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

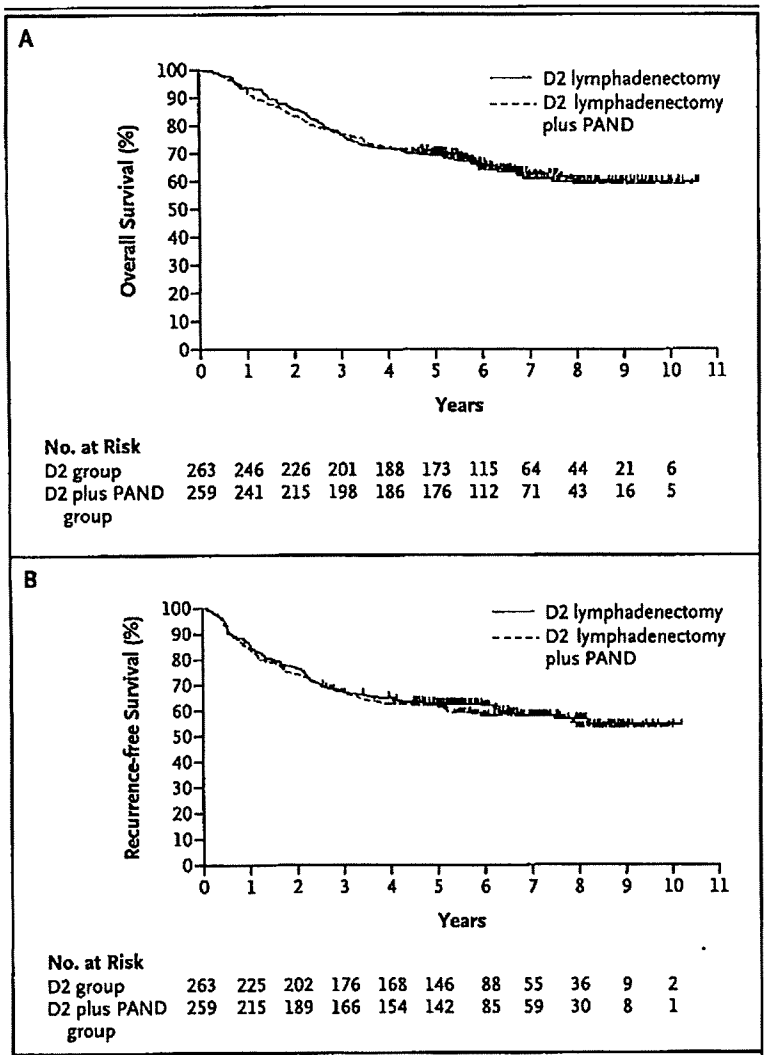

Figure 2. Kaplan–Meier Estimates of Overall Survival (Panel A) and Recurrence-free Survival (Panel B).

