Preservation of the vagal trunk entering the celiac axis might change the location of the ectopic pacemaker point in the rho-shaped Roux limb, or it might drive the contractions of the proximal part of the limb in a reverse or orad direction toward the stomach in the early phase, 1–2 weeks after operation. According to the hypothesis noted above, the gastric remnant produces acid that passes into the RY limb and may disturb its motility. In this study, the remnant stomach, with preservation of the vagal trunk, might also have produced more acid than is produced in the early postoperative phase following surgery with vagotomy.

The limitation of our study was the small number (35 in each group) of patients. The negative results of our study may result from the study design with low power due to small number of patients. Furthermore, this study was conducted in a non-blinded fashion, because surgical RCT has various difficulties for blinding to patients or doctors. However, the DGE occurrence in rRY was twice as high as that in RY, suggesting that the possible superiority of rRY is low, even if we conducted a large RCT in a blinded fashion.

This RCT was conducted in one hospital where about 200 gastrectomies are performed annually. It is well known that single-institutional RCTs have an issue regarding the generalizability of the results; however, a RCT comparing surgical methods has the additional issue of quality control of surgical techniques. On this point, our study has the advantage of homogeneity, because all surgeries were performed by three surgeons (M.H., K.F., and T.T.) with sufficient experience of gastric surgery.

To our knowledge, this is the first RCT report in the world concerning the occurrence of DGE following gastric surgery. Our findings show that DGE occurred to a similar extent and that operative morbidity and nutritional status after operation did not significantly differ between the RY and rRY groups. Our findings suggest that RY reconstruction after distal gastrectomy may be as simple and effective as conventional reconstruction.

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D2 Lymphadenectomy Alone or with Para-aortic Nodal Dissection for Gastric Cancer

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ABSTRACT

BACKGROUND

Gastrectomy with D2 lymphadenectomy is the standard treatment for curable gastric cancer in eastern Asia. Whether the addition of para-aortic nodal dissection (PAND) to D2 lymphadenectomy for stage T2, T3, or T4 tumors improves survival is controversial. We conducted a randomized, controlled trial at 24 hospitals in Japan to compare D2 lymphadenectomy alone with D2 lymphadenectomy plus PAND in patients undergoing gastrectomy for curable gastric cancer.

METHODS

Between July 1995 and April 2001, 523 patients with curable stage T2b, T3, or T4 gastric cancer were randomly assigned during surgery to D2 lymphadenectomy alone (263 patients) or to D2 lymphadenectomy plus PAND (260 patients). We did not permit any adjuvant therapy before the recurrence of cancer. The primary end point was overall survival.

RESULTS

The rates of surgery-related complications among patients assigned to D2 lymphadenectomy alone and those assigned to D2 lymphadenectomy plus PAND were 20.9% and 28.1%, respectively (P=0.07). There were no significant differences between the two groups in the frequencies of anastomotic leakage, pancreatic fistula, abdominal abscess, pneumonia, or death from any cause within 30 days after surgery (the rate of death was 0.8% in each group). The median operation time was 63 minutes longer and the median blood loss was 230 ml greater in the group assigned to D2 lymphadenectomy plus PAND. The 5-year overall survival rate was 69.2% for the group assigned to D2 lymphadenectomy alone and 70.3% for the group assigned to D2 lymphadenectomy plus PAND; the hazard ratio for death was 1.03 (95% confidence interval [CI], 0.77 to 1.37; P=0.85). There were no significant differences in recurrence-free survival between the two groups; the hazard ratio for recurrence was 1.08 (95% CI, 0.83 to 1.42; P=0.56).

CONCLUSIONS

As compared with D2 lymphadenectomy alone, treatment with D2 lymphadenectomy plus PAND does not improve the survival rate in curable gastric cancer. (ClinicalTrials.gov number, NCT00149279.)

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N Engl J Med 2008;359:453-62.

Reprinted from THE NEW ENGLAND JOURNAL OF MEDICINE
(ISSN 0028-4793) Vol. 359:453-462 (July 31, 2008).

Printed in the U.S.A. Fax: (781) 893-8103 www.nejm.org

GASTRIC CANCER IS THE SECOND LEADING cause of cancer death worldwide, although its incidence is decreasing.[1] About 60% of new cases of gastric cancer occur in eastern Asia; the incidence of new cases in Japan is 100,000 per year. Chemotherapy helps to prolong survival in cases of advanced disease, but surgical resection is the most effective treatment for curable gastric cancer. Reports from the Gastric Cancer Registry and other retrospective studies[2-4] have made radical gastrectomy with extended (D2) removal of regional lymph nodes the standard for the treatment of curable gastric cancer in Japan. Two randomized, controlled European trials that compared the less extended D1 dissection with the D2 procedure failed to show a survival benefit for D2 dissection,[5,6] but lack of experience with the surgical procedure and with postoperative care were thought to account for the poor outcome of patients who underwent D2 lymphadenectomy.[7-9] In 2001, the American Intergroup 0116 study showed that chemoradiotherapy after limited lymphadenectomy (D0 or D1) decreased the local recurrence rate and increased long-term survival,[10] a result suggesting that chemoradiotherapy eliminates the residual lymph-node metastases that could be removed by D2 lymphadenectomy. In 2006, a randomized trial in Taiwan showed a significant benefit in overall survival for a D2 or D3 procedure as compared with D1 dissection, with no increase in operative mortality.[11] These trials indicate that adequate local control is essential for the treatment of gastric cancer. Hence, the standard of care for curable gastric cancer in eastern Asia and the United States is either gastrectomy with D2 lymphadenectomy and without postoperative chemoradiation or D0 or D1 gastrectomy with postoperative chemoradiation.[12-14]

Once the gastric tumor invades the subserosa (stage T2b), the serosa (stage T3), or the adjacent structures (stage T4), metastases can spread to the para-aortic lymph nodes, which are termed N3 nodes according to the *Japanese Classification of Gastric Carcinoma*, second English edition,[15] and M1 nodes according to the International Union Against Cancer (UICC) tumor–node–metastasis (TNM) classification.[16] In advanced gastric cancer, the incidence of microscopic metastases in the para-aortic region is 10 to 30%.[17-19] Because the 5-year overall survival rate of patients with para-aortic nodal metastases can be as high as 20% after systematic dissection,[20] extensive surgery has been performed in Japan since the 1980s for stage T2b, T3, and T4 gastric cancers. However, to our knowledge there has never been a large prospective study to investigate whether para-aortic nodal dissection (PAND) for gastric cancer has a survival benefit. Here we report the final results of a multi-institutional, randomized, controlled trial by the Japan Clinical Oncology Group (JCOG9501) that was conducted to determine whether the addition of systematic PAND to standard gastrectomy with D2 lymphadenectomy improves survival rates among patients with curable gastric cancer. An interim analysis found no differences between the two procedures in the rates of short-term major complications or in-hospital death.[21]

METHODS

ELIGIBILITY

In this trial, we enrolled patients who were younger than 75 years of age and who had histologically proven gastric adenocarcinoma that was considered potentially curable. Additional eligibility criteria, as determined from intraoperative findings, were the presence of a stage T2b, T3, or T4 tumor, the absence of gross metastases to the para-aortic nodes, and negative cytologic findings in peritoneal-lavage fluid. Diagnosis of metastases by examination of frozen sections of para-aortic nodes was not allowed, because sampling of the nodes would involve dissection. The study protocol was approved by the JCOG protocol review committee and the institutional review boards of each of the 24 participating hospitals. In accordance with JCOG policy in 1995 (the year in which enrollment began), all patients gave written informed consent before undergoing randomization.

RANDOMIZATION AND DATA MANAGEMENT

After confirming the eligibility of the patient during surgery, the surgeon contacted the JCOG Data Center by telephone to receive a randomly generated assignment of the patient to standard D2 lymphadenectomy alone or D2 lymphadenectomy plus PAND. Assignments were made by the minimization method according to clinical T stage (T2b vs. T3 or T4), Borrmann macroscopic type (type 0, 1, or 2 vs. type 3 or 5), and institution (patients with Borrmann type 4 tumors were excluded because there was no chance of cure for such patients if they had para-aortic nodal metastases). The surgeon then performed the assigned operation according to the methods described in the protocol.

