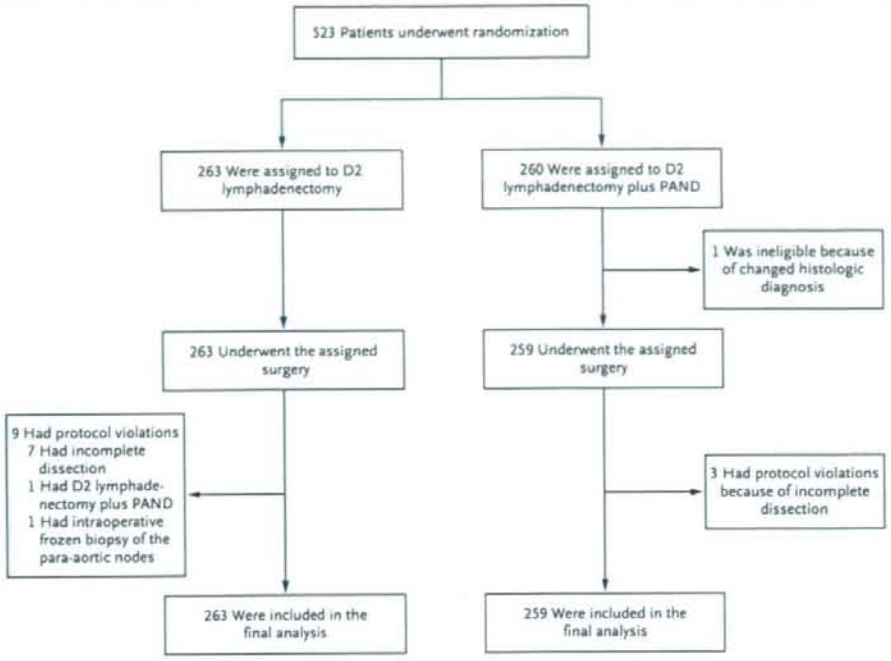

Figure 1. **Disposition of the Patients.**
PAND denotes para-aortic nodal dissection.

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

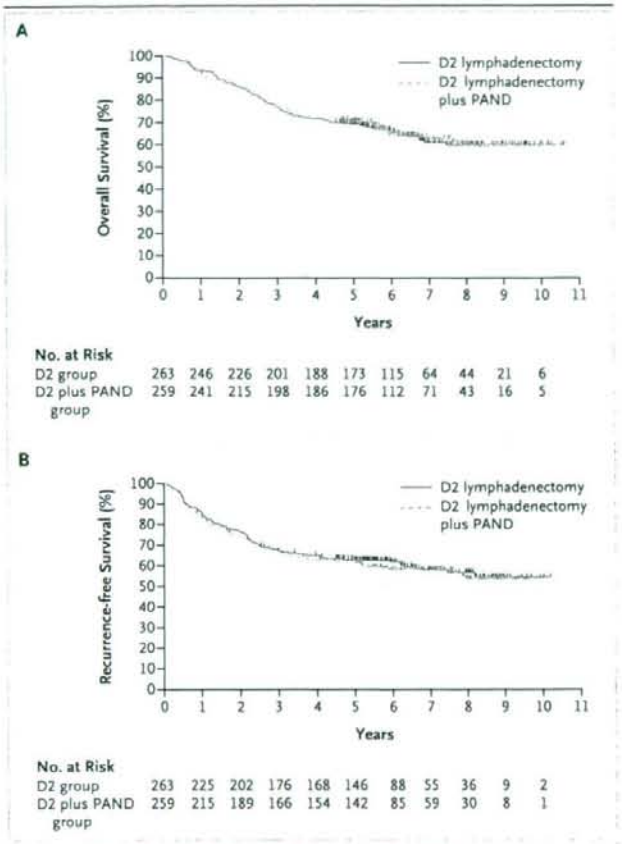

Figure 2. **Kaplan–Meier Estimates of Overall Survival (Panel A) and Recurrence-free Survival (Panel B).**

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-

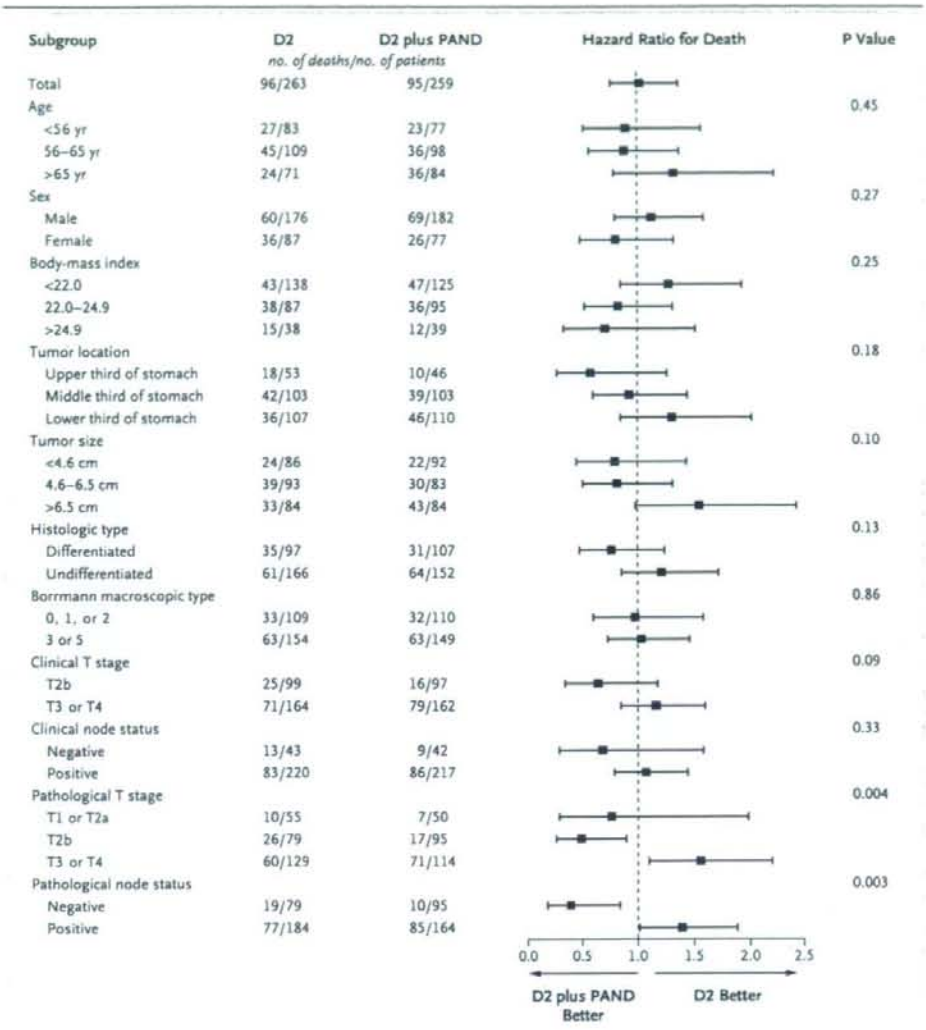

Figure 3. **Tests for Heterogeneity of Treatment Effect According to the Clinicopathological Characteristics of the Patients.**

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.

