trial is required that evaluates OS between the AS group and the continuous chemotherapy group from the point that the tumor was converted to resectable status following chemotherapy.

It is controversial which group of patients benefit from adjuvant surgery from the aspect of non-curative clinical factors. In previous studies, the candidate non-curative clinical factors for adjuvant surgery varied among the N factor (12, 15), M factor (liver metastasis) (12) and P factor (13, 14). In our study, the most common non-curative clinical factor in the AS group was the P factor (85.7%). The survival of patients in the AS group with the P factor alone was better than that of patients in the non-AS group with the P factor alone (Figure 2C), which suggests that the P factor is a promising candidate as a non-curative clinical factor for adjuvant surgery.

In conclusion, the results of this study indicate that adjuvant surgery was safe and well-tolerated by patients with initially unresectable stage IV gastric cancer, even after chemotherapy, and may possibly improve the prognosis after tumor down-staging with induction chemotherapy, especially in patients who have one non-curative clinical factor, such as peritoneal dissemination.

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