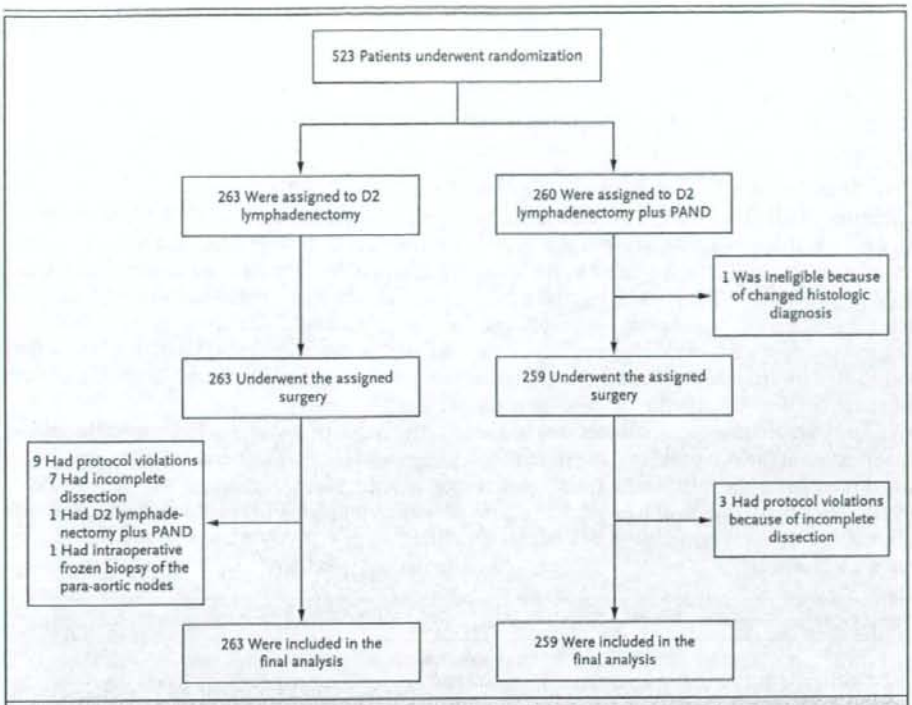

Figure 1. Disposition of the Patients.
PAND denotes para-aortic nodal dissection.

The JCOG data center performed data management, central monitoring, and statistical analysis. The center also provided twice-yearly monitoring reports, each of which was submitted to and reviewed by an independent JCOG data and safety monitoring committee. None of the surgeons who performed the operations were involved in data analysis. For quality assurance, the JCOG audit committee made site visits to monitor whether the study was being conducted according to protocol.

SURGERY

D2 lymphadenectomy alone and D2 lymphadenectomy plus PAND were performed as described previously.[21,22] The dissected lymph nodes were classified according to the *Japanese Classification of Gastric Carcinoma*, first English edition.[23] The method of reconstruction of the gastrointestinal tract was not specified.

During the planning of the study, all participating surgeons reached agreement concerning the technical details of both procedures. All operations either were performed by surgeons who had previously performed more than 100 gastrectomies with D2 dissection or took place at institutions with specialized units where more than 80 gastrectomies were performed annually. In addition to reviewing the twice-yearly monitoring reports, the surgeons observed videos of both types of procedures obtained in a sample of patients (at least three patients from each institution during the course of the study) and discussed the technical details of the operations to ensure uniformity of treatment. To assess adherence to the lymphadenectomy protocol, the dissection status of all regional nodal stations and the number of dissected nodes in the para-aortic area were recorded on case report forms, which were also reviewed by the surgeons.

POSTOPERATIVE EVALUATION

Pathologic findings were categorized according to the first English edition of the *Japanese Classifica-*

tion of Gastric Carcinoma[23]; thus, some lymph nodes currently classified as N2 or N3 were recorded as N3 or N4 in this study. Stage T2 was subdivided into stages T2a and T2b, as specified by the UICC TNM classification.[16] The rates of hospital death, defined as death during the period of hospitalization for the operation or death from any cause within 30 days after surgery, and surgery-related complications were calculated by dividing the number of patients in whom an event occurred by the total number of enrolled patients. Patients were followed every 3 months until April 2006, which was 5 years after the last patient had been enrolled. Adjuvant therapy was not allowed before the recurrence of cancer.

STATISTICAL ANALYSIS

The primary end point of this study was overall survival, defined as the time from randomization to death. The secondary end points were recurrence-free survival, surgery-related complications, and hospital death. Recurrence-free survival was defined as the time from randomization to the first recurrence of cancer or death from any cause.

The expected 5-year survival rate of the group assigned to D2 lymphadenectomy alone was 50%. We initially planned to recruit 412 patients (206 in each group), a number that would allow the detection of a 12% increase in survival in the group assigned to D2 lymphadenectomy plus

Table 1. Characteristics of the Patients.*

Characteristic	D2 Lymphadenectomy Alone (N=263)	D2 Lymphadenectomy plus PAND (N=260)	P Value†
Age — yr			0.34
Median	60	61	
Range	25–75	27–75	
Sex — no. (%)			0.40
Male	176 (66.9)	183 (70.4)	
Female	87 (33.1)	77 (29.6)	
Body-mass index — no. (%)‡			0.64
<22.0	138 (52.5)	126 (48.5)	
22.0–24.9	87 (33.1)	95 (36.5)	
≥25.0	38 (14.4)	39 (15.0)	
Tumor location — no. (%)			0.83
Upper third of stomach	53 (20.2)	47 (18.1)	
Middle third of stomach	103 (39.2)	103 (39.6)	
Lower third of stomach	107 (40.7)	110 (42.3)	
Tumor size — cm			0.71
Median	5.5	5.5	
Range	2.0–17.0	2.0–15.2	
Histologic type — no. (%)			0.33
Differentiated	97 (36.9)	107 (41.2)	
Undifferentiated§	166 (63.1)	153 (58.8)	
Borrmann macroscopic type — no. (%)			0.86
0, 1, or 2	109 (41.4)	110 (42.3)	
3 or 5	154 (58.6)	150 (57.7)	
Clinical T stage — no. (%)¶			1.00
T2b	99 (37.6)	98 (37.7)	
T3 or T4	164 (62.4)	162 (62.3)	

Table 1. (Continued).*

Characteristic	D2 Lymphadenectomy Alone (N=263)	D2 Lymphadenectomy plus PAND (N=260)	P Value†
Clinical node status — no. (%)			1.00
Negative	43 (16.3)	42 (16.2)	
Positive	220 (83.7)	218 (83.8)	
Pathological T stage — no. (%)¶			0.31
pT1	9 (3.4)	14 (5.4)	
pT2a	46 (17.5)	37 (14.2)	
pT2b	79 (30.0)	95 (36.5)	
pT3	121 (46.0)	109 (41.9)	
pT4	8 (3.0)	5 (1.9)	
Pathological node status — no. (%)			0.10
Negative	79 (30.0)	96 (36.9)	
Positive	184 (70.0)	164 (63.1)	
No. of positive nodes			0.30
Median	3	2	
Range	0–47	0–112	
Residual tumor — no. (%)			0.50
R0	261 (99.2)	260 (100)	
R1	2 (0.8)	0	

* PAND denotes para-aortic nodal dissection.
† P values were calculated with the use of Fisher's exact test except for comparisons of age, tumor size, and number of positive nodes, for which the Wilcoxon test was used.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The undifferentiated type included two cases of adenosquamous carcinoma in the group assigned to D2 lymphadenectomy alone and one case of malignant lymphoma in the group assigned to D2 lymphadenectomy plus PAND.
¶ The T stage was determined according to the first English edition of the *Japanese Classification of Gastric Carcinoma*.[23] Stage T2 was subdivided into T2a (invasion confined to the muscularis propria) and T2b (subserosal invasion) according to the 6th edition of the International Union Against Cancer tumor–node–metastasis classification.[16]

PAND, with a one-sided alpha level of 0.05 and a power of 80%. We planned this study with a one-sided test because D2 lymphadenectomy plus PAND is more invasive than D2 lymphadenectomy alone and should in principle result in better survival than D2 lymphadenectomy alone. Because differences smaller than 12% would be clinically meaningful, the protocol was amended to increase the sample size to 520 (260 in each group) to detect an 8% increase in survival in the group assigned to D2 lymphadenectomy plus PAND (hazard ratio, 0.73), with a total accrual period of 5.5 years and an additional 5 years of follow-up. The data and safety monitoring committee approved this change in July 2000 without knowledge of any survival data.

Two interim analyses were planned, with adjustments for repeated comparisons taken into account by the O'Brien–Fleming alpha-spending function.[24] At the first and second interim analyses in March 2002 and March 2004, the data and safety monitoring committee reviewed the results and approved continuation of the planned follow-up.

Data from all eligible patients were analyzed for overall survival and recurrence-free survival on an intention-to-treat basis. Survival curves were estimated by the Kaplan–Meier method and compared with the use of the log-rank test, with stratification according to the factors used in the randomization, except for the institution where the surgery was performed. Hazard ratios were calculated by Cox regression analysis after adjustment for baseline stratification factors except for

institution. Analyses of two prespecified subgroups (Borrmann macroscopic type and clinical T stage) and nine post hoc subgroups were also conducted to evaluate interactions between treatment and subgroup with the use of Cox regression; we report the result of all these analyses. No more than one significant interaction test result ($P<0.05$) would be expected on the basis of chance alone as a result of multiple testing.

Two-sided P values were calculated for all tests and are reported here. Because the study was planned to use a one-sided test, we also present one-sided P values for the results of the survival analyses. P values less than 0.05 were considered to indicate statistical significance. Analyses were performed with the use of SAS software, version 9.13.