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

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REFERENCES

1. Kelley JR, Duggan JM. Gastric cancer epidemiology and risk factors. J Clin Epidemiol 2003;56:1-9.
2. de Aretxabala X, Konishi K, Yonemura Y, et al. Node dissection in gastric cancer. Br J Surg 1987;74:770-3.
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.
4. 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.
5. 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.
6. 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.
7. 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.
8. Sierra A, Regueira FM, Hernández-Lizoáin JL, Pardo F, Martínez-Gonzalez 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.
9. Degiuli 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.
10. 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.
11. 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.
12. 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.
13. Sasako M, Saka M, Fukagawa T, Katai H, Sano T. Modern surgery for gastric cancer — Japanese perspective. Scand J Surg 2006;95:232-5.
14. Sano T. Tailoring treatments for curable gastric cancer. Br J Surg 2007;94: 263-4.
15. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma. 2nd English ed. Gastric Cancer 1998;1: 10-24.
16. Sobin LH, Wittekind C, eds. TNM classification of malignant tumours. 6th ed. New York: Wiley-Liss, 2002.
17. 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.
18. Isozaki H, Okajima K, Fujii K, et al. Effectiveness of paraaortic lymph node dissection for advanced gastric cancer. Hepatogastroenterology 1999;46:549-54.
19. 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.
20. 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.
21. 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.
22. 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.
23. Japanese Research Society for Gastric Cancer. Japanese classification of gastric carcinoma. 1st English ed. Tokyo: Kanehara, 1995.
24. Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983;70:659-63.
25. 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.
26. 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.
27. 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.
28. Begg CB, Cramer LD, Hoskins WJ, Brennan MF. Impact of hospital volume on operative mortality for major cancer surgery. JAMA 1998;280:1747-51.
29. 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.
30. 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.
31. 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.
32. 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.
33. Peeters KC, Hundahl SA, Kranenbarg 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.
34. 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.
35. 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.]

Original article

Outcome of pylorus-preserving gastrectomy for early gastric cancer

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Background: Pylorus-preserving gastrectomy has been introduced as a function-preserving operation for early gastric cancer in Japan. The aim of this study was to investigate the safety and radicality of the procedure.

Methods: Between 1995 and 2004, 611 patients with apparent early gastric cancer in the middle third of the stomach had pylorus-preserving gastrectomy. The short-term surgical and long-term oncological outcomes of these operations were assessed.

Results: The accuracy of preoperative diagnosis of early gastric cancer was 94·3 per cent. Nodal involvement was seen in 62 patients (10·1 per cent). There were no postoperative deaths. Complications developed in 102 patients (16·7 per cent). Major complications, such as leakage and abscess, were observed in 19 (3·1 per cent). The most common complication was gastric stasis, occurring in 49 (8·0 per cent). The overall 5-year survival rate in patients with early gastric cancer was 96·3 per cent.

Conclusion: Pylorus-preserving gastrectomy is a safe operation with an excellent prognosis in patients with early gastric cancer. It is recommended as the standard procedure for early gastric cancer in the middle third of the stomach.

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Introduction

Since the 1950s, gastric cancer has been the most common cause of death among neoplasms of the digestive system in Japan. Gastrectomy with extended (D2) lymphadenectomy has become firmly established as the standard operation[1–4]. In recent years, early gastric cancer (EGC) has accounted for nearly 50 per cent of all gastric cancers in Japan[5]. EGC has an excellent prognosis after surgical treatment, with 5-year survival rates of more than 90 per cent being reported by both Western and Japanese investigators. Japanese surgeons have therefore revised their strategy of focusing on highly radical operations. This has led to function-preserving surgery to minimize postgastrectomy problems with the intention of creating a better quality of life, while maintaining a high level of radicality[6,7].

Pylorus-preserving gastrectomy (PPG) is a function-preserving procedure devised by Maki and colleagues[8] in 1967. Its purpose is to maintain the reservoir function of the stomach in order to relieve dumping syndrome and prevent bile reflux. Preservation of nerve supply and blood flow to the pyloric antrum is intended to maintain pyloric function. In 1995 the technique was first adopted at this institution to treat EGC in the middle or lower third of the stomach, with clear advantages over distal gastrectomy (Billroth I) in terms of long-term functional outcomes[9]. The aim of the present study was to focus on short-term surgical and long-term oncological outcomes, investigating the safety and radicality of PPG to determine whether it could be recommended as the standard operation for EGC in the middle third of the stomach.

Methods

Between 1995 and 2004, 611 patients with EGC diagnosed before surgery underwent PPG at the National Cancer Center Hospital, Tokyo. Short- and long-term outcomes were analysed. All tumours were adenocarcinomas in either the mucosal or submucosal layer. The study included all patients with EGC in the middle third of the stomach diagnosed before surgery, excluding those who were candidates for endoscopic mucosal resection (EMR)[10]. Current recommendations for EMR are tumours confined

to the mucosal layer, type I, IIa or depressed type IIc with no ulcer or ulcer scar (no fold convergence endoscopically), well or moderately differentiated adenocarcinomas, and tumours smaller than 2·0 cm (the distance between the distal transection line and the pyloric ring should be more than 2·5 cm because the remnant pyloric antrum must have a certain capacity for peristalsis to occur and move gastric contents into the duodenum[11]).

The surgical specimens were examined and scored according to the Japanese Classification of Gastric Carcinoma[12]. Postoperative follow-up included clinical and laboratory examinations every 6 months for the first 2 years, and annually thereafter at least until 6 years after operation. Information was obtained from follow-up records and the city registry office. The last follow-up date was 30 September 2006.

Surgical procedures

Fig. 1 shows the anatomy for PPG. The greater omentum was preserved and the gastrocolic ligament was cut at least 3 cm from the gastroepiploic vessels. The stomach was transected with a macroscopic margin at least 2 cm from the tumour border. Lymph nodes from stations 1 (right cardia), 3 (lesser curvature), 4sb (left gastroepiploic artery), 4d (right gastroepiploic artery), 6 (infrapyloric), and 7, 8a, 9 and 11p (suprapancreatic) were excised, but those at station 5 (suprapyloric) were left intact. Pyloroplasty was not performed. The hepatic and pyloric branches of the vagus nerves were routinely preserved, and the coeliac branch was routinely preserved from 2003. The root of the right gastric artery was preserved and transected just distally to the first branch. The left gastric artery was divided at its origin when the coeliac branch was sacrificed, and slightly more distally when the coeliac branch was preserved. Infrapyloric vessels were routinely preserved from 2003. The anastomosis was made using a sero-submucosal technique with absorbable sutures.

