Macdonald et al. [9], in 2001, confirmed the effectiveness of the combination of 5-fluorouracil with radiotherapy as an adjuvant after curative gastric surgery in a randomized clinical trial, the Japanese guidelines have not changed up to now, probably because of differences in the local control rates after different types of surgery between the United States and Japan. The local recurrence rate is negligible after systematic lymph node dissection (D2 or more) in Japan. However, in the United States, the local recurrence rate is usually much higher with less aggressive surgery (D0 or D1). The incidence of local, invisible, residual cancer cells in eligible patients in the study of Macdonald et al. [9] were quite different from those in the Japanese candidates for adjuvant therapy. That is why we still think that survival benefits of adjuvant chemotherapy after curative resection of gastric cancer have not yet been proved in Japan; only metaanalyses will show the survival benefit of adjuvant chemotherapy.

S-1 is expected to be a promising agent for adjuvant use. The high response rate of S-1 in advanced gastric cancer gives a rationale for expecting a certain survival benefit with S-1 in the adjuvant setting.

Because the standard treatment of locally advanced gastric cancer is still surgery, a randomized controlled trial with a surgery-alone arm is essential to prove the efficacy of adjuvant chemotherapy.

According to the "Results", no grade 4 adverse reactions were observed.

In the FAS, excluding the patients with recurrence, 17 of the 28 patients (60.7%) received the planned eight courses of S-1. Drug compliance was acceptable. In every course, drug compliance was over 85% in the FAS.

Problems in this study were a higher incidence of adverse reactions when compared with that in the phase II trials and postmarketing surveillance [10], and a high incidence of patient refusal, due to adverse reactions in the first course, which was not seen during the postmarketing surveillance of 110 patients who received S-1 within 30 days after surgical resection of gastric cancer (as mentioned in "results"). The reasons for these problems, especially the early appearance of anorexia, may be the influence of surgery, because the patients in this study had rather advanced disease and had received D2 or more aggressive gastrectomy with frequent combined organ resections. It is difficult to deny the possibility of gastro-intestinal (GI) toxicity of S-1; however, the adverse reaction was not bone marrow suppression, which is a dose-limiting toxicity of S-1. In this protocol, S-1 administration was started within 4 weeks after surgery. In the early postoperative period, patients have not yet recovered from surgical stress, and the limitation of food intake due to aggressive gastrectomy is a possible cause of exacerbation of adverse reactions such as anorexia and nausea. To prevent these problems, a delay in the start of drug administration seems necessary for adjuvant use. Except for these problems, the administration of S-1 for 1 year seems feasible as postoperative adjuvant chemotherapy for gastric cancer.

Based on this feasibility study, a prospective randomized controlled trial was started in 2001 to evaluate the efficacy of S-1 as adjuvant chemotherapy; in this trial S-1 administration is started within 6 weeks after surgery.

We expect that a significant survival benefit of S-1, with less toxicity, will be shown by this trial, and that this could be the standard treatment after curative gastrectomy.

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ORIGINAL REPORT

Extended Lymph Node Dissection for Gastric Cancer: Who May Benefit? Final Results of the Randomized Dutch Gastric Cancer Group Trial

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ABSTRACT

Purpose
The extent of lymph node dissection appropriate for gastric cancer is still under debate. We have conducted a randomized trial to compare the results of a limited (D1) and extended (D2) lymph node dissection in terms of morbidity, mortality, long-term survival and cumulative risk of relapse. We have reviewed the results of our trial after follow-up of more than 10 years.

Patients and Methods
Between August 1989 and June 1993, 1,078 patients with gastric adenocarcinoma were randomly assigned to undergo a D1 or D2 lymph node dissection. Data were collected prospectively, and patients were followed for more than 10 years.

Results
A total of 711 patients (380 in the D1 group and 331 in the D2 group) were treated with curative intent. Morbidity (25% *v* 43%; $P < .001$) and mortality (4% *v* 10%; $P = .004$) were significantly higher in the D2 dissection group. After 11 years there is no overall difference in survival (30% *v* 35%; $P = .53$). Of all subgroups analyzed, only patients with N2 disease may benefit of a D2 dissection. The relative risk ratio for morbidity and mortality is significantly higher than one for D2 dissections, splenectomy, pancreatectomy, and age older than 70 years.