RESULTS

PATIENTS

Between July 1995 and April 2001, 523 patients were randomly assigned to D2 lymphadenectomy alone (263 patients) or D2 lymphadenectomy plus PAND (260 patients). One patient was deemed ineligible after enrollment because of a change in the histologic diagnosis to malignant lymphoma. Protocol violations occurred in 12 patients. In one patient, an intraoperative biopsy of a frozen section of a para-aortic node was performed. Another patient assigned to D2 lymphadenectomy alone underwent D2 lymphadenectomy plus PAND. The remaining 10 patients did not undergo all aspects of the lymph-node dissection required in the protocol. At the time of final analysis in April 2006, two patients had been lost to follow-up for more than 1 year, but they had already been followed for more than 5 years after surgery. Figure 1 shows the disposition of the patients.

The characteristics of the two groups were well balanced (Table 1). Total gastrectomy was performed in 102 patients assigned to D2 lymphadenectomy alone (38.8%) and in 97 patients assigned to D2 lymphadenectomy plus PAND (37.3%); 98 patients assigned to D2 lymphadenectomy alone (37.3%) and 93 assigned to D2 lymphadenectomy plus PAND (35.8%) also underwent splenectomy. Only 9 patients assigned to D2 lymphadenectomy alone (3.4%) and 12 assigned to D2 lymphadenectomy plus PAND (4.6%) underwent distal pancreatectomy. The median operation time for gastrectomy with D2 lymphadenectomy plus PAND was 300 minutes, which was 63 minutes longer than that for gastrectomy with D2 lymphadenectomy alone ($P<0.001$). The median blood loss was 230 ml greater (660 ml vs. 430 ml, $P<0.001$) and blood transfusions were more frequent (30.0% vs. 14.1%, $P<0.001$) in patients undergoing D2 lymphadenectomy plus PAND than in those undergoing D2 lymphadenectomy alone.

OPERATIVE COMPLICATIONS AND DEATHS

As reported previously,[21] the overall incidence of surgery-related complications was 20.9% (55 of 263 patients) in the group assigned to D2 lymphadenectomy alone and 28.1% (73 of 260 patients) in the group assigned to D2 lymphadenectomy plus PAND ($P=0.07$). The incidence rates of the four major surgery-related complications in the group assigned to D2 lymphadenectomy alone and the group assigned to D2 lymphadenectomy plus PAND were 2.3% and 1.9%, respectively, for anastomotic leakage, 5.3% and 6.2% for pancreatic fistula, 5.3% and 5.8% for abdominal abscess, and 4.6% and 1.5% for pneumonia. None of these differences were statistically significant. The frequency of minor complications, such as ileus, lymphorrhea, left pleural effusion, and severe diarrhea, was significantly higher in the group assigned to undergo D2 lymphadenectomy plus PAND than in the group assigned to undergo D2 lymphadenectomy alone (20.0% vs. 9.1%, $P<0.001$). The rate of hospital death was 0.8% (two deaths in each group).

OVERALL AND RECURRENCE-FREE SURVIVAL

After median follow-up periods of 5.6 years in the group assigned to D2 lymphadenectomy alone and 5.7 years in the group assigned to D2 lymphadenectomy plus PAND, 96 patients assigned to D2 lymphadenectomy alone and 95 assigned to D2 lymphadenectomy plus PAND had died, and 100 patients assigned to D2 lymphadenectomy alone and 98 assigned to D2 lymphadenectomy plus PAND had had recurrences of cancer. Table 2 lists the site of first tumor recurrence for the two groups. The most frequent site was the peritoneum (38.1% of all recurrences), and the pattern of recurrence was similar in the two groups. The 5-year overall survival rate for 22 of 260 patients (8.5%) who had histologically detected metastases in the para-aortic lymph nodes after undergoing D2 lymphadenectomy plus PAND was 18.2% (95% confidence interval [CI], 5.7 to 36.3).

Figures 2A and 2B show the overall and recur-

rence-free survival rates for all eligible patients. The 5-year overall survival rate was 69.2% (95% CI, 63.2 to 74.4) for the group assigned to D2 lymphadenectomy alone and 70.3% (95% CI, 64.3 to 75.4) for the group assigned to D2 lymphadenectomy plus PAND. The hazard ratio for death was 1.03 (95% CI, 0.77 to 1.37) in the group assigned to D2 lymphadenectomy plus PAND, and the stratified log-rank test showed no significant difference between the groups (one-sided P=0.57, two-sided P=0.85). After adjustment of eight baseline variables (age, sex, body-mass index, tumor location, tumor size, Borrmann macroscopic type, clinical T stage, and clinical N stage) with the use of Cox regression analysis, the hazard ratio was essentially unchanged (hazard ratio, 1.03; 95% CI, 0.78 to 1.38; P=0.83).

The 5-year recurrence-free survival rate was 62.6% (95% CI, 56.4 to 68.2) in the group assigned to D2 lymphadenectomy alone and 61.7% (95% CI, 55.4 to 67.3) in the group assigned to D2 lymphadenectomy plus PAND. The hazard ratio for recurrence in the group assigned to D2 lymphadenectomy plus PAND was 1.08 (95% CI, 0.83 to 1.42; one-sided P=0.72; two-sided P=0.56).

Although there were no significant interactions between treatment effect and any baseline clinical findings, there were significant interactions between treatment effect and pathologic T stage and nodal status (Fig. 3). Among the 174 node-negative patients, the 5-year overall survival rate was 78.4% (95% CI, 67.6 to 86.0) in the group assigned to D2 lymphadenectomy alone and 96.8% (95% CI, 90.5 to 99.0) in the group assigned to D2 lymphadenectomy plus PAND. Conversely, among the 348 node-positive patients, the 5-year overall survival rate was 65.2% (95% CI, 57.9 to 71.6) in the group assigned to D2 lymphadenectomy alone and 54.9% (95% CI, 46.9 to 62.1) in the group assigned to D2 lymphadenectomy plus PAND. The hazard ratios for death in the group assigned to D2 lymphadenectomy plus PAND were 0.39 (95% CI, 0.18 to 0.84; P=0.009) for node-negative patients and 1.39 (95% CI, 1.02 to 1.89; P=0.04) for node-positive patients.

Table 2. Site of First Tumor Recurrence.*

Site	D2 Lymphadenectomy Alone (N=109)	D2 Lymphadenectomy plus PAND (N=106)
	no. (%)	
Peritoneum	43 (39.4)	39 (36.8)
Lymph nodes	24 (22.0)	23 (21.7)
Liver	21 (19.3)	24 (22.6)
Others	21 (19.3)	20 (18.9)

* In nine patients in the group assigned to D2 lymphadenectomy alone and seven patients in the group assigned to D2 lymphadenectomy plus para-aortic nodal dissection (PAND), more than one site was involved at the time of first recurrence.

DISCUSSION

The clinical value of systematic PAND in addition to D2 gastrectomy in curable gastric cancer has been controversial. In this randomized trial, we found no improvement in overall or recurrence-free survival with D2 lymphadenectomy plus PAND gastrectomy as compared with D2 lymphadenectomy alone. The pattern of recurrence was similar in the two groups, and D2 lymphadenectomy plus PAND did not reduce the rate of recurrence of cancer in the lymph nodes. There were no significant differences between the two groups in the rates of surgery-related complications. D2 lymphadenectomy plus PAND, however, was associated with a longer operation time, greater blood loss, and a significant increase in minor complications. For all these reasons, we cannot recommend D2 lymphadenectomy plus PAND for patients with curable gastric cancer.

Multiple studies have reported a close relation between the number of cases treated in a hospital and outcomes in the surgical treatment of cancer.[25-29] In two European randomized trials comparing D1 with D2 gastrectomy, the mortality rates in patients treated with D2 gastrectomy reached 10% or higher.[30,31] The excessive number of early deaths in these studies may have obscured any potential difference in long-term survival between patients undergoing D1 and D2 gastrectomy. The Dutch trial was conducted in 80 hospitals, including small community hospitals, by 11 surgeons who had little experience with D2 gastrectomy before the study. The limited experience of the surgeons made it difficult for them to learn how to perform the procedure safely and effectively, and the small volume of cases limited the ability of the hospitals to manage major surgical complications. By contrast, in a Taiwanese single-institution trial comparing D1 gastrectomy with D2 or more extensive gastrectomy, all the surgeons had performed at least 80 D2 procedures before

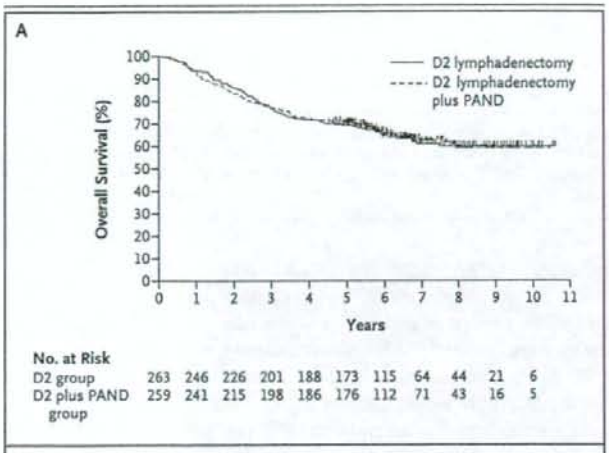

Figure 2. Kaplan–Meier Estimates of Overall Survival (Panel A) and Recurrence-free Survival (Panel B).