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-

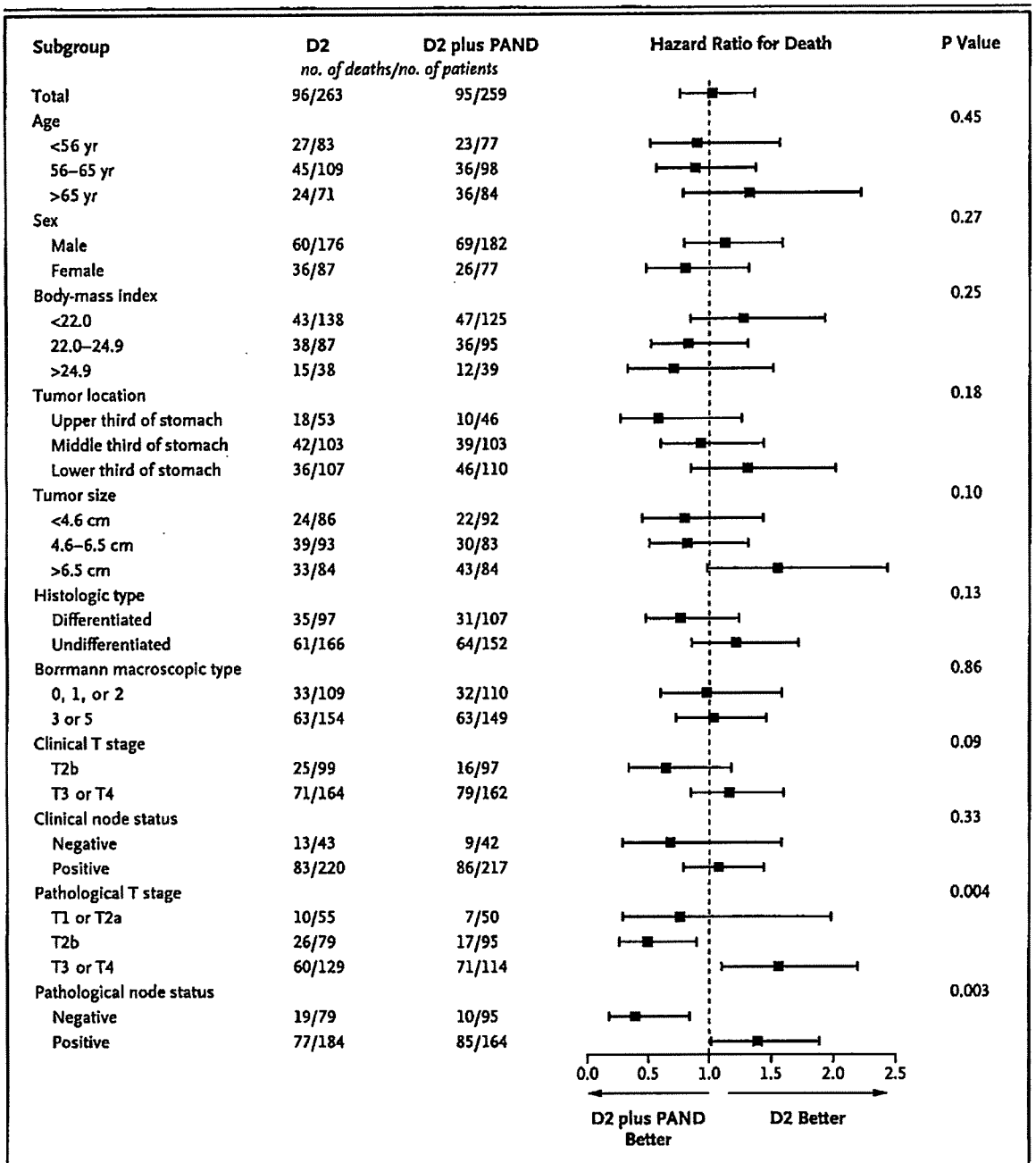

Figure 3. Tests for Heterogeneity of Treatment Effect According to the Clinicopathological Characteristics of the Patients.

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.

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REVIEW ARTICLE

Yukinori Kurokawa · Mitsuru Sasako

Recent advances in chemotherapy and chemoradiotherapy for gastrointestinal tract cancers: adjuvant chemoradiotherapy for gastric cancer

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Abstract Chemoradiotherapy (CRT) is one of the effective modalities for the local control of gastric cancer. Advances in CRT as an adjuvant treatment have been made in the West. The INT0116 trial demonstrated that postoperative chemotherapy with 5-fluorouracil (FU) plus leucovorin and concomitant 45-Gy radiation significantly improved the survival of gastric cancer patients who received gastrectomy with D0 or D1 lymph node dissection. As the result of this trial, the standard treatment for curable gastric cancer in the United States has been considered as a combination of surgery and postoperative CRT. The great interest in CRT in the adjuvant setting for gastric cancer has induced oncologists, particularly in the West, to conduct new clinical trials using various kinds of anticancer drugs. However, there is no rationale for adjuvant CRT after D2 dissection. Large-scale randomized controlled trials in Japanese patients have shown significant improvement of overall survival brought about by postoperative adjuvant chemotherapy with S-1. The results of these studies have suggested that even D2 surgery alone brings about much better survival for patients than limited surgery plus adjuvant CRT. Thus, strategies for the postoperative treatment of gastric cancers should be classified according to the degree of surgery.

Key words Chemoradiation · Radiation · Stomach · INT0116

Introduction

The primary role of radiotherapy or chemoradiotherapy (CRT) for patients with malignancies is local control of the tumor. A combination of radiotherapy plus a fluoropyrimidine (5-fluorouracil [5-FU]) used as a radiation sensitizer, could result in the good control of small amounts of residual or recurrent gastric cancer.[1] In the early 1980s, a randomized controlled trial (RCT) examining the effect of postoperative CRT for gastric cancer patients was conducted in the United States.[2] The CRT regimen was 37.5 Gray with combination chemotherapy using 5-FU (three courses of rapid intravenous infusion). The results showed 5-year overall survival (OS) rates and local recurrence rates of 4% and 54%, respectively, in the surgery-alone group and 23% and 39%, respectively, in the CRT group. Although only 62 patients were registered in this study, it was the first RCT to show that postoperative CRT might be a promising modality after surgery for gastric cancer patients.

In the early 1990s, a British RCT was conducted to evaluate the efficacy and the safety of postoperative radiotherapy and postoperative chemotherapy.[3] A total of 436 gastric cancer patients were randomized to either a surgery-alone group, a postoperative radiotherapy group, or a postoperative chemotherapy group. In the radiotherapy group, a midline dose of 45 Gy was given over 35 days, with the option of a further 5-Gy boost to a reduced field. In the chemotherapy group, 4 mg/m^2 mitomycin, 30 mg/m^2 doxorubicin, and 600 mg/m^2 5-FU were given on a 3-weekly basis for eight cycles. Neither the radiation group nor the chemotherapy group demonstrated a survival benefit when compared to the surgery-alone group; 5-year OS rates in the surgery-alone group, the radiation group, and the chemotherapy group were 20%, 12%, and 19%, respectively. This negative result triggered the acceleration of the use of postoperative CRT or preoperative chemotherapy for gastric cancer patients in the West.

Intergroup (INT) 0116 trial

In the late 1990s, an American RCT (INT0116) was conducted to evaluate the survival benefit of adjuvant CRT for gastric cancer.[4] A total of 556 patients with resected

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adenocarcinoma of the stomach or gastroesophageal junction were randomly assigned to either a surgery-alone group or a CRT group. In this trial, the treatment in the CRT group consisted of 425 mg/m^2 bolus 5-FU per day and 20 mg/m^2 leucovorin for 5 days, followed by 45-Gy radiation at 1.8 Gy per day, 5 days per week for 5 weeks, with a 400 mg/m^2 5-FU bolus and 20 mg/m^2 leucovorin per day on the first 4 and the last 3 days of radiotherapy. One month after the completion of radiotherapy, two 5-day cycles of 5-FU and leucovorin were given. Radiation was focused on the level-2 lymph node stations and both the proximal and distal resection margins. As a result, the CRT group showed a significant improvement in OS ($P = 0.005$) with the hazard ratio for death of 1.35 (95% confidence interval, 1.09 to 1.66). Local recurrence occurred in 29% of the patients in the surgery-alone group and in 19% of those in the CRT group. Grade 4 adverse events occurred in 32% of the patients in the CRT group, and 3 patients (1%) died from toxic effects of the CRT. The proportion of patients who completed the CRT was 64%. Since the reporting of this result, the standard treatment for curable gastric cancer in the United States has been considered as a combination of surgery and postoperative CRT.