Conclusion
Overall, extended lymph node dissection as defined in this study generated no long-term survival benefit. The associated higher postoperative mortality offsets its long-term effect in survival. For patients with N2 disease an extended lymph node dissection may offer cure, but it remains difficult to identify patients who have N2 disease. Morbidity and mortality are greatly influenced by the extent of lymph node dissection, pancreatectomy, splenectomy and age. Extended lymph node dissections may be of benefit if morbidity and mortality can be avoided.

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INTRODUCTION

Gastric cancer is a common malignancy worldwide. Even in a low-incidence country like the Netherlands, it is ranked fifth with respect to incidence. Despite declining incidence, mortality of gastric cancer remains high. Surgery is the only possible curative treatment, and results of gastrectomy have improved throughout the years with respect to survival, morbidity, and postoperative mortality.[1,2]

It is not clear, however, if extended lymph node dissection contributes to this improvement. Despite promising results in nonrandomized studies, improved survival has never been demonstrated in randomized trials.[3-6] In all these randomized trials, postoperative morbidity and mortality were significantly higher in the extended (D2) dissection group. Within the Dutch Gastric Cancer Trial (DGCT), the number of early gastric cancers was surprisingly high, and it has been argued that any beneficial effect of extended lymph node dissection, which would be expected in more advanced disease, might have been attenuated. We have