PAND denotes para-aortic nodal dissection.

participating in the study, and there were no deaths in either group. The procedures in our study either were performed by experienced surgeons or took place in 24 specialized hospitals with a high volume of cases, and our patients had no major coexisting conditions. These two features accounted for very low mortality rates (0.8%) and good long-term survival in both groups.

There were no significant interactions between treatment effect and any baseline clinical findings. We also conducted a post hoc subgroup analysis based on pathologic T stage and node status, variables that were determined after randomization. Surprisingly, among patients with pathologically negative nodes, survival rates were better in those assigned to D2 lymphadenectomy plus PAND than in those assigned to D2 lymphadenectomy alone, whereas in patients with any metastatic nodes, survival rates in the group assigned to D2 lymphadenectomy plus PAND were worse than those in the group assigned to D2 lymphadenectomy alone. This paradoxical interaction with nodal pathologic findings needs cautious interpretation, because it was detected in a post hoc subgroup analysis and was thus subject to biases and errors resulting from multiple testing; moreover, this finding should not influence clinical decisions, since we have no accurate method of assessing lymph-node metastases before surgery, and intraoperative frozen-section diagnosis of all dissected lymph nodes (of which the median number is >50) is not feasible. In fact, the proportion of patients with pathologically negative nodes (33.5%) was twice as high as that determined from clinical findings (16.3%). Within the range of the first- and second-tier nodal stations, a high probability of residual nodal metastasis, as calculated by a computer program based on the large database at the National Cancer Center Tokyo, was associated with a poor prognosis. This finding was confirmed in two randomized trials of surgery for gastric cancer conducted in Europe and the United States.[32,33] Our results are contradictory, since treatment with D2 lymphadenectomy plus PAND should reduce the probability of residual metastases in node-positive patients but not in node-negative patients, in whom there is no possibility of nodal metastases in the para-aortic area. Since this result from a post hoc subgroup might be a false positive owing to multiple testing, the possible survival benefit of D2 lymphadenectomy plus PAND in node-negative patients will need to be clarified in further studies.

One limitation of this study is that the incidence of metastases in the para-aortic nodes (8.5%) was lower than expected. A previous report showed that the most reliable predictor of metastases in the para-aortic nodes was the pathologic status of nodes at station 7.[34] In our 76 patients with metastases at this station, however, 5-year overall survival rates after D2 lymphadenectomy plus PAND (36.4%; 95% CI, 20.6 to 52.3) were not significantly better than those after D2 lymphadenectomy alone (44.2%; 95% CI, 29.2 to 58.2; hazard ratio, 1.09; 95% CI, 0.62 to 1.93; P=0.76). D2 lymphadenectomy plus PAND in node-positive patients results in worse survival rates; it is un-

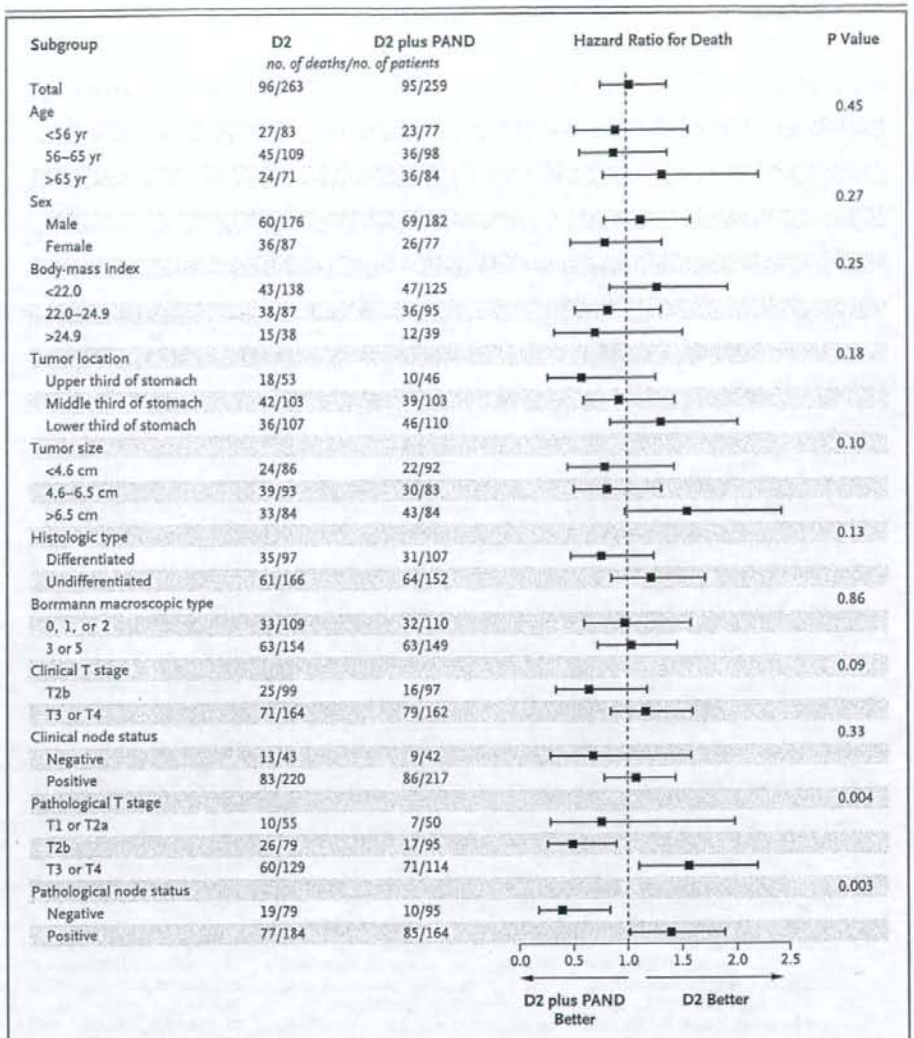

Figure 3. Tests for Heterogeneity of Treatment Effect According to the Clinicopathological Characteristics of the Patients.

D2 denotes D2 lymphadenectomy, and PAND para-aortic nodal dissection. The figure shows P values for interactions and hazard ratios for death in the group assigned to D2 lymphadenectomy plus PAND, with 95% confidence intervals. The body-mass index is the weight in kilograms divided by the square of the height in meters.

likely that D2 lymphadenectomy plus PAND would have resulted in better survival rates if we had had more patients with para-aortic node metastases.

A large phase 3 trial recently demonstrated that adjuvant therapy with S-1, an orally active fluoropyrimidine, significantly improved survival in Japanese patients with stage II or III gastric cancer.[35] As was suggested in the case of chemoradiation,[10] there may be some interaction between surgery and adjuvant treatment. In our study, which was performed before the S-1 trial, no patients received any adjuvant treatment.

In conclusion, extended D2 lymphadenectomy plus PAND should not be used to treat curable stage T2b, T3, or T4 gastric cancer. D2 gastrectomy is associated with low mortality and reasonable survival times when performed in selected institutions that have had sufficient experience with the operation and with postoperative management.

Supported in part by grants-in-aid for cancer research (5S-1, 8S-1, 11S-3, 11S-4, 14S-3, 14S-4, 17S-3, 17S-5) and for the Second Term Comprehensive 10-Year Strategy for Cancer Control (H10-Gan-027, H12-Gan-012) from the Ministry of Health, Labor, and Welfare of Japan.

No potential conflict of interest relevant to this article was reported.

We thank Dr. Kenichi Yoshimura and Dr. Naoki Ishizuka for data analysis; Ms. Kyoko Hongo, Ms. Chizuko Takeuchi, and Ms. Harumi Kaba for data management; and Dr. Haruhiko Fukuda for directing the JCOG Data Center and overseeing the management of this study.

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Int J Clin Oncol (2008) 13:117–120
DOI 10.1007/s10147-007-0743-1

FROM THE ASCO-JSCO JOINT SYMPOSIUM

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Current status of chemoradiotherapy for gastric cancer in Japan

Received: November 5, 2007

Abstract Chemoradiotherapy (CRT) is the latest modality to be explored as a treatment for gastric cancer. Advances have been made in the United States with CRT as preoperative or postoperative adjuvant treatment. The rationale for preoperative or postoperative adjuvant CRT is to increase the curability of surgery or to prevent local recurrence, because standard surgery (D0 or D1) is not sufficient to control local relapse and improve survival where disease has become advanced. D2 is standard in Japan and D2 gastrectomy plus postoperative adjuvant chemotherapy with S-1 is currently standard for stage II and III cancer. Predominant recurrence patterns associated with these advanced disease stages are peritoneal dissemination and hematogenous metastasis. Local relapse or regional nodal recurrence is infrequent. CRT has been provided at only a limited number of institutions in Japan. The response to and safety of CRT for gastric cancer, in combination with various chemotherapeutic agents, are currently being studied in patients with unresectable or recurrent disease. Considering the high response rate, CRT seems to be an attractive option. In the near future, an examination will be made to ascertain whether neoadjuvant CRT in combination with extensive surgery has survival benefits in the treatment of locally advanced disease. Prior to this, a phase I/II study should be conducted in patients with unresectable or recurrent disease.