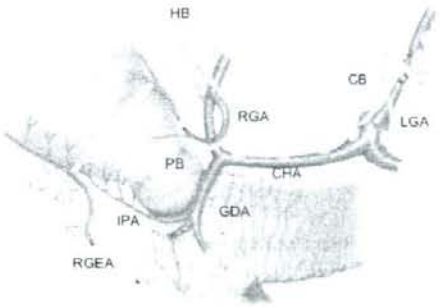

Fig. 1 Anatomy for pylorus-preserving gastrectomy. CB, coeliac branch; CHA, common hepatic artery; GDA, gastroduodenal artery; HB, hepatic branch; IPA, infrapyloric artery; LGA, left gastric artery; PB, pyloric branch; RGA, right gastric artery; RGEA, right gastroepiploic artery

Statistical analysis

All analyses were performed on an intention-to-treat basis. Survival rates were calculated by the Kaplan–Meier method. Statistical analyses were performed using SPSS® version 14.0 (SPSS, Chicago, Illinois, USA). $P < 0.050$ was considered significant.

Results

The mean age of the 611 patients was 58·1 (range 26–86) years; 376 were men and 235 were women (*Table 1*). Mean body mass index was 23·0 (range 14·9–33·3) kg/m^2. Tumours were in the middle third of the stomach in 532 patients. Before surgery, 248 tumours (40·6 per cent) were diagnosed as mucosal and 363 (59·4 per cent) as submucosal cancers.

EGC (343 in the mucosa, 233 in the submucosa) was confirmed in 576 (94·3 per cent) of the 611 patients and non-early cancer (23 in the muscularis propria, 11 in the subserosa, one in the serosa) in the other 35 (5·7 per cent). The accuracy of preoperative diagnosis of EGC by endoscopy and upper gastrointestinal series was 94·3 per cent. The incidence of nodal involvement was 10·1 per cent overall (62 of 611 patients), 3·8 per cent (13 patients) in mucosal cancers and 17·6 per cent (41 patients) in submucosal cancers (*Table 2*). Of the 13 patients with node-positive mucosal cancer, ten had pathological node stage (pN) 1 disease and the other three had pN2 disease.

Table 1 Characteristics of 611 patients included in the study

	No. of patients (n = 611)
Age (years)*	58·1(11·4) (26–86)
Sex ratio (M : F)	376 : 235
Body mass index (kg/m^2)*	23·0(3·0) (14·9–33·3)
Tumour location	
Upper third	7
Middle third	532
Lower third	72
Preoperative tumour stage	
Mucosa	248
Submucosa	363

*Values are mean(s.d.) (range).

Table 2 Nodal status by histological type and depth of invasion

Variables	N0	N1	N2	Total
Histological type*				
Differentiated type	208	22	2	232
Undifferentiated type	341	28	10	379
Depth of invasion				
Mucosa	330	10	3	343
Submucosa	192	36	5	233
Muscularis propria	18	3	2	23
Subserosa	9	1	1	11
Serosa	0	0	1	1
Total	549	50	12	611

*According to the Japanese Classification of Gastric Carcinoma. Differentiated type includes papillary adenocarcinoma and tubular adenocarcinoma. Undifferentiated type includes poorly differentiated adenocarcinoma, signet-ring cell carcinoma and mucinous adenocarcinoma.

Table 3 Postoperative morbidity

	No. of patients (n = 611)
Major complications	
Postoperative bleeding	4 (0·7)
Anastomotic leakage	2 (0·3)
Pancreas-related abscess	9 (1·5)
Other intra-abdominal abscess	4 (0·7)
Minor complications	
Gastric stasis	49 (8·0)
Thrombophlebitis	1 (0·2)
Atelectasis or pneumonia	20 (3·3)
Intestinal obstruction	2 (0·3)
Cholecystitis	1 (0·2)
Wound infection	10 (1·6)

Values in parentheses are percentages.

Of 41 patients with node-positive submucosal cancer, 36 had pN1 and five had pN2 disease.

All operations were carried out with curative intent. The coeliac branch of the vagus nerve was preserved in 400 patients (65·5 per cent). The mean(s.d.) length of the pyloric cuff was 3·3(1·1) cm. The median duration of operation was 200 (range 93–466) min, median blood loss was 260 (range 21–1989) ml and median postoperative hospital stay was 14 (range 5–83) days.

Postoperative complications developed in 102 (16·7 per cent) of 611 patients (*Table 3*). Major complications occurred in 19 (3·1 per cent): postoperative bleeding in four (0·7 per cent), anastomotic leakage in two (0·3 per cent), intra-abdominal abscess in four (0·7 per cent) and pancreas-related abscess in nine (1·5 per cent). Gastric stasis was the most frequent complication, occurring in 49 patients (8·0 per cent) who had severe symptoms requiring fasting and intravenous fluid support. Total parenteral nutrition was used in nine patients with delayed emptying. No other treatment for gastric stasis was used. Passage to the duodenum was examined by contrast radiology. The first study was performed on the fourth postoperative day in all patients. Further examinations were performed at least once a week for those with delayed emptying, until there was radiological evidence of adequate emptying. Reoperation was performed successfully in four patients (0·7 per cent) for postoperative bleeding.

Median follow-up was 50 (range 5–130) months. Five patients developed a second primary gastric carcinoma in the remnant stomach. In four, the tumour was located proximal to the anastomosis and in one it was distal. Three were treated by EMR and two by gastrectomy, all with curative intent.

Six patients developed recurrence and five died, three as a result of liver metastases and two from peritoneal metastases. One patient, who had recurrent non-early cancer (muscularis propria) with three positive nodes, developed nodal metastases along the hepatoduodenal ligament but was still alive at the time of writing. Another 19 patients died from other causes.

Overall 5- and 10-year survival rates were 96·1 and 89·1 per cent respectively. Overall 5- and 10-year survival rates in patients with EGC were 96·3 and 91·5 per cent respectively.

Discussion

PPG is a safe operation in patients with EGC, with an operative mortality rate of zero and an overall 5-year survival rate of 96·3 per cent. The rate of postoperative complications was 16·7 per cent, although these were major in only 3·1 per cent of patients. Gastric stasis was the most common complication, occurring in 8·0 per cent. PPG compares favourably with Billroth I or II reconstruction in reducing rapid gastric emptying and biliary reflux[13–15]. It has the major advantages of good weight recovery, and prevention of dumping syndrome and gallstones[9,13,15,16]. The real concerns raised by sparing the pyloric antrum are gastric stasis during the early postoperative period, secondary cancer in the remnant stomach and the implications for long-term survival.

The critical risk factors for gastric stasis after PPG remain unclear. The pathophysiological mechanism of stasis is commonly thought to be some combination of anastomotic oedema and nerve dysfunction caused by mechanical and chemical injury[17–19]. The overall incidence of gastric stasis in the present series of PPGs was 8·0 per cent. Other authors have reported gastric stasis

in 20–80 per cent of patients who had PPG with or without preservation of the pyloric branch of the vagus nerve[20–23]. Kodama and colleagues[13] reported that 23 per cent of patients who had PPG developed remnant gastric stasis and that 6 per cent had severe stasis that required intravenous therapy, consistent with the present results. Preserving the infrapyloric vessels as well as the first gastric branch of the right gastric artery to secure blood flow to the pyloric antrum and anastomosis, along with the nerve along the infrapyloric vessels, may maintain pyloric function and prevent gastric stasis. This surgical technique also seems to be useful for increasing the distance from the pyloric ring.