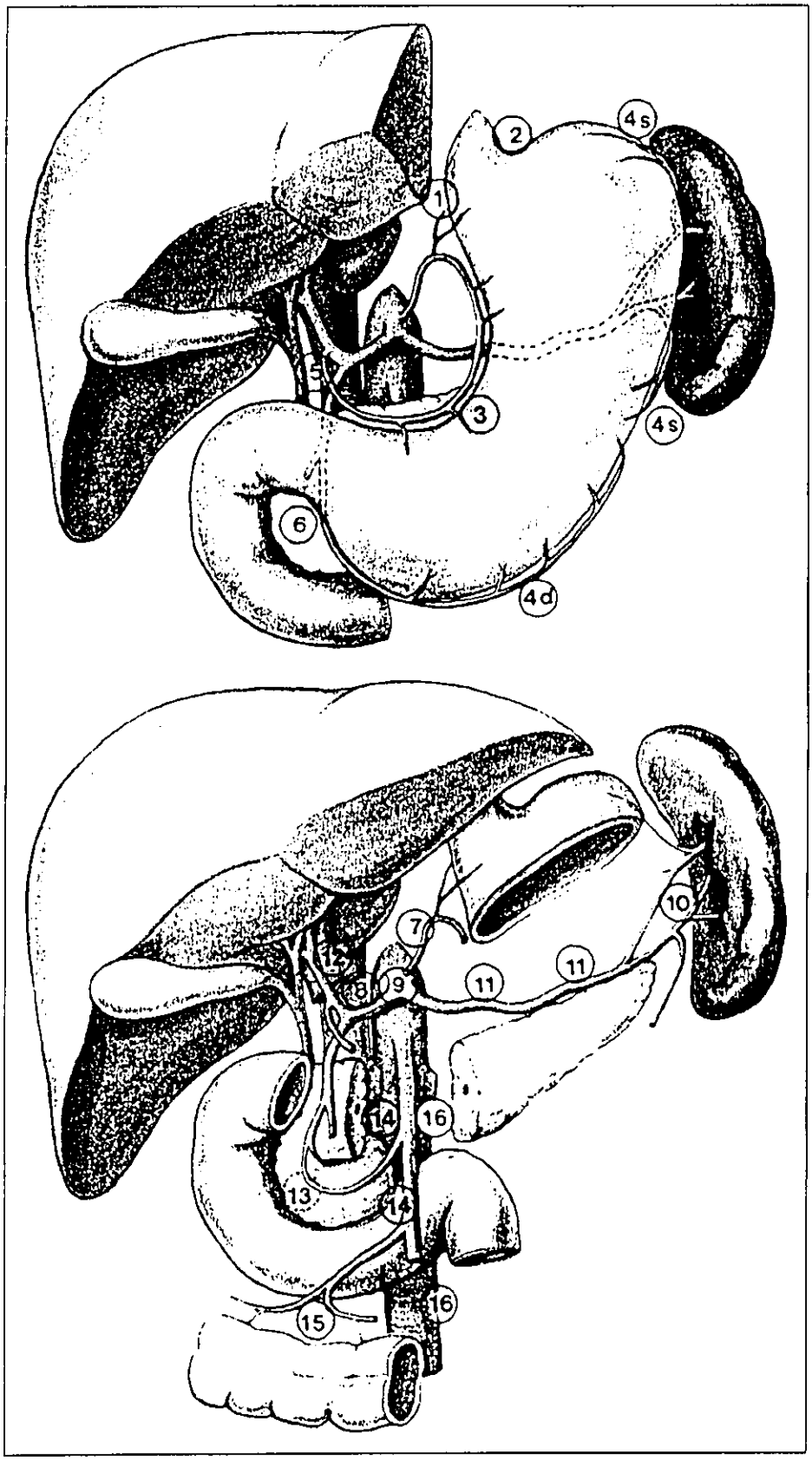

Fig 1. Lymph node stations surrounding the stomach. 1, right cardial nodes; 2, left cardial nodes; 3, nodes along the lesser curvature; 4, nodes along the greater curvature; 5, suprapyloric nodes; 6, infrapyloric nodes; 7, nodes along the left gastric artery; 8, nodes along the common hepatic artery; 9, nodes around the celiac axis; 10, nodes at the splenic hilus; 11, nodes along the splenic artery; 12, nodes in the hepatoduodenale ligament; 13, nodes at the posterior aspect of the pancreas head; 14, nodes at the root of the mesenterium; 15, nodes in the mesocolon of the transverse colon; 16, para-aortic nodes

Table 1. Characteristics of 711 Patients and Tumors After Resection With Curative Intent* and Status at Last Follow-Up

Characteristic	Dissection Group			
	D1 (n = 380)		D2 (n = 331)	
	No. of Patients	%	No. of Patients	%
Median age, years	67		65	
Sex				
Male	215		187	
Female	165		144	
Median No. of lymph nodes investigated	17		30	
Status after resection				
Location of tumor				
More than two thirds of stomach	25	7	24	7
Upper third (C)	39	10	34	10
Middle third (M)	108	28	92	28
Distal third (A)	207	54	180	54
Unknown	1	< 1	1	< 1
Pathologic stage of disease				
T0	2	< 1	3	< 1
T1	98	26	85	26
T2	181	48	152	46
T3	94	25	82	25
T4	3	< 1	9	2
Tx	2	< 1	0	0
Lymph node involvement	205	54	185	56
R0 resection	339	89	293	89
Type of gastrectomy				
Total	115	30	128	38
Partial	265	70	205	62
Resection of spleen	41	11	124	37
Resection of tail of pancreas	10	3	98	30
Status at last follow-up				
Alive				
Without recurrence	112	98	116	99
With recurrence	2	2	1	1
Dead				
Hospital death	15	4	32	10
Without recurrence†	82	31	86	40
With recurrence				
Locoregional	56	21	40	19
Locoregional and distant	98	37	55	26
Distant	30	11	33	15

NOTE. Some data have previously been reported.[6]
Abbreviations. D1, limited lymph node dissection group; D2, extended lymph node dissection group.
*Because of rounding, percentages may not total 100.
†These numbers include hospital deaths.

therefore reviewed the results of our randomized limited lymph node dissection (D1) versus extended lymph node dissection (D2) trial after follow-up of more than 10 years and focused on subgroups and prognostic factors.