Key words Gastric cancer · Chemoradiotherapy · Adjuvant therapy · Unresectable/Recurrent cancer · Surgery · Lymphadenectomy

Introduction

Chemoradiotherapy (CRT) is the latest modality to be explored as a treatment for gastric cancer. A report from Japanese Society for Therapeutic Radiation and Oncology (JASTRO) in 2005 showed that, in common malignancies, radiation therapy (RT) was used in breast cancers (20%), lung cancers (20%), urological cancers (12%), head and neck cancers (11%), esophageal cancers (7%), and malignancies of the central nervous system and gynecological cancers (6%). Abdominal malignancies, with the exception of pancreatic and biliary malignancies, are rarely candidates for RT in Japan. The limited numbers of personnel available for carrying out RT, such as radiation oncologists, medical physicists, and radiation technologists, may be a primary reason for this. Thus, because we are unfamiliar with the use of RT for abdominal organs, no standardization of the irradiation field and technique has been established. CRT as treatment for gastric cancer has been tried in the West. In the 1970s, phase III trials for advanced tumors were conducted to demonstrate the superiority of CRT over chemotherapy (CT) or RT.[1,2] In the 1990s, postoperative CRT became established, and a well-known phase III trial[3] showed that postoperative CRT in conjunction with CT improved survival over surgery alone, though the quality of surgery in the study was criticized. Since the 2000s, high pathologic response and curative resection rates have been reported for neoadjuvant CRT.[4–6] The rationale for neoadjuvant CRT is to increase the curability of surgery and to prevent local recurrence, because surgery alone is considered insufficient to prevent local relapse, the rate of which has been reported to be 38%–93%.[7] In contrast, only one phase III trial of the use of RT for gastric cancer has been conducted in Japan. This trial compared intraoperative RT for advanced disease with surgery alone, and showed that intraoperative RT may have a potential benefit.[8] RT/CRT has been employed for the palliation of symptoms, such as gastric or biliary obstruction, pain due to bone or lymph node metastasis, and bleeding. Among these conditions, pain control seemed to be the main reason for using RT/CRT in gastric cancer. Since the 2000s, case reports and the results of a phase II study of CRT for unresectable/recurrent tumor have been published.[9] Japan lags well behind the West in the use of RT/CRT for gastric cancer.

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Adjuvant treatment, in conjunction with gastrectomy, for advanced gastric cancer

Surgery has been a central treatment of gastric cancer, though the extent of lymph node dissection has been a controversial subject between the West and the East. Control of local failure is an important issue in the West because of the high local relapse rate. While D1 or D0 has been common in the West, D2 has been standard in Japan, and the combined resection of invaded organs or radical lymphadenectomy has been employed in advanced disease to increase curability and the local control rate. Randomized studies have been carried out to establish the optimal level of lymph node dissection.[10–12] The percentages of local recurrence in these trials were: 41% in D1 and 29% in D2 in the Dutch trial;[10] 30% in D1 and 19% in D2 (old definition: D3) in the Taiwanese trial;[11] and 24% in D2 and 23% in D3 in the Japan Clinical Oncology Group (JCOG) 9501[12] (Table 1) D2 surgery in the treatment of gastric cancer is indicated to control local recurrence, and this surgery appears to correspond to a "plateau level", because no difference in local recurrence rate (including lymph node and peritoneal recurrence) was observed between D2 and D3 surgery.

Evidence for the benefit of adjuvant treatment in patients with resected gastric cancer has been provided by phase III trials conducted both in the West and Japan (Table 2). It was shown that postoperative CT with fluorouracil (F) + leucovorin (L) followed by CRT (45 Gy with FL) conferred about a 10% survival benefit compared to surgery alone in the INT 0116 trial.[3] Though D2 surgery was required in the protocol, the result showed that the surgery actually performed was D0 (54%) and D1 (36%). The study concluded that when insufficient surgery (D0/1) is carried out, postoperative CRT is mandatory. Adjuvant CRT may provide better local control, but the question needs to be asked if CRT provides a survival benefit after D2 surgery. In Japan, a randomized phase III study[14] was conducted in patients with stage II/III gastric cancer, comparing surgery alone with postoperative CT (S-1, 80 mg/m^2 for 1 year). The level of surgery was D2. The results of the study demonstrated that treatment with S-1 conferred a significant survival benefit (3-year overall survival rate of 80.5% in the S-1 arm vs 70.1% in the control arm). Postoperative CT alone seems to be sufficient after D2 surgery. It is interesting to observe the results of the Korean study,[15] in which patients were treated with the same CRT regimen as in the INT 0116 trial after D2 surgery, and a comparison was made with patients who underwent surgery alone during the same period. Patient backgrounds in the Korean study were almost identical to those in the ACTS-GC trial[14] in terms of T and N stages. The 3-year survival of the patients receiving CRT in

Table 1. Results of three randomized trials evaluating lymph-node dissection in gastrectomy

	Dutch trial[10]	Taiwanese trial[11]	JCOG trial[12]
Morbidity	D1, 25% D2, 43%	D1, 7% D2, 17%	D2, 20.9% D3, 28.1%
Mortality	D1, 4% D2, 10%	D1, 0% D2, 0%	D2, 0.8% D3, 0.8%
5-Year overall survival	D1, 45% D2, 47%	D1, 54% D2, 60%; SD	D2, 69.2% D3, 70.3%
Stage migration	30% in D2	8% in D2	9% in D3
LN metastasis	N2 (Number), 12%	N2 (Station), 24%	N3 (Station), 8.8%
Percentage of local recurrence[a]	D1, 41% D2, 29%	D1, 30% D2, 19%	D2, 24%[b] D3, 23%

SD, significant difference
[a] Includes local recurrence and local plus distant metastasis
[b] Lymph-node and peritoneal metastasis

Table 2. Results of adjuvant treatments for gastric cancer

	INT 0116[3] RCT	MAGIC Trial[13] RCT	ACTS-GC[14] RCT	Korea[15] Non-RCT
Control arm	Surgery n = 275	Surgery n = 250	Surgery n = 530	Surgery n = 446
Test arm adjuvant therapy	Postoperative FL + RT (45 Gy) n = 281	Perioperative ECF n = 253	Postoperative S-1 n = 529	Postoperative FL + RT (45 Gy)
Survival	Control arm 5-Y, 28% Test arm 5-Y, 45%	Control arm 5-Y, 25% Test arm 5-Y, 35%	Control arm 3-Y, 70% Test arm 3-Y, 81%	Control arm 3-Y, 61%; 5-Y, 51% Test arm 3-Y, 66%; 5-Y, 57%
Surgery	D0, 54% D1, 36%	D1, 20% D2, 41%	D2	D2
Treatment compliance	64%	40%	65.8%	75.2%
T3 (C vs T)	61% vs 62%	55% vs 44%	43% vs 44%	38% vs 44%
N(+) (C vs T)	84% vs 85%	73% vs 69%	87% vs 91%	91% vs 94%

F, fluorouracil; L, leucovorin; E, epirubicin; C, cisplatin; RT, radiation therapy; RCT, randomized control trial; Y, year

Table 3. Ongoing investigations of adjuvant therapy for gastric cancer

CT Trials
MAGIC-B ($n = 1100$)
Perioperative ECX +/– BV
SAKK 43199 ($n = 240$)
Preoperative DCF (four cycles) vs postoperative DCF
RT Trials
CALGB 80101 ($n = 536$)
ECF + CRT + ECF vs FL + CRT + EL
CRITICS ($n = 788$)
Perioperative ECX (three cycles) +/– RT
GI Cancer Intergroup (in planning)
Preoperative CT (FLC) followed by CRT (F + TXL + 45-Gy RT) vs preoperative CT (TXL/C) followed by postoperative CRT (FL + 45-Gy RT)

E, epirubicin; L, leucovorin; X, xeloda; BV, bevacizumab; C, cisplatin; D, docetaxel; TXL, paclitaxel; RT, radiation therapy

the Korean study was 66%, whereas that in the ACTS-GC trial was 81%. Adjuvant CRT is not necessary after D2 surgery, so that a randomized study comparing D2 plus adjuvant CRT with D2 plus adjuvant CT would not be warranted in Japan. Another agent (cisplatin, or CPT-11 [irinotecan], or taxanes) in combination with S-1 could be the next candidate for adjuvant CT in stage III gastric cancer. A JCOG feasibility study of S-1 plus cisplatin for three courses followed by S-1 for 1 year after D2 is ongoing and needs to be completed before a future phase III trial can be started.