It is unclear how sparing the pyloric antrum influences the growth of second primary gastric cancers. Preventing bile reflux may decrease the incidence of second primary gastric cancers in the long term[24]. Intestinal metaplasia in the pyloric antrum has been considered the major cause of multicentric carcinogenesis of the stomach[25,26]. Follow-up endoscopy detected a secondary primary cancer in six patients (1·0 per cent) in the present series, and only one tumour was located distal to the anastomosis. Takeda and colleagues[27] reported an incidence of EGC in the remnant stomach after partial gastrectomy of 1·8 per cent and an incidence of second primary gastric cancer within 10 years of surgery of 0·86 per cent. The carcinogenesis induced by bile reflux usually occurs more than 20 years after the initial operation[28], so a longer follow-up may be necessary to prove benefit after PPG.

As the suprapyloric nodes have long been classified as N1 nodes, a major concern with PPG is the impact of not dissecting them on long-term survival. However, pathological studies in EGC have shown a very low incidence of metastasis to this station from cancers arising in the middle or lower thirds of the stomach: only 0·6 per cent (12 of 2089) for pathological tumour (T) stage 1 gastric cancers from 1980 to 1999 at the National Cancer Center Hospital (M. Saka, unpublished data). In the present study, the overall 5-year survival rate was 96·1 per cent in all patients and the overall recurrence rate was 1·0 per cent. Follow-up should be continued, as EGC may recur 5 years after treatment[29,30]. Although Katai and colleagues[31] reported local node recurrence soon after surgery, which may be increased after operation without suprapyloric node dissection, the excellent outcome of patients with EGC treated by PPG seems comparable to the outcome of conventional distal gastrectomy.

This study has confirmed the safety and radicality of PPG within the confines of the Japanese Classification of Gastric Carcinoma. It is recommended as the standard procedure for EGC in the middle third of the stomach.

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References

1 Adachi Y, Kitano S, Sugimachi K. Surgery for gastric cancer: 10-year experience worldwide. *Gastric Cancer* 2001; **4**: 166–174.
2 Roukos DH. Current status and future perspectives in gastric cancer management. *Cancer Treat Rev* 2000; **26**: 243–255.
3 Everett SM, Axon ATR. Early gastric cancer in Europe. *Gut* 1997; **41**: 142–150.
4 Hochwald SN, Brennan MF, Klimstra DS, Kim S, Karpeh MS. Is lymphadenectomy necessary for early gastric cancer? *Ann Surg Oncol* 1999; **6**: 664–670.
5 The research group for population-based cancer registration in Japan. Cancer incidence in Japan. In *Cancer Mortality and Morbidity Statistics: Japan and the World – 1999; Gann Monograph on Cancer Research No. 47*, Tominaga S, Oshima A (eds). Japan Scientific Societies Press/Karger: Tokyo, 1999; 83–144.
6 Nakamura K, Ueyama T, Yao T, Xuan ZX, Ambe K, Adachi Y *et al.* Pathology and prognosis of gastric carcinoma. Findings in 10 000 patients who underwent primary gastrectomy. *Cancer* 1992; **70**: 1030–1037.
7 Shimizu S, Tada M, Kawai K. Early gastric cancer: its surveillance and natural course. *Endoscopy* 1995; **27**: 27–31.
8 Maki T, Shiratori T, Hatafuku T, Sugawara K. Pylorus-preserving gastrectomy as an improved operation for gastric ulcer. *Surgery* 1967; **61**: 838–842.
9 Nunobe S, Sasako M, Saka M, Fukagawa T, Katai H, Sano T. Symptom evaluation of long-term post operative outcomes after pylorus-preserving gastrectomy for early gastric cancer. *Gastric Cancer* 2007; **10**: 167–172.
10 Eguchi T, Gotoda T, Oda I, Hamanaka H, Hasuike N, Saito D. Is endoscopic one-piece mucosal resection essential for early gastric cancer? *Dig Endosc* 2003; **15**: 113–116.
11 Nakane Y, Michiura T, Inoue K, Sato M, Nakai K, Yamamichi K. Length of the antral segment in pylorus-preserving gastrectomy. *Br J Surg* 2002; **89**: 220–224.
12 Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma – 2nd English edition. *Gastric Cancer* 1998; **1**: 10–24.
13 Kodama M, Koyama K, Chida T, Arakawa A, Tur G. Early postoperative evaluation of pylorus-preserving gastrectomy for gastric cancer. *World J Surg* 1995; **19**: 456–461.
14 Isozaki H, Okajima K, Momura E, Ichinona T, Fujii K, Izumi N *et al.* Postoperative evaluation of pylorus-preserving gastrectomy for early gastric cancer. *Br J Surg* 1996; **83**: 266–269.
15 Imada T, Rino Y, Takahashi M, Suzuki M, Tanaka J, Shinozawa M *et al.* Postoperative functional evaluation of