PATIENTS AND METHODS

Patients with gastric adenocarcinoma were enrolled in the DGCT between August 1989 and July 1993. Eligible patients were randomly assigned for D1 (conventional) or D2 (extended) lymph node dissection if at laparotomy, no signs of distant lymph node, hepatic or peritoneal metastases were found. In case of metastases, palliative surgery without formal lymph node dissection was done. The trial protocol has previously been published.[7]

D1 and D2 dissection were defined according to the guidelines of the Japanese Research Society for the Study of Gastric Cancer.[8] These guidelines are also recommended by the American Joint Committee on Cancer, in its fourth Manual for Staging of Cancer, and by the International Union Against Cancer.[9,10] In these guidelines, 16 different lymph node compartments (stations) are identified surrounding the stomach (Fig 1). In general, the perigastric lymph node stations along the lesser (stations 1, 3, and 5) and greater (stations 2, 4, and 6) curvature are grouped N1, whereas the nodes along the left gastric (station 7), common

hepatic (station 8), celiac (station 9), and splenic (stations 10 and 11) arteries are grouped N2.

D1 dissection entails removal of the involved part of the stomach (distal or total), including greater and lesser omentum. The spleen and pancreas tail are only resected when necessitated by tumor invasion. For a D2 dissection, the omental bursa is removed with the front leave of the transverse mesocolon, and the mentioned vascular pedicles of the stomach are cleared completely. Standard resection of the spleen and pancreatic tail was only done in proximal tumors to achieve adequate removal of D2 lymph node stations 10 and 11.

Patients were randomly assigned before surgery to ensure standardization of surgery. Patients randomly assigned to D1 dissection had their operation performed by their local surgeon, supervised by the trial coordinator. For D2 dissections, one of nine referent surgeons performed the operation at the local hospital. These referent surgeons had been trained in D2 dissection by a Japanese surgeon from the National Cancer Center Hospital in Tokyo. Apart from standardizing surgery, they ensured that the specimen was adequately divided into lymph node stations, which were then further investigated by the local pathologist. Operations were classified as R0 if there was microscopic complete tumor removal, without N3 or N4 involvement and no malignant cells on cytology of abdominal washing. For analysis of differences in relapse rates, only patients were included who had had a R0 resection and who did not die because of complications. None of the curative patients had adjuvant radiotherapy or chemotherapy.

In the hospital, death was defined as death within 30 days of surgery or during hospital stay, if this was longer than 30 days. For stage grouping, the new (2002) tumor-node-metastasis system classification system was used.[11] In this new classification lymph nodes are no longer characterized by location but by the number of metastatic regional lymph nodes. N1 stands for 1 to 6, N2 for 7 to 15, and N3 for more than 16 metastatic regional lymph nodes.

For statistical analysis the SPSS program (SPSS Inc, Chicago, IL) was used. A P value of .05 was considered statistically significant. Overall survival was calculated from the day of random assignment until either day of death (event) or day of last follow-up (censored). Relapse was also calculated from the day of random assignment; the data of a patient were censored when at last follow-up contact the patient was alive with no evidence of disease. The χ^2 test was applied to evaluate differences in proportions, and the Mann-Whitney test was used to assess the significance of differences in hospital stay. The log-rank test was used to evaluate difference between survival and relapse curves, although the assumption of proportional hazards was not always satisfied. The Cox proportional hazard model was used to test for interaction between prognostic factors and lymph node dissection.

For the subgroup analysis, no adjustment for multiple testing was applied. Interpretation of the results of subset analyses have to be judged carefully and any significant results must be viewed as hypotheses that require validation in subsequent studies. A P value of .05 may not be strict enough for these subgroups.

RESULTS

Of 1,078 patients randomly assigned in the DGCT, 996 were eligible. At the time of surgery, 285 patients (29%) had peritoneal, hepatic or distant lymph node metastasis, or locally irresectable tumor and they underwent noncurative treatment deemed appropriate by their surgeon.