The benefits of neoadjuvant treatment are that it may control micrometastasis, increase resectability and curability, and have high treatment compliance compared to postoperative treatment. Neoadjuvant CRT designed and conducted in the United States has been reported in various studies.[4–6]

A phase II study[5] (Radiation Therapy Oncology Group [RTOG] 9904) comprising preoperative FLC followed by CRT (45 Gy with F and paclitaxel) showed an R0 resection rate of 77% and pathological complete response (pCR) rate of 26%, and median survival was 23.2 months in 50% of patients who underwent D2 surgery. Though preoperative CRT had a high clinical response, toxicities were substantial; grade 4 toxicities were reported in 21% of patients and 4% had surgical complications higher than grade 3. While neoadjuvant CRT yielded a high pCR rate and good curability of surgery, the benefit of RT in conjunction with CT needs to be confirmed. A European study, the MAGIC trial[13] compared three preoperative courses of epirubicin (E), cisplatin (C), and F (ECF) + three postoperative courses of ECF with surgery alone. The result showed that perioperative ECF conferred a survival benefit when compared with surgery alone. Considering the level of compliance for preoperative and postoperative ECF (86% vs 42%), it appears that chemotherapy has the greatest effect when administered preoperatively, with downstaging of both T and N stages observed. Neoadjuvant treatments may confer a survival benefit in gastric cancer. Neoadjuvant treatment has generated a high level of interest, and there are now many ongoing phase III trials in the West (Table 3). Among them, the CRITICS trial has been designed to compare perioperative EC xeloda (X) with and without RT, which may prove the significance of RT. At present in Japan, candidates for neoadjuvant treatment are patients with a poor prognosis, such as type 4 and large type III tumor (more than 8 cm in size), tumor with N3 or bulky N2 metastasis, or locally advanced tumor, because prognosis after curative resection with adjuvant S-1 is reasonably good even in patients with T3 or node-positive tumors. Although neoadjuvant treatment is time-consuming, it has good compliance. A randomized phase III trial (JCOG 0501) is now ongoing. The aim of this study is to evaluate the survival benefit of S-1 plus cisplatin as neoadjuvant chemotherapy in gastric cancer patients with resectable type 4 (linitis plastica type) and large type III tumor in comparison with surgery plus postoperative S-1. The result of this study could confirm that neoadjuvant CT has a useful role to play in such patients.

CRT for unresectable/recurrent tumor and current status of CRT in Japan

Prospective trials[1–2] in patients with unresectable tumors have been conducted to compare CRT with RT or CT alone, and these studies have shown that CRT had a survival benefit over RT or CT alone. However, because the quality of these studies was poor and sample sizes were small, the results were not convincing. There have been no recent prospective trials using CRT for unresectable/recurrent tumor, and the role of CRT in this setting is therefore uncertain. Primary treatment for this category of tumor is CT, because recent advances in CT have resulted in improved survival. For instance, as a result of two randomized trials conducted in Japan (JCOG 9912[16] and SPIRITS[17]), S-1 plus cisplatin has become a standard regimen for unresectable/recurrent gastric cancer in this country. In both of these studies,[16,17] the median survival time (MST) for patients receiving S-1 was 11 months and for those receiving S-1 plus cisplatin, the MST was 13 months; the 2-year survival rates were 15% and 24%, respectively. The effectiveness of CRT in the treatment of unresectable/recurrent tumor should be evaluated by conducting phase I or II trials.

A phase II trial (Saikawa et al.[9]) has been conducted at Keio University in 13 patients with unresectable disease, using a combination of S-1 (60 mg/m^2 per day, days 1–21) and low-dose cisplatin (6 mg/m^2 per day, 5 days/week for 3 weeks) with concurrent RT (2 Gy × 5/week for 4 weeks, total 40 Gy) as a first-line treatment. (Table 4) The response rate was 76.9%, peritoneal dissemination disappeared in 3 of 3 patients, and improvement in quality of life (QOL) was obtained in 84.6%. Patients enrolled in the study represented a wide range of tumor stages; some of them underwent subsequent surgical resection and some patients had metastatic disease. Though survival data were not available, CRT may have the potential to make palliative surgical resection unnecessary.

Table 4. Current status of chemoradiotherapy for unresectable/recurrent gastric cancer in Japan

Unresectable cancer
Saikawa et al.[9], phase II trial for advanced cancer (first-line treatment)
S-1, 60 mg/m^2, days 1–21
Cisplatin, 6 mg/m^2 per day, days 1–5, 8–12, 15–19 (5 days/week)
RT, 2 Gy · × 5/week for 4 weeks, total 40 Gy
Response rate, 77% (10 PR, 2 NC, 1 PD)
Primary, 63.8% (7 PR, 6 Nc)
Lymph node, 77% (10 PR, 3 NC)
Peritoneum, 100% (3 CR)
Improvement in QOL, 85% (11/13)
Recurrent cancer
Fujitani et al., pilot study for recurrent cancer (second- to fifth-line treatment): unpublished data
S-1, 40 mg/m^2, days 1–33
docetaxel, 20 mg/m^2, days 1, 8, 15, 22, 29
RT, 1.8 Gy × 5/week for 5 weeks, total 45 Gy
Response rate, 33% (3/9)
Alleviation of symptoms, 100% (6/6)
MST, 251 days
MMTG study group, phase I study (first- to second-line treatment)
Paclitaxel (50, 60, 70, 80) mg/m^2, days 1, 15, 29
Cisplatin (20, 25) mg/m^2, days 1, 15, 29
RT, 1.8 × 5/week for 5 weeks, total 45 Gy
Ongoing

We conducted a pilot CRT study for recurrent tumor as second- to fifth-line treatment, the regimen of which was S-1 and weekly docetaxel with concurrent RT (45 Gy). The response rate was 33% (3/9 patients) and alleviation of symptoms was observed in 100% (6/6 patients). Toxicities were substantial; grade 3–4 leucopenia was observed in 22% of the patients and one treatment-related death (TRD) occurred. The Multi-modality therapy for gastric cancer (MMTG) study group have proposed a phase I trial of CRT (2004, Yoshikawa). In the trial, it is planned to escalate the dose of taxol (days 1, 15, 29) from 40 to 80 mg/m^2 with two different doses of cisplatin (20 or 25 mg/m^2) in conjunction with concurrent RT (1.8 Gy/day, 5 days/week for 5 weeks, total 45 Gy). Recruitment is ongoing for this trial.

Summary

CRT has definite benefits in gastric cancer, with a high pCR rate and good local control, so that this modality should be introduced as a treatment option for Japanese patients. There is no rationale for using CRT in patients after D2 surgery in the adjuvant setting. Intensive adjuvant CT with S-1 plus cisplatin will be evaluated. CRT may be the best modality in the neoadjuvant setting for high-risk advanced tumors, such as type IV or large type III, N3/bulky N2 metastasis, or locally advanced (T4) tumors, or where there is esophageal invasion. The benefit of neoadjuvant S-1 plus cisplatin followed by postoperative S-1 will be evaluated in the phase III JCOG 0501 trial for large type III or type IV tumors. The role of neoadjuvant RT in addition to CT is yet to be clarified and we have to wait for the results of ongoing trials. We have little evidence to support the use of CRT as first-line treatment for unresectable/recurrent tumors; therefore, phase I/II trials should be conducted first to determine its potential benefits in this setting. However, our experience suggests that CRT may be suitable as second- or third-line treatment in such patients.

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Japanese Journal of Clinical Oncology Advance Access published February 16, 2008

Jpn J Clin Oncol
doi:10.1093/jjco/hyn003

Original Article

Multi-Center Phase II Study for Combination Therapy with Paclitaxel/Doxifluridine to Treat Advanced/Recurrent Gastric Cancer Showing Resistance to S-1 (OGSG 0302)

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Received September 7, 2007; accepted January 2, 2008

Background: A pre-clinical study demonstrated that paclitaxel induced thymidine phosphorylase in the tumor tissues. The combination of paclitaxel and doxifluridine is expected to exert extra anti-tumor effects. We evaluated the efficacy of this combination in patients with unresectable or recurrent gastric cancer who had been previously treated with S-1.

Methods: Registration was started to enroll 35 patients with advanced/recurrent gastric cancer, who were selected among those with measurable lesions fitting to response evaluation criteria in solid tumors, and with resistant to S-1 treatment. This regimen is consisted of paclitaxel, 80 mg/m^2, iv on days 1 and 8; and doxifluridine, 600 mg/m^2, po on days 1–14. The treatment was repeated every three weeks. Primary endpoint was response rate (RR); and secondary endpoints were overall survival (OS), progression free survival (PFS) and onset rate of adverse events.

Results: From September 2003 to March 2005, 35 patients were registered: including 28 men; 7 women; median age of 66 years (range, 49–75 years); and performance status (PS) levels were, zero with 21 and one with 14 patients. In 33 eligible patients, except two, clinical usefulness was evaluated resulting in RR of 18.2% (partial response, 6; stable disease, 15; progressive disease, 10; and not evaluable, 2 patients). Median survival time was 321 days and median PFS was 119 days. Severe adverse events were found in three patients to discontinue the present treatment.

Conclusions: The combination of paclitaxel and doxifluridine might be a treatment of choice as a second line chemotherapy for patient undergone S-1 treatment.