pylorus-preserving gastrectomy for early gastric cancer compared with conventional distal gastrectomy. *Surgery* 1998; **123**: 165–170.
16 Enjoji A, Ura K, Ozeki K, Tsukamoto M, Ikematsu Y, Kanematsu T. Cyclic motor activity of the gallbladder maintained in a pylorus-preserving gastrectomy in dog. *Jpn J Surg* 1996; **26**: 489–495.
17 Zhang D, Shimoyama S, Kaminishi M. Feasibility of pylorus preserving gastrectomy with a wider scope of lymphadenectomy. *Arch Surg* 1998; **133**: 993–997.
18 Nishikawa K, Kawahara H, Yumiba T, Nishida T, Inoue Y, Ito *et al.* Functional characteristics of the pylorus in patients undergoing pylorus-preserving gastrectomy for early gastric cancer. *Surgery* 2002; **131**: 613–624.
19 Tomita R, Fujisaki S, Tanjoh K. Pathophysiological studies on the relationship between postgastrectomy syndrome and gastric emptying function at 5 years after pylorus-preserving distal gastrectomy for early gastric cancer. *World J Surg* 2003; **27**: 725–733.
20 Shiratori T, Hongo M, Ishii M. Interpretation of gastric emptying curve by RI method. *J Smooth Muscle Res* 1994; **30**: 433.
21 Tomita R, Munakata K, Kurosu Y, Aoki N, Tanjoh K, Abe Y. Gastric emptying time after distal subtotal mgastrectomy with or without the pylorus-preserving. *J Smooth Muscle Res* 1994; **20**: 229.
22 Griffith CA. Selective vagotomy plus suprapyloric antrectomy: an alternative antidumping operation. In *Surgery of the Stomach and Duodenum* (4th edn), Nyphus LM, Wastei C (eds). Little, Brown: Boston, 1986; 337–363.
23 Sasaki I, Fukushima K, Naito H, Matsuno S, Shiratori T, Maki T. Long-term results of pylorus-preserving gastrectomy for gastric ulcer. *Tohoku J Exp Med* 1992; **168**: 539–548.
24 Ohashi M, Katai H, Fukagawa T, Gotoda T, Sano T, Sasako M. Cancer of the gastric stump following distal gastrectomy for cancer. *Br J Surg* 2007; **94**: 92–95.
25 Honmyo U, Misumi A, Murakami A, Haga Y, Akagi M. Clinicopathological analysis of synchronous multiple gastric carcinoma. *Eur J Surg Oncol* 1989; **15**: 316–321.
26 Kosaka T, Miwa K, Yonemura Y, Urade M, Ishida T, Takegawa S *et al.* A clinicopathological study on multiple gastric cancers with special reference to distal gastrectomy. *Cancer* 1990; **65**: 2602–2065.
27 Takeda J, Toyonaga A, Koufuji K, Kodama I, Aoyagi K, Yano S *et al.* Early gastric cancer in the remnant stomach. *Hepatogastroenterology* 1998; **45**: 1907–1911.
28 Thorban S, Böttcher K, Etter M, Roder JD, Busch R, Siewert JR. Prognostic factors in gastric stump carcinoma. *Ann Surg* 2000; **231**: 188–194.
29 Ichiyoshi Y, Toda T, Minamisono Y, Nagasaki S, Yakeishi Y, Sugimachi K. Recurrence in early gastric cancer. *Surgery* 1990; **107**: 489–495.
30 Sano T, Sasako M, Kinoshita T, Maruyama K. Recurrence of early gastric cancer. Follow-up of 1475 patients and review of the Japanese literature. *Cancer* 1993; **72**: 3174–3178.
31 Katai H, Maruyama K, Sasako M, Sano T, Okajima K, Kinoshita T *et al.* Mode of recurrence after gastric cancer surgery. *Dis Surg* 1994; **11**: 99–103.

Original article

Treatment strategy after non-curative endoscopic resection of early gastric cancer

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Background: Endoscopic resection (ER) is indicated for patients with early gastric cancer who have a negligible risk of lymph node metastasis (LNM). Histological examination of the resected specimen may indicate a possible risk of LNM or a positive resection margin. These patients are considered to have undergone non-curative ER. The aim of this study was to determine the appropriate treatment strategy for such patients.

Methods: A total of 298 patients who had non-curative ER were classified into those with a positive lateral margin only (group 1; 72 patients) and those with a possible risk of LNM (group 2; 226 patients).

Results: Surgery was performed within 6 months of non-curative ER in 19 patients in group 1 and 144 in group 2. In group 1, nine patients were found to have local residual tumours, all limited to the mucosal layer without LNM. In Group 2, 13 patients had residual disease, including four local tumours without LNM, two local tumours with LNM and seven cases of LNM alone. The rate of LNM after surgery was 6·3 per cent in group 2.

Conclusion: Surgery remains the standard treatment after non-curative ER in patients with a possible risk of LNM.

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Introduction

The percentage of all gastric cancers diagnosed as early gastric cancer (EGC) varies between countries, reaching nearly 60 per cent in Japan[1–4]. Endoscopic resection (ER) has been accepted as the standard treatment for those patients with EGC who have a negligible risk of lymph node metastasis (LNM)[5,6]. However, endoscopic prediction of EGC in terms of tumour depth or lateral spread is not always accurate even when endoscopic ultrasonography is used[7–10]. The success of ER is subsequently determined histologically. It is considered to have been non-curative if tumours are subsequently diagnosed as having either a possible risk of LNM or a positive lateral margin (*Table 1*)[11–13].

Patients who have undergone non-curative ER generally need additional treatment, but there are only a few published reports of surgical outcomes after non-curative ER in small series[14,15]. The aim of this study was to evaluate additional treatment strategies after non-curative ER based on retrospective analysis of a large series of consecutive patients.

Methods

A total of 1783 EGCs were treated with ER, including 495 endoscopic mucosal resections[5,6] and 1288 endoscopic submucosal dissections (ESDs)[9], with curative intent at the National Cancer Centre Hospital, Tokyo, between March 1989 and December 2003. A total of 298 lesions (16·7 per cent) were subsequently diagnosed as having undergone non-curative ER after histological evaluation.

The medical records of the 298 patients who had non-curative ER were analysed retrospectively with regard to

The Editors are satisfied that all authors have contributed significantly to this publication

Table 1 Histological criteria for curative endoscopic resection

Early gastric cancer with no risk of lymph node metastasis
Differentiated adenocarcinoma
No lymphatic or venous invasion
Intramucosal cancer regardless of tumour size without ulcer finding
or intramucosal cancer ≤ 30 mm in size with ulcer finding
or minute submucosal cancer (sm1) ≤ 30 mm in size
Resection margin
Tumour-free lateral margin
Tumour-free vertical margin

demographics, concomitant disease, endoscopic tumour findings, histological findings in the ER specimen, additional surgical and non-surgical treatment after ER, histology of surgical specimens and clinical outcomes. Tumour location was classified into upper, middle and lower third of the stomach, based on the Japanese Classification of Gastric Carcinoma[16], and macroscopic type as elevated, depressed or mixed.

ER specimens were examined histologically using serial sections 2 mm in width according to recommendations in the Japanese Classification of Gastric Carcinoma[16]. Curability was assessed based on the histological criteria for curative ER (*Table 1*). The procedure was considered non-curative if the EGC criteria for no risk of LNM were not fulfilled or a positive resection margin was demonstrated.

Patients who had non-curative ER were classified into those with a positive lateral margin only (group 1) and those who did not fulfil the histological EGC criteria for no risk of LNM, irrespective of resected margin findings (group 2). Surgical treatment was generally recommended in group 2, whereas in group 1 additional treatment was based on the extent of lateral margin involvement and the time frame of each case. In the early years, surgical treatment was recommended for patients with an extensive positive lateral margin.

Groups 1 and 2 were each further divided into two subgroups: patients who underwent radical gastrectomy with lymph node dissection within 6 months of non-curative ER and those who did not.

Surgical specimens were examined according to the recommendations in the Japanese Classification of Gastric Carcinoma[16]. The entire resected stomach area, including the tumour or ER scar, was divided into slices 5 mm in width and LNMs were evaluated in the central portion of each lymph node. Local residual tumour was defined as any cancer diagnosed histologically at the ER site.

Statistical analysis

Clinical outcomes of patients who had surgery and those treated non-surgically were collected and analysed in January 2006. Disease-specific survival curves were calculated by the Kaplan–Meier method (Statview; Abacus Concepts, Berkeley, California, USA).