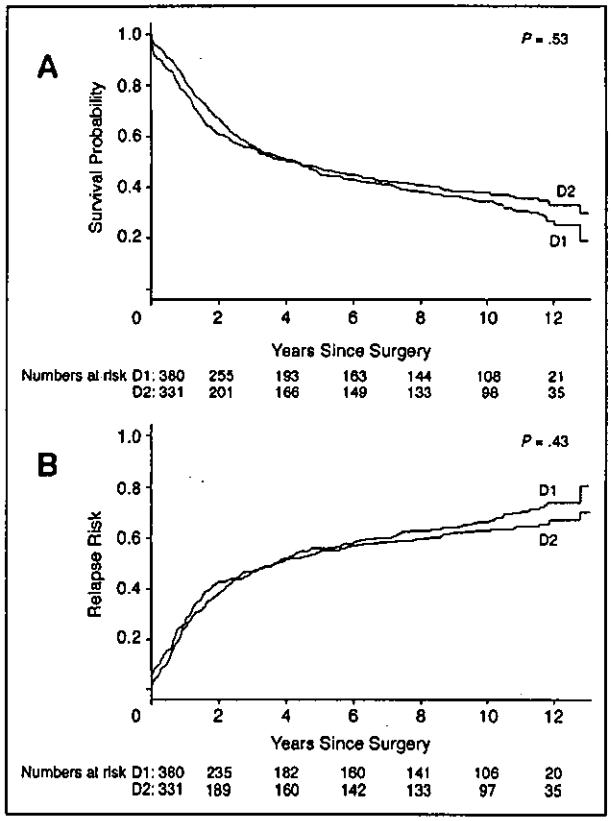

Fig 2. Survival probability (A) and relapse risk (B) of all patients treated with curative intent (n = 711). D1, limited lymph node dissection group; D2, extended lymph node dissection group.

This analysis focuses on the 711 patients (71%) who had a curative resection with D1 (n = 380) or D2 (n = 331) lymph node dissection. The characteristics of the 711 curative patients are well balanced between the two treatment groups, except for pancreatico-splenectomy, which was expected according to the protocol (Table 1).

Follow-up was continued until January 2003. Median follow-up for all eligible patients is 11 years (range, 6.8 to 13.1 years). Four-hundred eighty patients (68%) are now deceased, 35% without and 65% with recurrent disease (Table 1). In the hospital, death was 4% (n = 15) for the D1 group and 10% (n = 32) for the D2 group (P = .004). At 11 years, survival rates are 30% for D1 and 35% for D2 (P = .53) The risk of relapse is 70% for D1 and 65% for D2 (P = .43; Fig 2).

In a univariate analysis of all 711 patients, for none of the subgroups based on the selected prognostic variables was a significant impact found on survival rates between D1 and D2 dissection (Table 2). Analysis of interaction between covariates and lymph node dissection shows no significance. The only subgroup with a trend to benefit is the N2 disease group (Fig 3). Furthermore, there is no difference in survival after 11 years

Table 2. Univariate Analysis of Survival Rates 11 Years After Resection With Curative Intent (N = 711)

Variable	Dissection Group				
	D1		D2		
	No. of Patients	Survival %	No. of Patients	Survival %	P*
Age, years					
≤ 70	252	37	229	41	.74
> 70	128	19	102	24	.68
Pathologic stage					
T1	98	57	85	55	.90
T2	181	28	152	35	.54
T3	94	8	82	17	.80
Lymph nodes					
Negative	171	52	144	51	.93
Positive	209	13	187	23	.28
Lymph node stage					
N0	171	52	144	51	.93
N1	138	20	113	30	.46
N2	50	0	47	21	.08
N3	21	0	27	0	.30
Tumor-node-metastasis stage‡					
IA	75	60	69	58	.84
IB	97	47	72	44	.65
II	93	23	77	37	.10
IIIA	60	4	54	22	.38
IIIB	24	0	20	10	.55
IV	28	0	36	3	.19
Gastrectomy					
Partial	265	35	205	43	.20
Total	115	20	126	24	.94
All patients	380	31	331	35	.53

Abbreviations: D1, limited lymph node dissection group; D2, extended lymph node dissection group; TNM, tumor-node-metastasis.
*P values were derived by the log-rank test for the difference between the D1 and D2 groups.
†Stages T0 and T4 (five patients in the D1 group and 12 in the D2 group) have been omitted.
‡Stages according to the sixth edition of the TNM classification manual.[11] TNM stage 0 (four patients in the D1 group and three in the D2 group) has been omitted.

whether less than 15 lymph nodes, between 15 and 25 lymph nodes, or more than 25 lymph nodes are harvested.