Key words: gastric cancer – paclitaxel – doxifluridine – second line chemotherapy – S-1

INTRODUCTION

The incidence of gastric cancer is still high, and it remains one of the leading causes of death in the world. Gastric cancer is moderately sensitive to systemic chemotherapy, and it has been used in an attempt to control cancer-related symptoms and prolong survival. Previous randomized studies have shown that systemic chemotherapy can prolong survival and improve the quality of life (1–3). However, we cannot recommend any specific regimens, although standard chemotherapy with cisplatin (CDDP) or 5-FU for unresectable or recurrent gastric cancer is performed throughout the world. In addition, practice standards differ among countries; in Asia, especially in Japan, continuous infusion of 5-FU, single therapy with a new oral fluoropyrimidine, S-1, or

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combination chemotherapy involving either of the two procedures is frequently employed as a first-line treatment. Two-phase III studies regarding single and combination therapies with S-1 are being conducted in Japan. Second-line chemotherapy for patients who are resistant to S-1 alone or combination therapy with S-1 should also be established. However, at this stage, no standard chemotherapy can be offered. No randomized controlled trial has suggested the benefit of second-line chemotherapy in comparison with supportive care alone. Previously, some phase II studies regarding second-line chemotherapy for gastric cancer have been performed (4–6). However, no study has published any pretreatment-matched data on second-line chemotherapy. In a recent phase III study of postoperative adjuvant chemotherapy involving stage II/III gastric cancer patients who underwent D2 dissection, the efficacy of S-1 was demonstrated in comparison with surgery alone (7). In the future, S-1 will comprise a standard regimen of postoperative adjuvant chemotherapy in Japan, and a regimen for relapse in patients treated with S-1 should also be developed.

Paclitaxel, a taxane anti-cancer drug, promotes microtubule assembly and then exhibits its anti-tumor effect by arresting the cell cycle in G2/M phase. This mechanism of action is different from other anti-cancer drugs, and non-cross resistance with them was suggested. Therefore, paclitaxel has been expected to provide a second-line therapy for gastric cancer. Doxifluridine (5'-DFUR; intermediate metabolite of capecitabine) and capecitabine are pro-drugs that are achieved and converted into 5-FU by thymidine phosphorylase (TP). A synergistic effect on inhibition of tumor growth has been reported when these agents are combined with paclitaxel (8,9). The results of a basic study demonstrated that administration of paclitaxel selectively induced TP in the tumor tissues and that the combination of paclitaxel and 5'-DFUR exerted more than additive effects. Consequently, concomitant use of these two drugs is expected to exert extra anti-tumor effects and to enhance the survival advantage, and can be regarded as a promising regimen as a second-line therapy for gastric cancer. In view of these beneficial effects, we conduct a phase II study in patients with unresectable or recurrent gastric cancer who failed S-1 treatment.

PATIENTS AND METHODS

Eligibility

All eligible patients had to fulfill the following eligibility criteria: (1) histologically confirmed unresectable or recurrent gastric cancer; (2) at least one measurable lesion according to the response evaluation criteria in solid tumors (RECIST); (3) patients who failed previous S-1 monotherapy; (4) age between 20 and 75 years old; (5) Eastern Cooperative Oncology Group performance status (PS) ≤ 2; (6) a life expectancy > 3 months; (7) adequate bone marrow function (absolute neutrophil count $\geq 2000/mm^3$ and platelet count $\geq 1\ 00\ 000/mm^3$); (8) adequate liver function (serum bilirubin $\leq 1.25 \times$ upper normal limit (UNL) of range set by the institution and serum transaminase $\leq 2.5 \times$ UNL (in cases of hepatic metastasis, $\leq 5 \times$ UNL)); (9) adequate renal function (serum creatinine $\leq 1.5 \times$ UNL); (10) no other severe medical conditions; (11) no other active malignancies; (12) no peripheral neuropathy; (13) no history using doxifluridine in adjuvant setting; and (14) provision of written informed consent.

Definition of S-1 Treatment Failure

Patients had to fulfill either of the following two conditions: (1) patients with unresectable or recurrent gastric cancer who received S-1 monotherapy in more than 4 weeks and confirmed tumor progression during the treatment period or after the treatment withdrawal; or (2) patients who have relapsed within 26 weeks after the completion of S-1 monotherapy in the adjuvant setting.

Treatment Schedule and Evaluation of Toxicity

Moriwaki et al. conducted a phase I clinical trial in order to study the feasibility of paclitaxel/doxifluridine combined therapy. Based on the results, we determined the dose and schedule of this study (10). The two drugs were administered as follows: paclitaxel (Taxol; Bristol-Myers Squibb Company, Tokyo, Japan) 80 mg/m^2 over 60 min iv infusion on day 1 and 8; doxifluridine (Fulturon; Chugai Pharmaceutical Company, Tokyo, Japan) 600 mg/m^2/day po on days 1–14. This treatment was repeated every three weeks (one cycle each) until disease progression or unacceptable toxicity was seen. The evaluation of disease status was planned every two cycles. Toxicity was graded according to the National Cancer Institute common toxicity criteria (NCI-CTC version 2.0). A new cycle of treatment could begin if the total leukocyte count was $\geq 2000/mm^3$, the neutrophil count was $1000/mm^3$, the platelet count was $\geq 75\ 000/mm^3$ and all relevant non-hematological toxicities were grade 1 or lower. Dose reductions were planned for diarrhea as follows: at grade 2 to keep the same dose level and to delay the treatment of one week, at grade 3 to delay the treatment of one week and to reintroduce paclitaxel at 70 mg/m^2 and doxifluridine 400 mg/m^2 /day, and for neutropenia as follows: at grade 3 to delay the treatment of one week, at grade 4 to delay the treatment of one week and to reintroduce paclitaxel at 70 mg/m^2 and doxifluridine 400 mg/m^2/day.

Endpoints and Evaluation of Treatment

Primary endpoint was response rate (RR). Tumor response was evaluated every two cycles by means of CT scan or MRI. Measurable lesions were assessed according to the RECIST. Secondary endpoints were overall survival (OS), progression free survival (PFS), time to treatment failure (TTF) and incidence of adverse events. Intention-to-treatment (ITT) analysis was used to evaluate patients for response, survival and toxicity.

Table 1. Patient characteristics

Patien characteristics ($n = 35$)	
Gender: males/females	28/7
Age: median (range), years	66 (49–75)
ECOG Performance status (PS): 0/1/2	21/14/0
Histology: differentiated/undifferentiated/ohter	22/12/1
Primary lesions: present/absent	10/25
Metastatic leasions: liver/lymph node/peritoneum/lung/ others	16/24/8/3/6
Prior S-1 treatment: adjuvant/advance	6/29
Median duration of S-1 administration for advanced/ recurrent disease, days	118
Efficacy of S-1monotherapy: effective/ineffective/ unknow	2/24/3

n, number of patients; ECOG, Eastern Cooperative Oncology Group.

Statistical Analysis

If over three patients among 18 patients have objective response, this study is regarded to be adequate to proceed further and to enroll more 18 patients assuming *P*0 of 15%, *P*1 of 35%, alpha error of 0.05 and beta error of 0.20 based on Simon two-stage phase II design. Thirty-five eligible patients were required to evaluate the activity of this combination. The planned duration of accrual was 2 years, and planned follow-up time was 6 months after the last patient registration. The duration of objective responses, TTP and OS were calculated from the date of starting chemotherapy until last follow-up or death. Survival was calculated employing the Kaplan–Meier product-limit analysis for the estimation of incomplete data.

RESULTS

Patients Characteristics

Thirty-five patients were enrolled into the trial from September 2003 to March 2005. All patients had developed progressive disease while receiving S-1 monotherapy in the first-line treatment or within 26 weeks after the completion of S-1 monotherapy in the adjuvant setting. Thirty-three patients were eligible for efficacy. Two patients were ineligible in terms of insufficient duration of S-1 treatment (< 4 weeks) and history of doxifluridine administration in adjuvant setting. Patients main clinical characteristics are listed Table 1. There were 28 males and 7 females with a median age of 66 years, with many patients being with in good general condition. All patients had an adenocarcinoma with a predominance of differentiated forms (62.9%). The metastatic sites of disease were: liver (45.7%), lymph-nodes (68.6%), peritoneum (22.9%), lung (8.6%) and other sites (17.1%). Six patients had relapsed early after adjuvant treatment with S-1. The doses of paclitaxel and doxifluridine were reduced in eight patients (22.8%), in line with the dose reduction criteria. Treatment administration was also delayed for a median of seven days (range 1–14 days) in 20 of 166 cycles.

Table 2. Overall response rate

Eligible patients (n =33)	n	%	95%CI
Overall response	6	18.2	7.0 to 35.5
Complete response (CR)	0		
Partial response (PR)	6		
Stable disease (SD)	15	45.5	28.1 to 63.7
Progressive disease (PD)	10	30.3	15.6 to 48.7
Not evaluable (NE)	2		
Disease control*	21	63.6	45.1 to 79.6

*Overall response and stable disease.
CI, confidence interval

Efficacy

According to an ITT analysis, the objective response rate (ORR) was 18.2% (6/33). Fifteen patients showed stable disease (SD), 10 patients progressed and disease control rate (PR + SD) was 63.6% (21/33) (Table 2). Median PFS was 119 days [95% confidence interval (CI), 89.7–148.3]

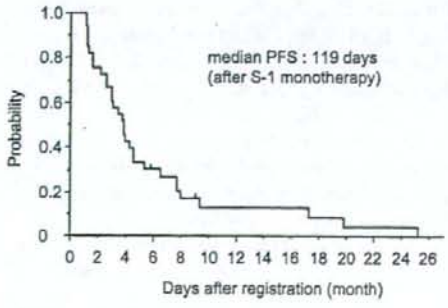

Figure 1. Progression-free survival (PFS).