However, most surgeons and oncologists who were familiar with D2 lymph node dissection could not accept the result of the INT0116 trial, because the surgical quality in this trial was an important issue. A detailed analysis of the type of surgery revealed that 54% and 36% of the patients, respectively, underwent D0 and D1 dissection, while only 10% underwent D2 dissection. In the subgroup analyses, the survival benefit of adjuvant CRT was not observed in the patients who received D2 dissection.[5] Recently, a Taiwanese RCT comparing D2 with D1 dissection without adjuvant therapy demonstrated the survival benefit of D2 dissection over D1; the 5-year survival rates of patients who received D2 and D1 dissections were 59.5% and 53.6%, respectively (log-rank; $P = 0.04$).[6] Furthermore, the latest Japanese RCT (Japan Clinical Oncology Group [JCOG] 9501),[7] which compared D2 with D2 plus paraaortic nodal dissection for stage T2b-T4 gastric cancer, demonstrated that there was no significant difference in survival between the two groups and that D2 dissection without adjuvant therapy brought about much better long-term survival than that in previous reports from outside eastern Asia. These Asian studies[6,7] indicated that D1 dissection was insufficient treatment for local control in patients with curable gastric cancer.

Of interest, the patient population enrolled in the CRT group in the INT0116 trial was quite similar to that enrolled in another Japanese RCT (JCOG9206-2),[8] which compared surgery alone with surgery followed by adjuvant chemotherapy with cisplatin, 5-FU, and uracil-tegafur (Table 1). The 5-year OS rates in the CRT group in the INT0116 trial and in the surgery-alone group in the JCOG9206-2 trial were 42% and 61%, respectively. Although a direct comparison of results from two different trials needs careful consideration in the interpretation, this suggests that D2 dissection without adjuvant therapy might produce better survival than D0/D1 dissection followed by CRT. Thus, the result of the INT0116 trial[4] can be generalized only to gastric cancer patients who received D0 or D1 lymph node dissection.

Table 1. Comparison between the INT0116 and the JCOG9206-2 trials

	INT0116[4]	JCOG9206-2[8]
Country	United States	Japan
Number of patients	281 (tested group)	133 (control group)
Treatment	Surgery plus adjuvant CRT	Surgery-alone
Proportion of patients with D2 or greater lymph node dissection	10%	99%
Proportion of pathological T3/4 cases	69%	69%
Proportion of pathological node-positive cases	86%	76%
Overall survival rate	3-Year: 50% 5-Year: 42%	3-Year: 66% 5-Year: 61%

Table 2. Comparison between Korean nonrandomized study and Japanese randomized studies

	Korean study[9]	JCOG9501[7]	ACTS-GC[10]
Country	Korea	Japan	Japan
Study design	Non-RCT	RCT	RCT
Number of patients	281 (tested group)	263 (control group)	529 (tested group)
Treatment	Surgery (D2) plus adjuvant CRT	Surgery alone (D2)	Surgery (D2) plus adjuvant chemotherapy (S-1)
Proportion of pathological T3/4 cases	48%	49%	45%
Proportion of pathological node-positive cases	51%	70%	90%
Overall survival rate	3-Year: 66% 5-Year: 57%	3-Year: 76% 5-Year: 69%	3-Year: 80%

Table 3. Ongoing studies of adjuvant chemoradiotherapy for gastric cancer

ClinicalTrials.gov identifier	NCT00052910 (CALGB80101)	NCT00323830	NCT00011960	NCT00123318	NCT00718913	NCT00183911
Country	United States	Korea	United States	Australia	Greece	United States
Study design	RCT	RCT	RCT	Non-RCT	Non-RCT	Non-RCT
Estimated number of patients	824	490	94	52	49	25
Target gastric cancer population	Stage IB-IV (M0)	Stage IB-IV (M0)	Stage IB-III	T3–4, N1–2, M0	T2–3, Any N, M0	Stage IB-IV (M0)
Chemotherapy regimen	5-FU + leucovorin vs epirubicin + cisplatin + 5-FU	Capecitabine + cisplatin	Paclitaxel + cisplatin, with vs without 5-FU	Epirubicin + cisplatin + 5-FU	Docetaxel + cisplatin + capecitabine	Floxuridine (intraperitoneal) + 5-FU + leucovorin
Radiation dose	45 Gy	With vs without 45 Gy	45 Gy	45 Gy	45 Gy	45 Gy
Degree of lymph node dissection	Any	D2	Any	D2	Any	Any