Lymph node stations 10 and 11 were resected in 112 and 124 patients, respectively. In the group of 18 patients with metastasis in station number 10, survival after 11 years is only 11%. In the group of 24 patients with lymph node metastasis in station 11, survival after 11 years is only 8%. If there are no metastases in lymph node stations 10 and 11, the 11-year survival is 27% and 35%, respectively.

The relative risk ratio for morbidity and mortality is significantly greater than one for D2 dissections, splenectomy, pancreatectomy, and age older than 70 years (mortality only; Table 3).

Patients older than 70 years have significantly higher morbidity and hospital mortality and significantly shorter survival compared with patients younger than 70 years. (Table 4).

DISCUSSION

For many years it has been debated whether an extended lymph node dissection for gastric cancer is beneficial. Theoretically, removal of a wider range of lymph nodes by extended lymph node dissection increases the chances for cure. Such resection, however, may be irrelevant if there are no lymph nodes affected, if the cancer has developed into a systemic disease, or if resection increases morbidity and mortality substantially.

Long-term follow-up of the largest randomized study of D1 and D2 dissection now clearly demonstrates that overall, no improved survival or decreased relapse rates can be obtained by D2 dissection. Extended lymph node dissection is even harmful in terms of increased morbidity and hospital mortality, although many reports deny this. Specifically, Japanese investigators have reported low operative morbidity and mortality,[12] but so far, studies have not been randomized. A randomized Japanese study between D2 and D4 dissections, that included 523 patients and closed in April 2001 found a hospital mortality of 0.8% in both groups. Dedicated centers in Western Europe have reported hospital mortality rates of less then 5% for extended lymph node dissections in selected patients.[13-15] In our study, patients younger than 70 years had a hospital mortality rate of 5.9%.

