

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

JULY 31, 2008

VOL. 359 NO. 5

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.

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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 studies²⁻⁴ 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

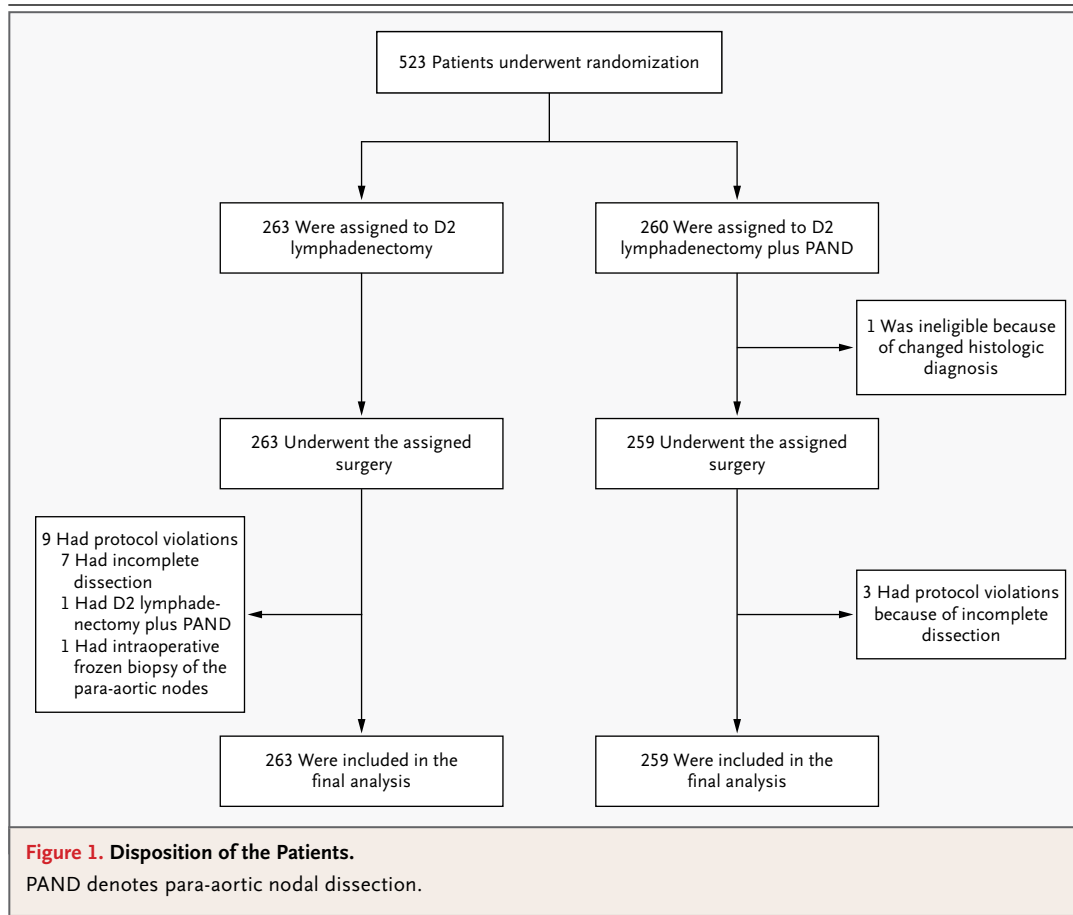
METHODS

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.



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 Carcinoma²³; 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 ad-

justments 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.