Table 2 Demographic and tumour characteristics of 298 patients who had non-curative endoscopic resection

	No. of patients*
Mean(s.d.) age (years)	66(10)
Sex ratio (M : F)	248 : 50
Concomitant disease	35 (11·7)
Other cancer	26
Heart disease	6
Renal failure	3
Gastric tumour location	
Upper third	69 (23·2)
Middle third	126 (42·3)
Lower third	103 (34·6)
Macroscopic type	
Elevated	99 (33·2)
Depressed	171 (57·4)
Elevated and depressed	28 (9·4)

*With parentheses in percentages unless indicated otherwise.

Table 3 Reasons for risk of lymph node metastasis in group 2

	Surgical treatment	Non-surgical treatment
Predominantly undifferentiated type	33 (73)	12 (27)
Positive lymphatic and/or venous invasion	61 (73)	22 (27)
Submucosal deep invasion (sm2)	93 (77·5)	27 (22·5)
Intramucosal cancer > 30 mm in size with ulcer finding	13 (35)	24 (65)
Minute submucosal cancer (sm1) > 30 mm in size	8 (36)	14 (64)
Positive vertical margin	17 (68)	8 (32)

Values in parentheses are percentages. Some patients had more than one reason.

Results

Patient demographics and endoscopic tumour findings are summarized in *Table 2*. Of 298 patients who had a non-curative ER, 72 with a positive lateral margin only were included in group 1 and 226 with a risk of LNM, regardless of the resection margin findings, were included in group 2. Factors generally considered to be associated with risk of LNM in group 2 are shown in *Table 3*. Patients in groups 1 and 2 represented 4·0 and 12·7 per cent respectively of all 1783 patients with EGC who were treated by ER.

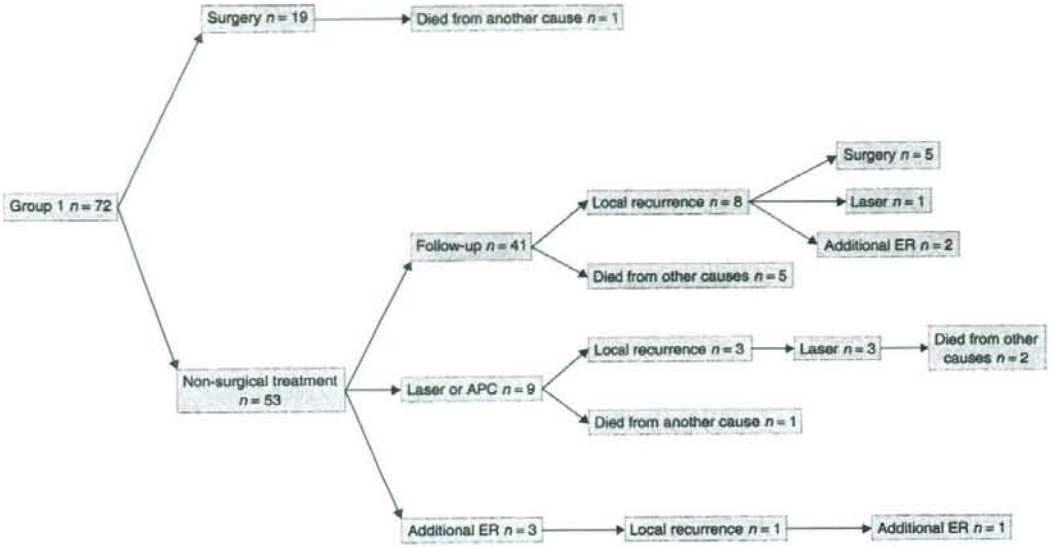

Fig. 1 Clinical courses in group 1 (patients with lateral margin involvement alone). APC, argon plasma coagulation; ER, endoscopic resection

In group 1, 19 patients underwent surgery within 6 months of non-curative ER and 53 had non-surgical treatment (*Fig. 1*). In Group 2, 144 patients had surgery within 6 months (*Fig. 2*). Reasons for not having surgery in the remaining 82 patients in group 2 included patient choice (47 patients), high surgical risk (21 patients; 15 very elderly, two with chronic renal failure, two with ischaemic heart disease and two with autoimmune disease) and concomitant cancer in other organs (14).

The median interval between non-curative ER and gastrectomy was 46 (range 3–170) days and there were no operation-related deaths. In group 1, nine patients had local residual tumours, all of which were limited to the mucosal layer without LNM (*Table 4*). In group 2, 13 patients had residual disease, including four with local tumours without LNM, two with local residual tumours and LNM, and seven with LNM alone. The rate of LNM after surgery was 6·3 per cent in group 2 (*Table 4*).

Clinical courses for patients in group 1 are shown in *Fig. 1*. The median follow-up period was 5·0 (range 0·5–17) years and there were no gastric cancer-related deaths.

Clinical courses for patients in group 2 are summarized in *Fig. 2*, and disease-specific survival curves are shown in *Figs 3* and *4*. The median follow-up time was 4·0 (range 0·5–16) years among those who had surgery. Three of these patients developed distant metastasis and received chemotherapy, but died from gastric cancer 1, 1·5 and 1·7 years after the non-curative ER. The 3- and 5-year disease-specific survival rates were both 97·8 per cent (*Fig. 3*). Patients in group 2 who did not have surgery were followed up for a median of 3·2 (range 0·5–16·9) years. Two patients died from distant metastasis 3·3 and 4·9 years after non-curative ER. The 3- and 5-year disease-specific survival rates were 100 and 91 per cent (*Fig. 4*).

Table 4 Relationship between outcome of endoscopic resection and surgical outcome

		Surgical outcome	
Outcome of endoscopic resection	No. of patients	Local residual tumour	LNM
Group 1 (positive lateral margin)	19 (11·7)	9 (47)	0 (0)
Group 2 (risk of LNM regardless of margin)	144 (88·3)	6 (4·2)	9 (6·3)
Total	163 (100)	15 (9·2)	9 (5·5)

Values in parentheses are percentages. LNM, lymph node metastasis.

Discussion

In this retrospective series, it was anticipated that all 1783 patients might satisfy the criteria for EGC

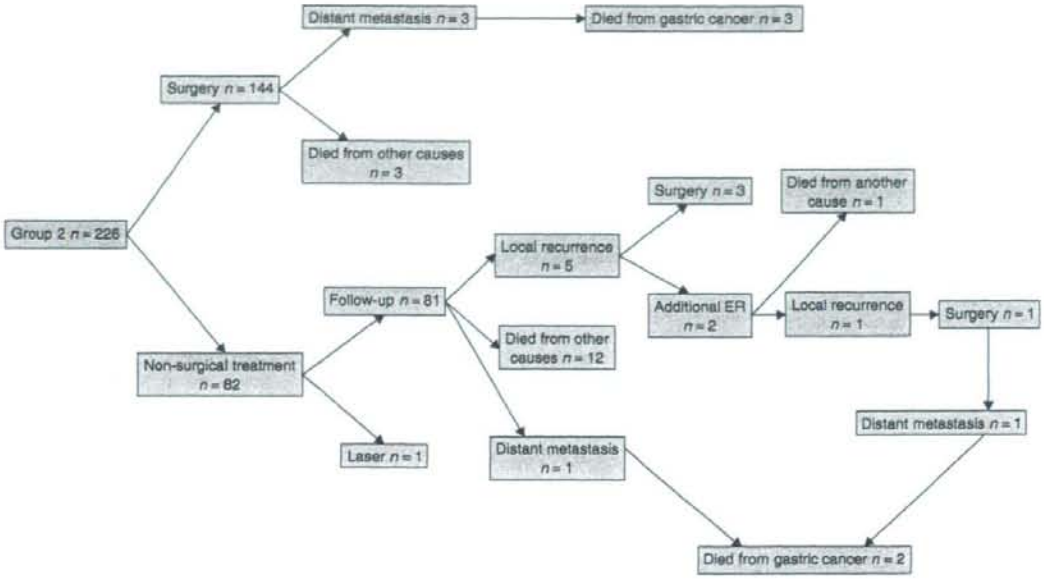

Fig. 2 Clinical courses in group 2 (patients at risk of lymph node metastasis, regardless of lateral margin involvement). ER, endoscopic resection