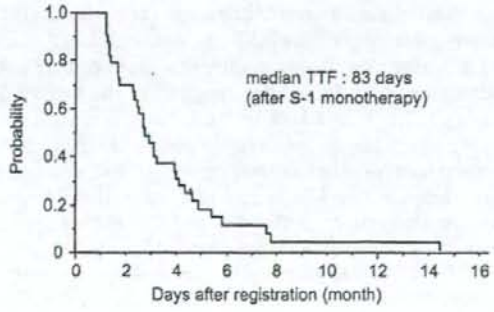

Figure 2. Time to treatment failure (TTF).

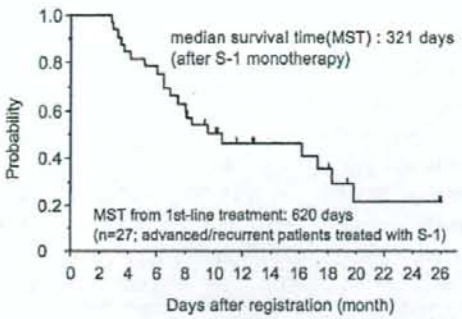

Figure 3. Overall survival.

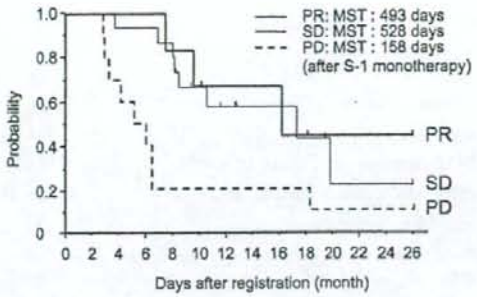

Figure 4. OS of the patients according to response. PR, partial response; SD, stable disease; PD, progressive disease.

(Fig. 1), and median TTF was 83 days (95% CI, 65.2–100.8) (Fig. 2). Median survival time (MST) was 321 days (95% CI, 49.2–592.8) (Fig. 3). The MST was 493, 528 and 158 days in PR, SD and PD patients, respectively (Fig. 4). The median follow-up period was 290 days (range: 182–792 days). According to information from the off-treatment forms at the failure of this regimen, at least 24 patients (72.7%) received third-line chemotherapy regimens: 17 patients in irinotecan-containing regimens.

Toxicity

The median number of treatment cycles was four (range 1–20). All patients were evaluable for toxicity (Table 3). No toxic deaths were observed. Hematological toxicity was mainly presented by neutropenia that was recorded in 21 patients (60%) but it was severe (grade 3) only in eight cases (22.9%). Only one patients (2.9%) experienced febrile neutropenia. Anemia was observed in 33 patients (94.3%) whereas grade 3–4 was only 17.1%; thrombocytopenia was of grade 1 in two patients (5.7%) whereas no major grade was observed. The most frequent non-hematological toxicity was anorexia (40%). Peripheral neuropathy was grade 3 in only one patient (2.9%).

DISCUSSION

In several phase III studies of gastric cancer conducted in the twentieth century, the MST was approximately 7 months (11,12). However, it was slightly prolonged to nine to ten months in phase III studies reported in the twenty first century (13,14). As a background factor, the appearance of some new anticancer agents (oral fluoropyrimidines, irinotecan and taxanes) has increased choices of first- and second-line therapies. The TTP or PFS of a conventional first-line therapeutic regimen with 5-FU and CDDP was approximately 4 months. In a recent phase III study, the TTP of 5-FU + CDDP was also approximately 4 months, with no marked difference. However, the MST in the 5-FU + CDDP group in a recent phase III study was prolonged by about 2 months in comparison with previous phase III studies, which was possibly associated with the effects of second-line or later therapy. Based on the background, the results of some phase II studies regarding second-line regimens have been published (4–6). Most of these phase II studies outside of Japan included 5-FU- or CDDP-based regimen-resistant patients. In Japan, S-1 monotherapy or S-1 + CDDP is frequently employed as a first-line treatment in clinical practice. It is important to establish second-line treatment for patients who are resistant to these therapies. In this study, we investigated patients who were resistant to S-1 monotherapy to unify the first-line treatment.

In pre-clinical studies, paclitaxel in combination with doxifluridine showed a synergistic activity (9). Based on the results of these experiments, Moriwaki et al. reported the results of a phase I study regarding combination therapy with paclitaxel and doxifluridine for gastric cancer (10). In their study, 22 of 28 patients were pretreated with 5-FU or S-1. The RR was 42%; the rates were 40 and 43% in the patients without and with pretreatment, respectively, suggesting the usefulness of this therapy as a second-line treatment for 5-FU-resistant patients. Based on the study results, we examined the efficacy and safety of combination therapy with paclitaxel and doxifluridine in S-1 monotherapy-resistant patients. In this study, the RR was 18.2–95% CI, 7.0–35.5, below the threshold of the expected RR. However, disease control rate (CR+PR+SD) was achieved in 63.6%. PFS was approximately 4 months, and the MST was 321 days. In several previous phase II studies, the RR ranged from 20 to 32% and the disease control rate ranged from 42.6 to 63%. The PFS ranged from 2.5 to 3.7 months, and the MST ranged from 5.2 to 7.8 months. Our results in this study were comparable to those for some second-line regimens previously reported. The main grade 3 or higher adverse events included neutropenia in 22.9% of our patients, leukopenia in 11.7% and anorexia in 8.6%. This second-line regimen may be safe under poor treatment conditions.

Concerning paclitaxel, two phase II studies were conducted in Japan, and 15 (22.7%) of 66 patients who had undergone chemotherapy responded to this agent (15,16). Based on the results of these phase II studies, we expected

Table 3. Adverse events.

Adverse events (n =35)	Grade				All grade	≥Grade 3
	1	2	3	4		
Hematological events						
Anemia	14	13	5	1	94.3%	17.1%
Leukopenia	5	10	4		54.3%	11.4%
Neutropenia	7	6	8		60.0%	22.9%
Lymphopenia		2			5.7%	–
Thrombocytopenia	2				5.7%	–
Non-hematological events						
Alkaline phosphatase	1		3		11.4%	8.6%
Alopecia	9	12			60.0%	–
Nail chages	1				2.9%	–
Dermatosis	1				2.9%	–
Nausea	7	2			25.7%	–
Anorexia	8	3	3		40.0%	8.6%
Stomach heaviness	1				2.9%	–
Diarrhea	9	1			28.6%	–
Constipation	2				5.7%	–
Taste disturbance	3				8.6%	–
Stomatitis	3				8.6%	–
Glossitis	1				2.9%	–
Peripheral neuropathy	7	2	1		28.6%	2.9%
Arthralgia	2				5.7%	–
Muscle pain	2				5.7%	–
Back pain	1				2.9%	–
Lumbago	1				2.9%	–
Bile reflux	1				2.9%	–
Fatigue	11	2	1		40.0%	2.9%
Lightheadedness		1			2.9%	–
Lightheadedness upon standing	1				2.9%	–
Common cold symptom	1				2.9%	–
Shortness of breath	1				2.9%	–
Fever	2	1			8.6%	–
Febrile neutropenia			1		2.9%	2.9%
Infection with grade 3 or 4 neutropenia			1		2.9%	2.9%
Epistaxis	1				2.9%	–
Edema	2				5.7%	–
Tearing	1				2.9%	–

that the combination of paclitaxel and doxifluridine would be administered as an optional extra. Unfortunately, our results could not positively suggest the usefulness of additional treatment with another fluoropyrimidine agent, doxifluridine, in patients pretreated with S-1. However, in Japan, postoperative adjuvant chemotherapy with S-1 may be performed in stage II/III gastric cancer patients after D2 dissection based on the results of the ACTS-GC trial (7). No prospective study of S-1 involving recurrent cancer patients has been conducted, and currently, combination therapy with paclitaxel and doxifluridine may be a treatment choice in clinical practice with respect to the disease control rate and mild toxicity. In the future, a clinical study of S-1 involving recurrent cancer patients will be performed with reference to the results of this study.

Acknowledgement

Investigators who participated in this study were Yasushi Nakane, Kansai Medical College, Osaka, Japan; Suguru Morimoto, Yao Municipal Hospital, Osaka, Japan; Takao Tamura, Kobe University, Hyogo, Japan; Akinori Hara, Saiseikai Suita Hospital, Osaka, Japan; Hiroki Fukunaga, Saiseikai Senri Hospital, Osaka, Japan; Shigemi Matsumoto, Kyoto University, Kyoto, Japan. We are indebted to the physicians and all other co-medical staff who contributed to this study. We also thank Ms Akiko Hotta and Ms Hiroko Maruyama at the OGSG data center for their excellent secretarial assistance.

Conflict of interest statement

None declared.

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