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-

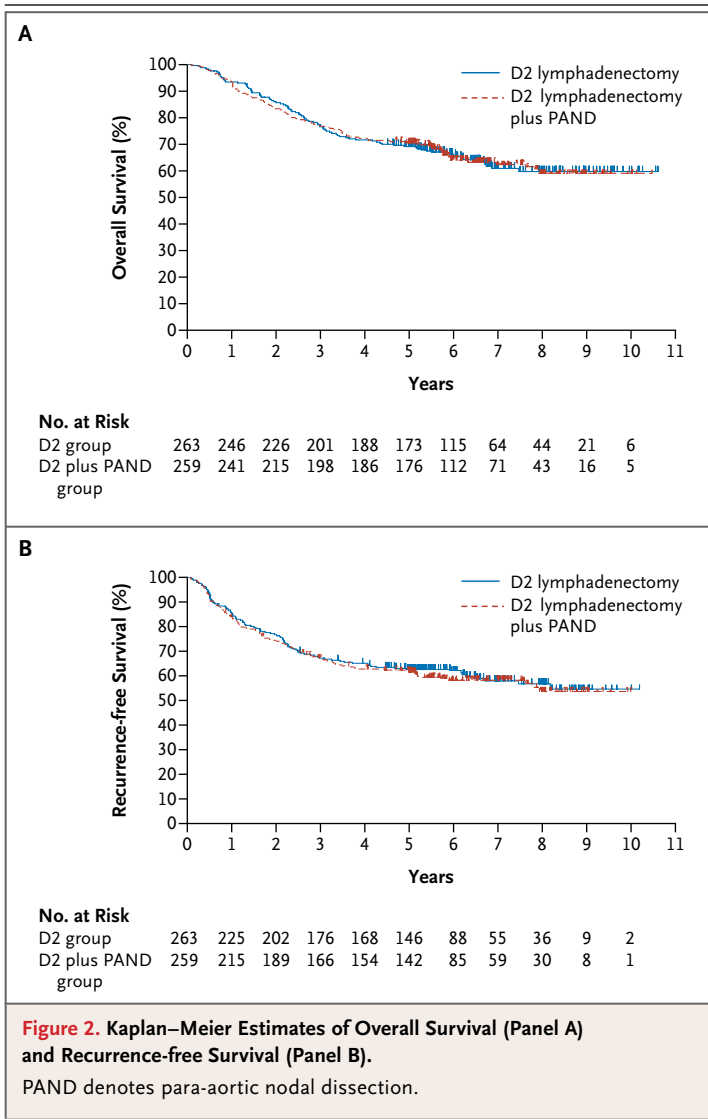
Table 2. Site of First Tumor Recurrence.*

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.