Adjuvant chemoradiotherapy after D2 lymph node dissection

The benefit of adjuvant CRT after curative gastrectomy with D2 lymph node dissection is controversial. A Korean nonrandomized study examined the survival benefit of adjuvant CRT after D2 dissection.[9] A total of 544 patients with curatively resected gastric cancer received adjuvant CRT (the same as that used for the INT0116 trial), while a total of 446 patients received surgery alone. The OS in patients with CRT was significantly better than that in patients without CRT (5-year OS rates, 57% vs 51%). The hazard ratio for death was 0.80 (95% confidence interval, 0.67 to 0.97), and the log-rank *P* value was 0.02. The proportion of patients with local recurrence within the radiation field was significantly lower in the CRT group (15%) when compared with that in the surgery-alone group (22%). In the CRT group, 75% of the enrolled patients completed treatment as planned, and only 1 patient (0.2%) died of toxicity. The authors concluded that adjuvant CRT was feasible even after D2 surgery and could improve survival. However, the survival in the CRT group reported in this Korean study was much worse than that in the surgery-alone group in the Japanese JCOG9501 trial[7] (Table 2). The proportion of patients with pathological T3/4 stage was similar in both studies, but the proportion of pathological node-positive cases in the Korean study was lower than that in the JCOG9501 trial. Of note, a large-scale RCT (ACTS-GC),[10] which compared surgery alone with adjuvant chemotherapy using S-1 for 1 year after D2 dissection, was conducted in patients with stage II/III gastric cancer in Japan. It demonstrated that there was a significant survival benefit of adjuvant chemotherapy, which led to the establishment of new standard treatment for stage II/III gastric cancer in Japan. The background of the patients in the Korean study[9] was very similar to that in the Japanese ACTS-GC trial regarding pathological T stage, but the ACTS-GC trial included many more pathological node-positive cases than the Korean study. Nevertheless, the 3-year OS rate in the adjuvant chemotherapy group was 80% in the ACTS-GC trial, while the 3-year OS rate in the adjuvant CRT group was 66% in the Korean study. This suggests either that the D2 dissection at this Korean institute may not have been sufficient as local control, or that chemotherapy without radiation was more effective than chemotherapy with radiation when patients underwent D2 dissection. Besides the Korean study, two feasibility studies of CRT based on the INT0116 trial were reported from Singapore and Hong Kong,[11,12] but the long-term outcomes in these retrospective studies were inferior to those in the Japanese randomized studies[7,8,10] noted above.

Ongoing studies of adjuvant CRT

Reflecting the great interest in the adjuvant setting of CRT for gastric cancer patients, there are many ongoing studies in Western countries and in Eastern Asia (Table 3). Among

them, only the Korean study and the Australian study limited the inclusion criteria to patients who received D2 surgery. The largest trial, CALGB80101, was planned to compare 5-FU plus leucovorin with ECF (epirubicin, cisplatin, 5-FU) in combination with radiation therapy. Because the ECF regimen as pre- and postoperative chemotherapy is one of the standard treatments for resectable gastric cancers in Europe, according to the positive result of the MAGIC trial,[13] the CALGB80101 trial should show which is the better chemotherapy regimen to be combined with radiation for gastric cancer patients who receive D0 or D1 surgery. In Korea, capecitabine, an oral fluoropyrimidine, is frequently used for the treatment of gastric cancers, so that an RCT is planned to compare capecitabine plus cisplatin with and without radiation, which may prove the significance of radiation after D2 surgery.

Conclusion

CRT has a certain benefit for gastric cancer due to its good local control, so that it is important to consider how to utilize this modality. The results of the INT0116 trial[4] led to adjuvant CRT for gastric cancer patients becoming one of the standard treatments after gastrectomy with D0 or D1 lymph node dissection. However, there is no rationale for employing CRT in patients after D2 surgery. The Japanese RCTs[7,8,10] have suggested that D2 surgery alone or D2 surgery plus adjuvant chemotherapy using S-1 brings about much better survival than D0/D1 surgery plus adjuvant CRT. Therefore, it seems reasonable that the target population for adjuvant CRT should be limited to gastric cancer patients who have received D0 or D1 surgery.

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The Number of Metastatic Lymph Nodes is a Significant Risk Factor for Bone Metastasis and Poor Outcome After Surgery for Linitis Plastica-type Gastric Carcinoma

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Abstract
Background Linitis plastica-type gastric carcinoma remains a disease with poor prognosis despite an aggressive surgical approach. Although a prominent pattern of disease failure is peritoneal carcinomatosis, some patients experience rapid disease progression without signs of the peritoneal disease.
Methods Clinicopathologic data from 178 patients with linitis plastica-type gastric cancer operated on between 1991 and 2000 were analyzed. Survival stratified by curability of surgery, pN stage, and patterns of failure were evaluated by using the Kaplan-Meier method, and χ^2 test was used to evaluate correlation between the number of metastatic lymph nodes in terms of pN categories and the incidence of various patterns of metastasis and recurrence. Cox regression hazard model was used to identify independent prognostic factors.
Results R0 resection was performed only among 82 patients (46% of those who underwent laparotomy). Node metastasis was frequent with only 22 patients classified as pN0. Peritoneal carcinomatosis was observed in 131 patients and was the commonest pattern of recurrence. Bone metastasis, found in 13 patients, was associated with poor outcome, and its incidence was significantly correlated with the number of metastatic nodes. pT4 status and pN3 status were identified as significant independent prognostic determinants.
Conclusion Treatment strategy for the linitis plastica should in general combine surgery with aggressive treatment directed toward peritoneal disease. However, patients with >16 metastatic nodes more often are associated with bone metastasis than those with modest nodal involvement and suffer from poor prognosis.