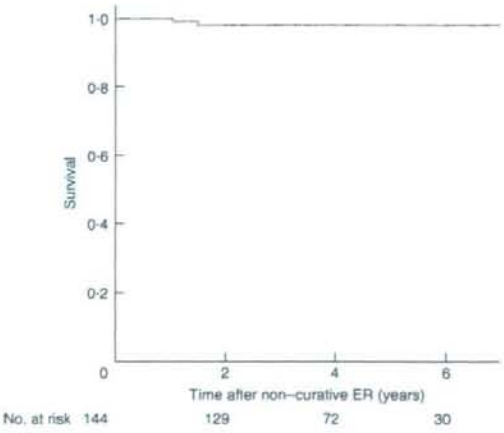

Fig. 3 Disease-specific survival for patients in group 2 who had surgery. ER, endoscopic resection

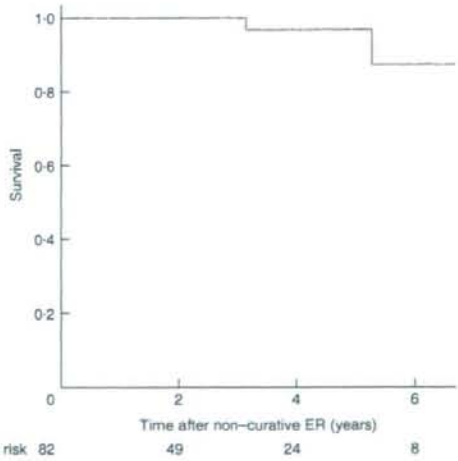

Fig. 4 Disease-specific survival for patients in group 2 who did not have surgery. ER, endoscopic resection

with no risk of LNM, but in fact 12·7 per cent did not. Several other articles have also reported that endoscopic staging of EGC is not always accurate, and is correct only 80–90 per cent of the time, even when using endoscopic ultrasonography[7–10]. Histological staging using resected specimens obtained by ER is

important, therefore, in deciding on the need for any additional treatment.

Differences exist between Japanese and Western pathologists with respect to the diagnostic criteria for determining gastric carcinoma[17]. A lesion diagnosed as non-invasive EGC in Japan could be diagnosed by biopsy as dysplasia in Western countries and might not receive any follow-up treatment. As the present series demonstrated, some EGCs that were considered to be non-invasive were confirmed to be invasive by histological examination after ER. ER is therefore recommended even for lesions diagnosed as high-grade dysplasia by Western pathologists so that histological staging can be carried out[18]. As the number of ER procedures increases in the future, the number of non-curative ERs will undoubtedly increase in Western countries as well.

Patients who had non-curative ER were divided into two groups in this study based on their different risk of LNM. None of the patients with lateral margin involvement only developed LNM, whereas lymph node involvement was confirmed in some patients who fulfilled the criteria for risk of LNM. The results provided valuable information on additional treatment strategy for both groups.

The LNM rate of 6·3 per cent among patients who had surgery in group 2 was lower than the reported incidence of nearly 20 per cent in patients with submucosal invasive cancer[7]. Lesions in the present study, which had been treated with curative intent by ER, had a lower risk of LNM than submucosal invasive cancer overall. Gastrectomy with lymph node dissection has a low operative mortality rate, particularly in Japan (less than 1 per cent), and results in an excellent prognosis for patients with EGC[2,3,19,20]. The LNM rate of 6·3 per cent in the present study cannot therefore be ignored. Similar results were obtained in two small series, in which one of six[14] and four of 24 patients[15] had LNM in surgical specimens after non-curative ER for submucosal invasive cancer.

The authors previously reported a 5-year disease-specific survival rate following gastrectomy of 96·7 per cent for submucosal invasive cancer[20]. A similar rate was found in the present study, even though there were three gastric cancer-related deaths from distant metastasis after salvage surgery in group 2. Additional gastrectomy is strongly recommended, therefore, in such patients.

The 5-year disease-specific survival rate among patients in group 2 who did not have salvage surgery was 91 per cent, a figure that was not markedly different from the rate in group 2 patients who did, or previously reported data[20]. This is probably because there were considerable differences in histological findings after ER between patients who had surgery and those who did not (*Table 3*). Histological findings strongly related to LNM, such as positive lymphatic and/or venous invasion and submucosal deep invasion, were much more frequent in surgical patients than in non-surgical patients. Although this may indicate that there is yet another group with a negligible risk of LNM, additional gastrectomy is recommended until such a group has been identified definitively.

Finally, it is important to note that none of the patients in group 1 had LNM. This suggests that any local residual tumour can be treated locally without lymph node dissection. Previous reports have also indicated in a small number of patients that none of the intramucosal lesions with a positive lateral margin had LNM[14,15]. Until recently, repeat ER of local residual tumour after an initial non-curative procedure was often difficult to perform because extensive fibrosis prevented a solution injected into the submucosa from raising the lesion sufficiently. The newly developed ESD technique has made it possible to treat even EGC associated with ulcerative changes[13] and to resect locally recurrent gastric cancer after non-curative ER[21]. As a result, subsequent ER using ESD has become feasible for certain patients with a positive lateral margin but no risk of LNM.

Surgery remains the standard treatment after non-curative ER because of the possibility of LNM in patients who meet the EGC criteria for risk of nodal metastasis, regardless of whether the resection margin is involved. A second ER may be possible, however, when the initial resection is deemed non-curative only because of a positive lateral margin.

References

1 Everett SM, Axon AT. Early gastric cancer in Europe. *Gut* 1997; **41**: 142–150.

2 Nakamura K, Ueyama T, Yao T, Xuan ZX, Ambe K, Adachi Y *et al.* Pathology and prognosis of gastric carcinoma. Findings in 10000 patients who underwent primary gastrectomy. *Cancer* 1992; **70**: 1030–1037.

3 Shimizu S, Tada M, Kawai K. Early gastric cancer: its surveillance and natural course. *Endoscopy* 1995; **27**: 27–31.