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



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-

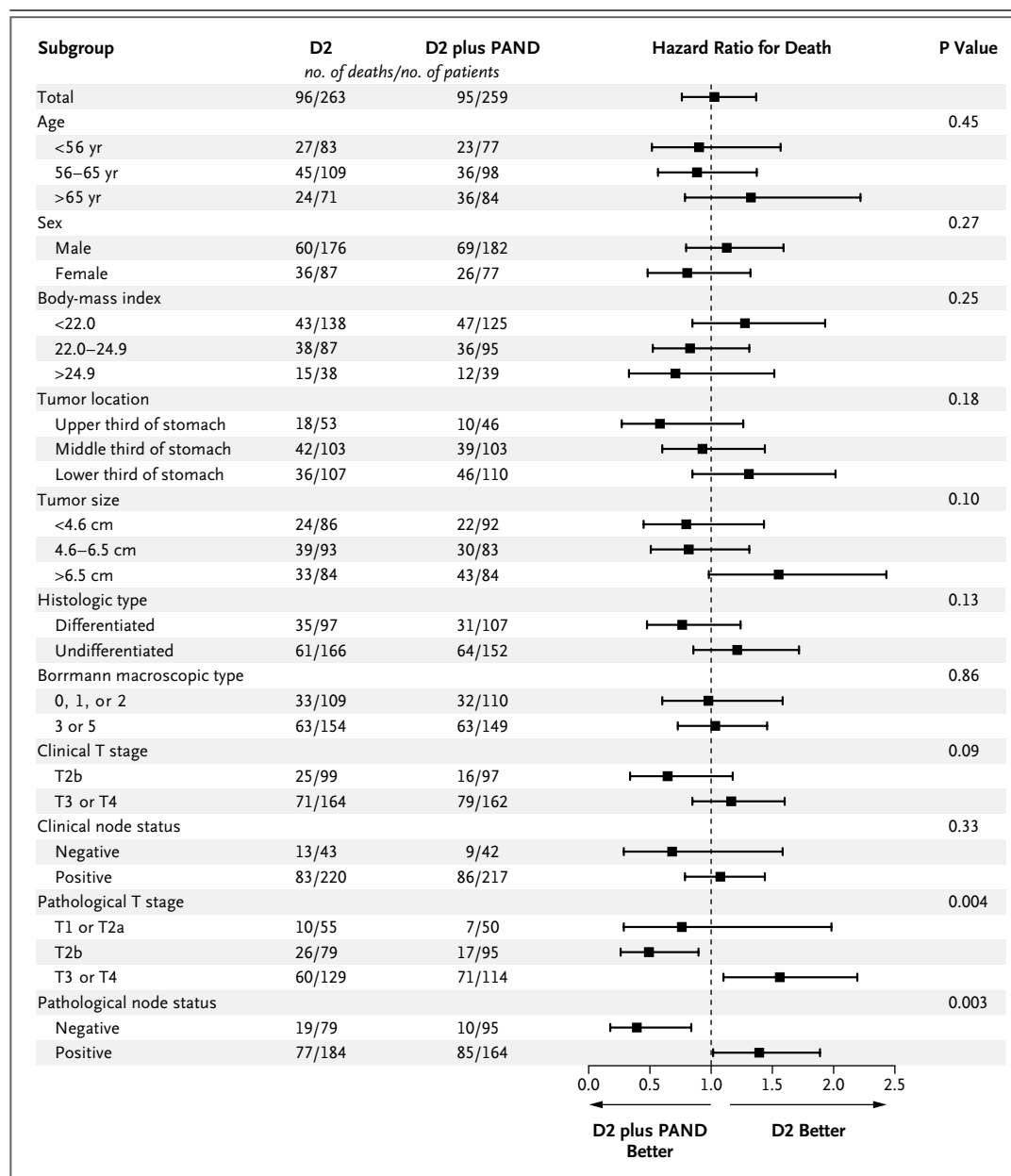


Figure 3. Tests for Heterogeneity of Treatment Effect According to the Clinicopathological Characteristics of the Patients.

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.