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Introduction

Linitis plastica-type gastric carcinoma is found in 12–14% of all cases of advanced gastric carcinoma in leading institutions in Japan and western countries [1]. It is diffusely infiltrative by nature and has a propensity toward involvement of the entire stomach, invasion of the gastric serosa, peritoneal seeding, and gross lymph node metastases [2]. In Japan, radical surgery with systemic extended lymphadenectomy has been considered effective in the management of gastric carcinoma in general [3, 4]. Authors, along with others, have shown some encouraging data, indicating that the advantageous effect of the extended surgery that has been suggested for gastric cancer in general in Japan also applies to the linitis plastica type [5–7], provided curative (R0) resection was performed. However, prognosis of the patients with this type of cancer, whose common pattern of failure is peritoneal dissemination, remains outstandingly poor in comparison with other types [8]. Given that free disseminated cancer cells are detected from the peritoneal washing by reverse-transcriptase polymerase chain reaction in up to 70–80% of patients who undergo surgery for the linitis plastica, all

efforts to cure the disease by surgery may begin to seem futile.

More recently, the authors and others have found that chemotherapy with modern cytotoxic agents exerts some promising effect on patients with free cancer cells in the peritoneal cavity. Two-year survival rate of the patients who were positive for peritoneal washing cytology treated with S-1 monotherapy was 47%, whereas <20% of similar patients in the historical control survived that far [9]. Intraperitoneal drug delivery of anticancer drugs also is a rational option to treat the disseminated cancer, and a high level of evidence in support of intraperitoneal administration of cisplatin and paclitaxel was reported for optimally debulked ovarian cancer [10], another cancer type that is frequently associated with the peritoneal disease. The authors also have begun to accumulate favorable in vivo [11] and pharmacokinetic data [12], suggesting that intraperitoneal administration of paclitaxel could be effective to combat peritoneal metastases derived from gastric cancer. It seems adequate to combine surgery with chemotherapy directed toward peritoneal disease when considering a multimodal treatment strategy for the linitis plastica. In practice, however, a certain population with this type of cancer are found to die early without any signs of peritoneal disease. To explore whether it is possible to customize perioperative therapy against patients with the linitis plastica, the authors analyzed pooled data of linitis plastica patients treated with the conventional policy of radical surgery alone or surgery followed by chemotherapy, and searched for clinicopathologic characteristics that predicts early disease failure.

Patients and methods

Between 1991 and 2000, a total of 2,244 patients with gastric carcinoma were identified in the prospective data file at Department of Surgery II, Nagoya University Graduate School of Medicine and Department of Gastroenterological Surgery, Aichi Cancer Center. Among them, 192 patients (8.6%) had gastric cancer of the linitis plastica type and fulfilled the following criteria to be included for analyses in the current study: 1)patients with primary gastric carcinoma who were preoperatively diagnosed as linitis plastica type by barium meal and endoscopy; 2) patients who were not given neoadjuvant chemotherapy; 3) patients with no signs of ascites, distant metastasis, or bulky paraaortic nodes metastases after the preoperative evaluation with physical examination and computerized tomography. This database allows for accurate storage and retrieval of patients based on the Japanese Classification of Gastric Carcinoma [13] and tumor-node-metastasis [14]. Fourteen of the 192 patients were lost to follow-up, and the remaining 178 patients form the basis of current study. Of these, patterns of disease failure are unknown in 6 patients. Of 150 patients who were treated with gastrectomy, details of the number of metastatic lymph nodes were unavailable in 2 patients.

Surgical procedure

Indication for gastrectomy was decided based on surgical findings at laparotomy, except in four patients who underwent staging laparoscopy. After laparotomy, abdominal cavity was thoroughly examined for tumor metastasis and peritoneal deposits in particular. A sample of peritoneal deposits was taken whenever they were detected and diagnosis of cancer metastasis was histologically confirmed by frozen sections. Gastrectomy was performed and chemotherapy given at the discretion of the surgeons for the patient who was diagnosed at laparotomy to have a small number of peritoneal deposits (P1–P2 by the Japanese Classification for Gastric Carcinoma [13]). Gastrectomy was avoided for those with extensive invasion to the retroperitoneum and for those with extensive peritoneal dissemination graded as P3 by the Japanese Classification of Gastric Carcinoma. When potentially curative R0 resection [14] was considered possible, total gastrectomy with splenectomy and D2 lymphadenectomy as proposed by Maruyama [15] had been the treatment of choice. Efforts were made to avoid distal pancreatectomy unless direct invasion to the pancreas was observed.

Histopathological evaluation of the resected specimens

The resected specimens were examined by the pathologists after hematoxylin and eosin staining, depth of cancer invasion (pT categories), and the number of metastatic lymph nodes (pN categories) were evaluated for clinical staging according to the Tumor-Node-Metastasis classification [14]. The nodal status was not evaluated histopathologically in 30 patients with disseminated or locally advanced disease, including 28 patients who did not undergo gastrectomy.

Follow-up program

The patients were followed for a median of 3,509 (range, 1,825–5,295) days or until death. Follow-up program consisted of interim history, physical examination, hematology, and blood chemistry panels, including serum CEA and CA19-9 values, which were performed every 3 months for the first postoperative year, and every 6 months

thereafter. Abdominal ultrasonography or computerized tomography was performed every 6 months. Autopsy or second-look surgery was not always performed, and failure analysis is based primarily on clinical observations and information obtained through computerized tomography, bone scintigram, physical examination, and clinical symptoms.