4 Kim JP, Lee JH, Kim SJ, Yu HJ, Yang HK. Clinicopathologic characteristics and prognostic factors in 10783 patients with gastric cancer. *Gastric Cancer* 1998; **1**: 125–133.

5 Rembacken BJ, Gotoda T, Fujii T, Axon AT. Endoscopic mucosal resection. *Endoscopy* 2001; **33**: 709–718.

6 Soetikno RM, Gotoda T, Nakanishi Y, Soehendra N. Endoscopic mucosal resection. *Gastrointest Endosc* 2003; **57**: 567–579.

7 Sano T, Okuyama Y, Kobori O, Shimizu T, Morioka Y. Early gastric cancer. Endoscopic diagnosis of depth of invasion. *Dig Dis Sci* 1990; **35**: 1340–1344.

8 Seto Y, Shimoyama S, Kitayama J, Mafune K, Kaminishi M, Aikou T *et al.* Lymph node metastasis and preoperative diagnosis of depth of invasion in early gastric cancer. *Gastric Cancer* 2001; **4**: 34–38.
9 Yanai H, Matsumoto Y, Harada T, Nishiaki M, Tokiyama H, Shigemitsu T *et al.* Endoscopic ultrasonography and endoscopy for staging depth of invasion in early gastric cancer: a pilot study. *Gastrointest Endosc* 1997; **46**: 212–216.
10 Yanai H, Matsubara Y, Kawano T, Okamoto T, Hirano A, Nakamura Y *et al.* Clinical impact of strip biopsy for early gastric cancer. *Gastrointest Endosc* 2004; **60**: 771–777.
11 Gotoda T, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T *et al.* Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer* 2000; **3**: 219–225.
12 Eguchi T, Gotoda T, Oda I, Hamanaka H, Hasuike N, Saito D. Is endoscopic one-piece mucosal resection essential for early gastric cancer? *Dig Endosc* 2003; **15**: 113–116.
13 Oda I, Gotoda T, Hamanaka H, Eguchi T, Saito Y, Matsuda T *et al.* Endoscopic submucosal dissection for early gastric cancer: technical feasibility, operation time and complications from a large consecutive series. *Dig Endosc* 2005; **17**: 54–58.
14 Korenaga D, Orita H, Maekawa S, Maruoka A, Sakai K, Ikeda T *et al.* Pathological appearance of the stomach after endoscopic mucosal resection for early gastric cancer. *Br J Surg* 1997; **84**: 1563–1566.
15 Nagano H, Ohyama S, Fukunaga T, Seto Y, Fujisaki J, Yamaguchi T *et al.* Indications for gastrectomy after incomplete EMR for early gastric cancer. *Gastric Cancer* 2005; **8**: 149–154.
16 Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma – 2nd English Edition. *Gastric Cancer* 1998; **1**: 10–24.
17 Schlemper RJ, Itabashi M, Kato Y, Lewin KJ, Riddell RH, Shimoda T *et al.* Differences in diagnostic criteria for gastric carcinoma between Japanese and Western pathologists. *Lancet* 1997; **349**: 1725–1729.
18 Schlemper RJ, Riddell RH, Kato Y, Borchard F, Cooper HS, Dawsey SM *et al.* The Vienna classification of gastrointestinal epithelial neoplasia. *Gut* 2000; **47**: 251–255.
19 Sue-Ling HM, Johnston D, Martin IG, Dixon MF, Lansdown MR, McMahon MJ *et al.* Gastric cancer: a curable disease in Britain. *BMJ* 1993; **307**: 591–596.
20 Sasako M, Kinoshita T, Maruyama K. Prognosis of early gastric cancer. *Stom Intest* 1993; **28**: 139–146.
21 Yokoi C, Gotoda T, Hamanaka H, Oda I. Endoscopic submucosal dissection allows curative resection of local recurrent early gastric cancer after prior endoscopic mucosal resection. *Gastrointest Endosc* 2006; **64**: 212–218.

Prognostic Significance of Peritoneal Washing Cytology in Patients with Potentially Resectable Gastric Cancer

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ABSTRACT

Background/Aims: The prognostic value of cytological examination of intraoperative washings in potentially resectable gastric cancer is controversial.

Methodology: Between February 1993 and August 2001, clinicopathological features and surgical outcome of 26 consecutive patients with gastric cancer with positive cytological findings of peritoneal washings without peritoneal dissemination were retrospectively analyzed.

Results: The overall 1, 2, 3-year survival rates for 26 patients were 69%, 35%, and 0%, respectively. The median survival was 17.5 months. The median survival of patients with curative resection (n=16) and non-curative resection (n=10) was 19 months and 12.5 months, respectively. There was no significant difference in survival between curative resection and non-curative resection (p=0.10). Recurrent disease frequently occurred as peritoneal dissemination (69%). No patient survived for more than 34 months.

Conclusions: Aggressive surgical resections do not provide any survival benefit for gastric cancer with positive cytological findings of peritoneal washings even in the absence of peritoneal dissemination.

KEY WORDS:
Peritoneal washing cytology; Gastric cancer; Peritoneal dissemination; Gastrectomy

INTRODUCTION

Gastric cancer with positive cytological findings of peritoneal washings is generally considered to be an advanced disease, because it is frequently associated with peritoneal dissemination (1-4). However, positive cytological findings of peritoneal washings without definite peritoneal dissemination are sometimes encountered in advanced gastric cancer. The prognostic value of cytological examination of intraoperative washings in potentially resectable gastric cancer is not fully understood (5-7). The efficacy of gastrectomy for gastric cancer with positive cytological findings of peritoneal washings without peritoneal dissemination is also controversial (8-9). In this study, we analyzed our 10-year experience of gastric cancer with positive cytological findings of peritoneal washings in the absence of peritoneal dissemination.

METHODOLOGY

Between February 1993 and August 2001, 26 consecutive patients with gastric cancer with positive cytological findings of peritoneal washings without peritoneal dissemination were retrospectively analyzed in this study. Clinicopathological features of these patients and surgical outcome after gastrectomy (curative or non-curative) were investigated. Patients with liver metastasis were excluded in this study. All 26 patients were followed after the operation. Follow-up of patients ranged from 2 to 34 months (median 17.5 months). The overall survival analysis included all deaths, such as in-hospital death or death of unrelated cause.

Specimens for cytological examination were obtained before manipulation of the tumor at laparotomy. Isotonic saline (100mL) was instilled into the pelvis. After manual agitation, the washings were retrieved by aspiration. After centrifugation for 3 minutes, direct smears were prepared and fixed in 95% ethanol. Two slides were prepared for each patient and were stained using the Papanicolaou method. All slides were reviewed by three cytopathologists.

The clinicopathological features of gastric cancer with positive cytological findings of peritoneal washings without peritoneal dissemination were investigated with regard to age, sex, tumor size, histopathological findings, and outcome.

Statistical analysis was performed by chi-squared test and Student's t-test, when appropriate. Cumulative survival rates were generated by Kaplan-Meier method. The overall survival curve includes all deaths. The survival curves were compared by gener-

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