REFERENCES

- Kelley JR, Duggan JM. Gastric cancer epidemiology and risk factors. *J Clin Epidemiol* 2003;56:1-9.
- de Aretxabala X, Konishi K, Yonemura Y, et al. Node dissection in gastric cancer. *Br J Surg* 1987;74:770-3.
- Maruyama K, Okabayashi K, Kinoshita T. Progress in gastric cancer surgery in Japan and its limits of radicality. *World J Surg* 1987;11:418-25.
- Sasako M, McCulloch P, Kinoshita T, Maruyama K. New method to evaluate the therapeutic value of lymph node dissection for gastric cancer. *Br J Surg* 1995;82:346-51.
- Bonenkamp JJ, Hermans J, Sasako M, van de Velde CJH. Extended lymph-node dissection for gastric cancer. *N Engl J Med* 1999;340:908-14.
- Cuschieri A, Weeden S, Fielding J, et al. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. *Br J Cancer* 1999;79:1522-30.
- Wu CW, Hsiung CA, Lo SS, Hsieh MC, Shia LT, Whang-Peng J. Randomized clinical trial of morbidity after D1 and D3 surgery for gastric cancer. *Br J Surg* 2004;91:283-7.
- Sierra A, Regueira FM, Hernández-Lizoáin JL, Pardo F, Martínez-González MA, A-Cienfuegos J. Role of the extended lymphadenectomy in gastric cancer surgery: experience in a single institution. *Ann Surg Oncol* 2003;10:219-26.
- Degliuli M, Sasako M, Calgaro M, et al. Morbidity and mortality after D1 and D2 gastrectomy for cancer: interim analysis of the Italian Gastric Cancer Study Group (IGCSG) randomised surgical trial. *Eur J Surg Oncol* 2004;30:303-8.
- Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001;345:725-30.
- Wu CW, Hsiung CA, Lo SS, et al. Nodal dissection for patients with gastric cancer: a randomised controlled trial. *Lancet Oncol* 2006;7:309-15.
- Douglass HO Jr, Hundahl SA, Macdonald JS, Khatri VP. Gastric cancer: D2 dissection or low Maruyama Index-based surgery — a debate. *Surg Oncol Clin N Am* 2007;16:133-55.
- Sasako M, Saka M, Fukagawa T, Katai H, Sano T. Modern surgery for gastric cancer — Japanese perspective. *Scand J Surg* 2006;95:232-5.
- Sano T. Tailoring treatments for curable gastric cancer. *Br J Surg* 2007;94:263-4.
- Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma. 2nd English ed. *Gastric Cancer* 1998;1:10-24.
- Sobin LH, Wittekind C, eds. TNM classification of malignant tumours. 6th ed. New York: Wiley-Liss, 2002.
- Baba M, Hokita S, Natsugoe S, et al. Paraaortic lymphadenectomy in patients with advanced carcinoma of the upper-third of the stomach. *Hepatogastroenterology* 2000;47:893-6.
- Isozaki H, Okajima K, Fujii K, et al. Effectiveness of paraaortic lymph node dissection for advanced gastric cancer. *Hepatogastroenterology* 1999;46:549-54.
- Maeta M, Yamashiro H, Saito H, et al. A prospective pilot study of extended (D3) and superextended para-aortic lymphadenectomy (D4) in patients with T3 or T4 gastric cancer managed by total gastrectomy. *Surgery* 1999;125:325-31.
- Yonemura Y, Segawa M, Matsumoto H, et al. Surgical results of performing R4 gastrectomy for gastric cancer located in the upper third of the stomach. *Surg Today* 1994;24:488-93.
- Sano T, Sasako M, Yamamoto S, et al. Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy — Japan Clinical Oncology Group study 9501. *J Clin Oncol* 2004;22:2767-73.
- Yoshikawa T, Sasako M, Sano T, et al. Stage migration caused by D2 dissection with para-aortic lymphadenectomy for gastric cancer from the results of a prospective randomized controlled trial. *Br J Surg* 2006;93:1526-9.
- Japanese Research Society for Gastric Cancer. Japanese classification of gastric carcinoma. 1st English ed. Tokyo: Kanehara, 1995.
- Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika* 1983;70:659-63.
- Birkmeyer JD, Siewers AE, Finlayson EVA, et al. Hospital volume and surgical mortality in the United States. *N Engl J Med* 2002;346:1128-37.
- Bach PB, Cramer LD, Schrag D, Downey RJ, Gelfand SE, Begg CB. The influence of hospital volume on survival after resection for lung cancer. *N Engl J Med* 2001;345:181-8.
- Schrag D, Cramer LD, Bach PB, Cohen AM, Warren JL, Begg CB. Influence of hospital procedure volume on outcomes following surgery for colon cancer. *JAMA* 2000;284:3028-35.
- Begg CB, Cramer LD, Hoskins WJ, Brennan MF. Impact of hospital volume on operative mortality for major cancer surgery. *JAMA* 1998;280:1747-51.
- Hillner BE, Smith TJ, Desch CE. Hospital and physician volume or specialization and outcomes in cancer treatment: importance in quality of cancer care. *J Clin Oncol* 2000;18:2327-40.
- Bonenkamp JJ, Songun I, Hermans J, et al. Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. *Lancet* 1995;345:745-8.
- Cuschieri A, Fayers P, Fielding J, et al. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. *Lancet* 1996;347:995-9.
- Hundahl SA, Macdonald JS, Benedetti J, Fitzsimmons T. Surgical treatment variation in a prospective, randomized trial of chemoradiotherapy in gastric cancer: the effect of undertreatment. *Ann Surg Oncol* 2002;9:278-86.
- Peeters KC, Hundahl SA, Kranenborg EK, Hartgrink H, van de Velde CJ. Low Maruyama index surgery for gastric cancer: blinded reanalysis of the Dutch D1-D2 trial. *World J Surg* 2005;29:1576-84.
- Nomura E, Sasako M, Yamamoto S, et al. Risk factors for para-aortic lymph node metastasis of gastric cancer from a randomized controlled trial of JCOG9501. *Jpn J Clin Oncol* 2007;37:429-33.
- Sakuramoto S, Sasako M, Yamaguchi T, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med* 2007;357:1810-20. [Erratum, *N Engl J Med* 2008;358:1977]

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