Statistical analysis

Survival analysis stratified by curability of surgery was performed with all 178 patients. Survival analysis with reference to the number of nodal metastasis was performed with 148 patients who underwent gastrectomy and had detailed data regarding the number of lymph nodes removed. Failure analyses were performed in 172 patients whose patterns of disease failure had been recognized. The Kaplan-Meier method was used to plot the survival curves. The Student's t test was used to evaluate the difference in the number of metastatic lymph nodes between a group of patients who developed bone metastasis and a group who did not. χ^2 test was performed to evaluate correlation between the number of metastatic lymph nodes and the incidence of bone, liver, or distant lymph node metastasis. Cox regression hazard model was used for multivariate analysis to find a significant independent prognostic factor.

Results

Patient demographics

Mean age of the patients was 59 ± 11.5 years (male:female ratio, 90:88). A total of 150 patients were treated with gastrectomy (115 total, 1 proximal, and 34 distal gastrectomies), and the remaining 28 underwent exploratory laparotomy or laparoscopy. Extended lymphadenectomy of D2 or more had been performed in 101 patients. R0 resection was performed only for 82 patients (46% of those who underwent laparotomy). Serosal invasion was found in 158 patients (89%), of which 54 had invasion to the adjacent structures (pT4). Node metastasis also was frequent, and only 22 patients were found after systemic lymphadenectomy to have no lymph node metastasis. The mean number of metastatic nodes was 15 among those who underwent gastrectomy and 10.2 among those treated by R0 resection. Despite the preoperative diagnosis through conventional imaging studies that these patients have no distant metastasis, peritoneal deposits were found at laparotomy in as many as 78 patients (44%), confirming the well-documented fact that laparoscopic examination is mandatory for accurate staging of advanced gastric cancer.

Operative mortality

Only seven patients died of causes other than cancer, of which two patients had recurrent disease at the time of death. One patient died on the 3rd postoperative day as a result of heart failure, and another on the 245th postoperative day after a prolonged effort to control the surgical complication. No other perioperative death was observed, and postoperative mortality rate was 1.1%.

Survival of the patients according to residual tumor classification, respectability, and the number of metastatic lymph nodes

The prognosis of 178 patients with linitis plastica in this study was poor, with a 50% survival time of 13.8 months. Median survival time of patients treated with R0 resection was 30.2 months, those treated with palliative resection was 8.2 months, and those who did not undergo a gastrectomy was 7.8 months, with no difference in survival between the latter two groups (Fig. 1). Survival analysis of the patients stratified by the pN categories according to the TNM classification revealed that only a subset with metastatic lymph nodes >16 (pN3) exhibited remarkably poor prognosis (Fig. 2). On the other hand, patients without nodal metastasis (pN0) did not survive any longer than the node-positive patients.

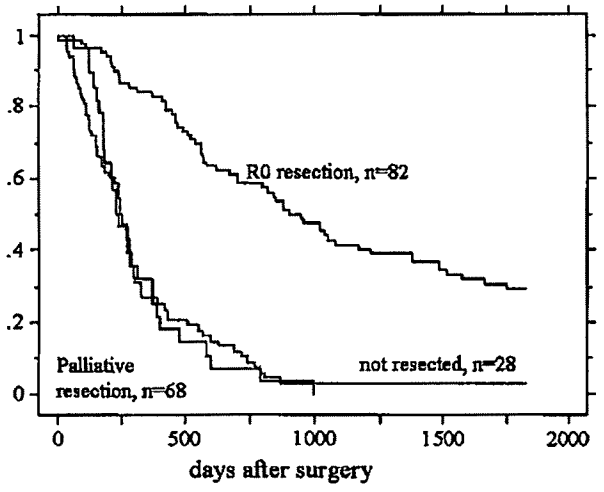

Fig. 1 Survival of patients with linitis plastica-type gastric carcinoma (n = 178) stratified according to the surgery performed: R0 resection (n = 82), palliative resection (n = 68), and exploratory laparotomy or laparoscopy (n = 28)

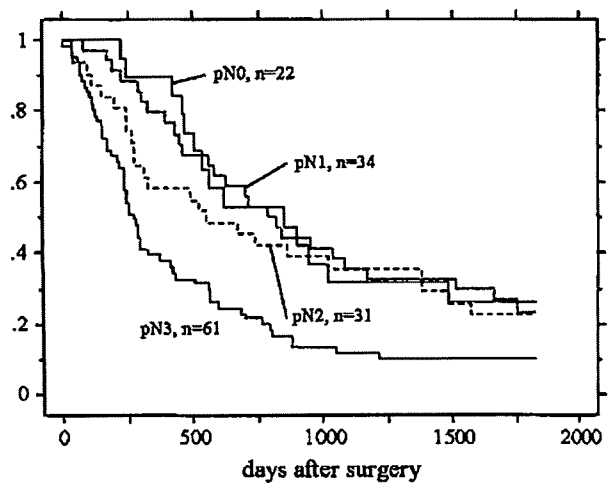

Fig. 2 Survival of patients with linitis plastica-type gastric carcinoma who underwent gastrectomy with systemic lymphadenectomy ($n = 148$) stratified according to the number of metastatic lymph nodes: pN0 = no metastatic lymph nodes ($n = 22$); pN1 = 1–6 metastatic nodes ($n = 34$); pN2 = 7–15 metastatic nodes ($n = 31$); pN3 = ≥16 metastatic nodes ($n = 61$)

Patterns of disease failure: the association with pN stage and prognosis

Clinically observed patterns of disease failure were peritoneal carcinomatosis in 131, distant lymph nodes in 17, bone or bone marrow metastasis sometimes leading to disseminated intravascular coagulation in 13, hepatic in 11, local in 6, and other sites in 8. Twenty-eight patients suffered from multiple patterns of metastasis, including eight patients with metastatic disease in three distinct sites. Survival of patients with metastases and recurrences to the bone, liver, and distant nodes were invariably brief, whereas a fraction of patients with peritoneal carcinomatosis survived longer (Fig. 3). χ^2 analysis showed a remarkable and statistically significant trend of patients with > 16 metastatic lymph nodes suffering from bone metastasis (Table 1), whereas there were only weak correlations between a high pN stage and hepatic metastasis or recurrences in the distant nodes (data not shown). The number of metastatic nodes among patients with bone metastasis was 26.7 ± 7.7 and was significantly greater than the number among other patients (14 ± 13.6; $p = 0.0026$). Peritoneal carcinomatosis occurred commonly and regardless of the nodal status in patients with linitis plastica-type gastric cancer.

Independent prognostic factors to predict and long-term survival

Univariate analyses identified sex, invasion to the adjacent structures (T4 status), finding of the peritoneal seeding (positive versus negative), hepatic metastasis and presence > 16 metastatic nodes (pN3 versus others), and R-classification (R0 versus R1 and R2) as significant prognostic factors. Of these, R-classification, pN3 status,

Fig. 3 Survival of patients with linitis plastica-type gastric carcinoma stratified by whether they suffered from a specific type of metastasis or recurrence. Although patients rarely had hepatic or bone metastasis, patients with these metastases had extremely poor prognosis

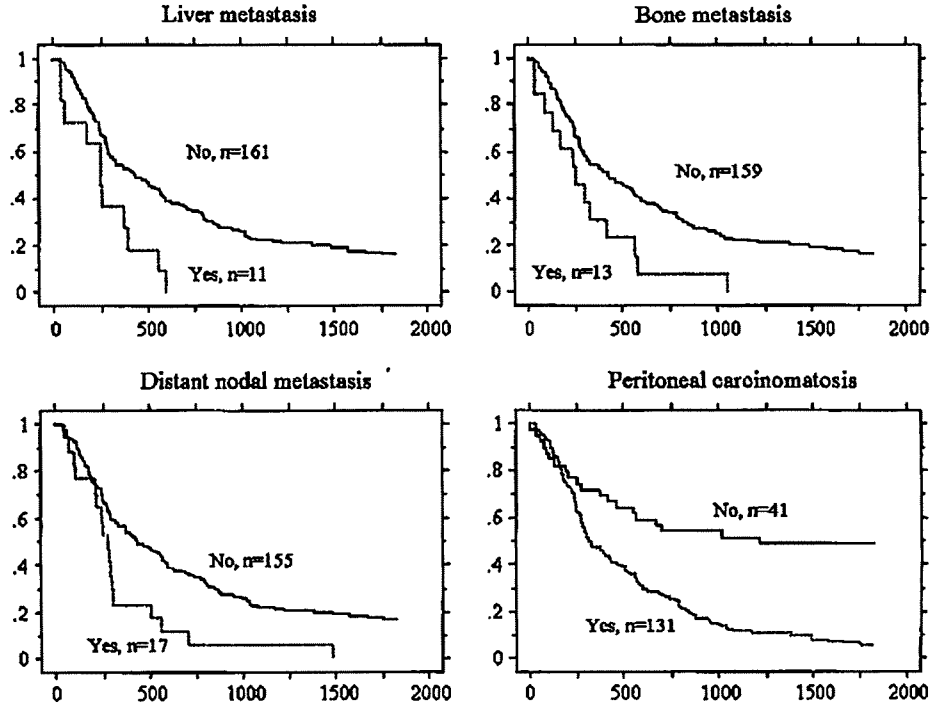

Table 1 Bone metastasis among patients with a greater number of metastatic lymph nodes

	Bone metastasis		
	No	Yes	
pN0 (no. of metastatic nodes 0)	19	0	19
pN1 (no. of metastatic nodes 1–6)	34	0	34
pN2 (no. of metastatic nodes 7–15)	30	1	31
pN3 (no. of metastatic nodes ≥16)	51	10	61
	134	11	145

$p = 0.009$

Of 150 patients who underwent gastrectomy, 3 patients with no information regarding patterns of disease failure and 2 in whom the number of metastatic lymph nodes had been unavailable were excluded

and sex were independent significant prognostic factors (Table 2).

Discussion

Prognosis of linitis plastica type gastric cancer remains dismal compared with other types of gastric carcinoma [8]. More radical approach with super-extended lymphadenectomies has been proposed in Japan several years ago [6, 7], but the current consensus derived from recent data is that patients with peritoneal deposits do not benefit from surgical treatments, as observed in the current study in which patients treated by palliative resection did not live longer than those who did not undergo gastrectomy. Furthermore, the authors have shown through molecular detection using CEA RT-PCR that free cancer cells can be found scattered in the peritoneal cavity of 70–80% of patients with the linitis plastica [16]. Although these findings are discouraging, some evidence pointing to the efficacy against peritoneal carcinomatosis through the use of recent cytotoxic agents, such as S-1 and paclitaxel have began to emerge [17, 18]. Clinical trials testing more intensive strategy to eliminate the intraperitoneal minimal disease, such as intraperitoneal chemotherapy [10, 12] or chemohyperthermia in combination with surgery [19–21], could now be seriously considered.

One drawback to this approach is the possibility that some patients may die due to rapid progression—particularly due to the pattern of failure other than the peritoneal metastasis. It is now clear that the risk factors for the early death are the invasion to the adjacent structure and a large number of metastatic lymph nodes. Bone metastasis, often leading to disseminated intravascular coagulation, was observed in 13 of 178 patients (7.3%) and was associated with a particularly poor prognosis. This pattern of failure is mostly observed among patients with pN3-stage disease (>16 metastatic nodes). A small proportion of patients with no nodal disease did not show favorable prognosis compared with those with node-positive disease. Thus, biology of node-negative cancer does not seem utterly different from that of node-positive cancer in terms of survival time and tendency to develop into peritoneal carcinomatosis. It remains clear, however, that a great number of metastatic nodes do reflect a particularly aggressive biology.

Our data delineated the well-documented fact that accurate preoperative staging for advanced gastric cancer cannot be obtained without laparoscopic exploration [22, 23]. Despite this knowledge, the authors have not been able to offer this procedure to all patients with potentially operable gastric cancer due to limited capacity of the operating facility. However, patients with linitis plastica now receive laparoscopy immediately before surgery to rule out extensive peritoneal disease, because the risk of finding peritoneal deposits has been repeatedly shown to be substantial for this type of gastric cancer [16]. Nevertheless, those with minimal metastatic disease may still be offered a multimodal treatment strategy, including surgical resection, in which case gastrectomy is performed immediately after the exploratory laparoscopy.

Conclusion

Although peritoneal carcinomatosis remains the most feared pattern of disease failure in the linitis plastica-type cancer, bone metastasis leading to early death is observed

Table 2 Multivariate analysis of relevant prognostic factors among patients with linitis plastica who were treated with gastrectomy and had data regarding the number of metastatic lymph nodes available ($n = 148$)

Variable		Hazard ratio	95% confidence interval	p value
R classification	R1 and R2	3.16	1.74–5.75	0.0002
No. of metastatic LNs	≥16	1.64	1.12–2.41	0.0112
Gender	Male	1.64	1.12–2.41	0.0112
Invasion to the surroundings	Positive	1.71	1.08–2.7	0.0213
Peritoneal deposits	Positive	1.04	0.62–1.74	0.8901
Hepatic metastasis	Positive	0.97	0.44–2.11	0.9464

in 7.3% of patients, and these patients were found to have extensive nodal disease. pN3 stage (>16 metastatic lymph nodes) is an adverse prognostic determinant, possibly resulting in early recurrences outside the peritoneal cavity. These patients may be candidates for aggressive systemic therapies rather than locoregional intraperitoneal therapies.

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Operation

D2リンパ節郭清：適応と手技

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D2リンパ節郭清：適応と手技

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I. 適　応

現行のガイドラインでは，治癒切除可能な進行胃癌のすべてと早期胃癌の一部にD2リンパ節郭清を行うように記載されている。しかし，早期胃癌の術式に関しては，組織型，術中のリンパ節所見（sN）および術前の病巣の大きさを加味して，郭清範囲を決定するようになっており，実際のところ，組織型を除いた他の2因子が的中する確率は良くて2/3と予想できる。したがって，結果的にD2郭清の適応ではなかった症例にD2を実施することは日常的に起こるし，その逆もしかりである。

実際D2郭清がD1＋βに比べて，どれだけ侵襲が大きいか，あるいは術後の合併症を増やすかということについては，明確な比較はされていないし，比較したとしても大きな差があるとは思えない。D1のみとD2には，ことにBMI 30以上の患者などでは，合併症発生率に差があることは想定できるが，幽門側胃切除でD2とD1＋βに差があるとは思われない。胃全摘では，脾摘や膵脾合併切除をD2の一部に含めれば話は別であるが，脾摘もしない不完全なD2とD1＋βとでどれだけの差があるかは疑わしい。縮小手術を行い，術後の病理がわかってから，再手術を行って追加郭清することを考えれば，少しでも不安がある場合にはD2を行うべきである。現行のガイドラインは，術中のリンパ節の迅速診断を多用する癌研のデータを元に作られたもので，一般病院では，やりそこねを避けることのほうが重要であり，SMであれば積極的にD2郭清を行う方針が無難と筆者は考えている。病変の部位による適応は取扱い規約を参照していただきたい。

結論としては，D2は術前にSMと診断されるすべての早期胃癌と治癒切除可能な進行胃癌のすべてに適応してよいと思われる。ただし，脾摘の適応と患者のリスク要因はこの議論と別に考える必要がある。

II. 手　技

1. 胃全摘・幽門側胃切除に共通の部分

a) 大網切除とbursectomy

適応補足：bursectomyについては，癌の浸潤を認めないBursa Omentalis切除の意義を示す明確なエビデンスはないので，絶対適応は後壁の腫瘍が浸潤もしくは炎症性に癒着する場合となる。相対適応は後壁に存在する進行癌でT4の可能性を否定できない症例。大網切除も同じであるが，大網付着部に浸潤している進行胃癌では，bursectomyはこだわらないとしても，完全な大網切除は行うほうがいいと思っている。しかし，No.6郭清を行うすべての症例

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