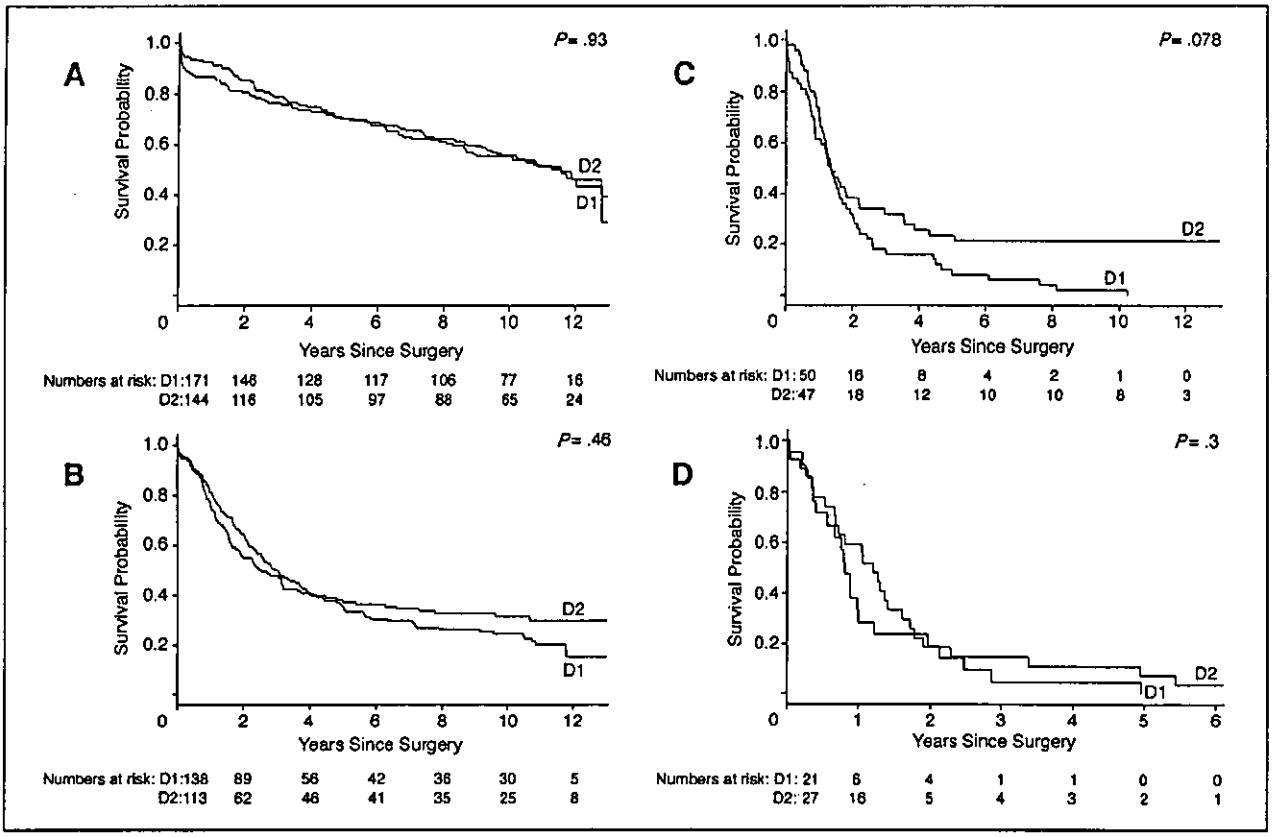

Fig 3. Survival of patients treated with curative intent according to N stage. (A), N0; (B), N1; (C), N2; (D), N3. D1, limited lymph node dissection group; D2, extended lymph node dissection group.

Splenectomy and pancreatectomy are important risk factors for morbidity and hospital mortality after D2 dissection,[16,17] with a significant adverse effect on survival as well.[18] Two Japanese studies showed no beneficial effect on survival if pancreatosplenectomy was combined with total gastrectomy, whereas morbidity was increased in these patients.[19,20] A randomized trial in Chile found no survival benefit from a splenectomy in patients with total gastrectomy, whereas morbidity was again significantly increased.[21] Another randomized trial to study the effect of splenectomy is underway in Japan.[22] In our study the risk ratio for morbidity and mortality was significant for pancreatectomy and splenectomy. The question is whether a survival benefit can be achieved with an extended lymph node dissection, if morbidity- and mortality-increasing procedures such as pancreatectomy and splenectomy can be avoided. A randomized English study supports this hypothesis for patients with stage II and III disease.[23] Pancreas and spleen sparing procedures have now become standard in Japan as well as many Western countries.

The main reason to do pancreatectomy and splenectomy in D2 dissection was not to compromise an adequate dissection of lymph node stations 10 and 11. Metastasis in these lymph nodes, however, confers a poor prognosis. In our study, patients with metastasis in these lymph nodes have a survival rate at 11 years of 8% and 11%, respectively, whereas patients without metastases have a survival rate of 27% and 35%, respectively. So the relevance of the dissection of these nodes has to be questioned as the survival benefit is small and morbidity and hospital mortality are significantly increased.

Total gastrectomy has a higher morbidity and hospital mortality rate than partial gastrectomy. A randomized trial in Italy showed that there is no survival benefit from a total gastrectomy if resection margins are free of tumor.[18] So total gastrectomy should only be performed if the localization of the tumor requires to do so.

With the aging of the populations of industrialized countries, more elderly patients with gastric cancer will be diagnosed. Population-based data from the Netherlands show that from 1982 to 1992, 27% of newly diagnosed patients were older than 80 years.[24] In a study on gastric cancer in the elderly by Klein Kranenbarg et al,[25] it was shown that there is no difference in resectability and curability rate between different age groups, but hospital mortality increases with increasing age, especially older than 70

Table 3. Relative Risk Ratio for Morbidity and Mortality After Resection With Curative Intent (n = 711)

Factor	Total No. of Patients	Morbidity				Mortality			
		No. of Patients	%	RR	95% CI	No. of Patients	%	RR	95% CI
Dissection									
D1	380	94	25			15	4		
D2	331	142	43	1.73	1.40 to 2.15	32	10	2.45	1.35 to 4.44
Splenectomy									
D1	41								
D2	124								
No, both groups	546	59	11			26	5		
Yes, both groups	165	54	33	3.03	2.19 to 4.19	21	13	2.67	1.55 to 4.62
Pancreatectomy									
D1	10								
D2	98								
No, both groups	603	70	12			34	5		
Yes, both groups	108	43	40	3.43	2.49 to 4.72	13	12	2.14	1.17 to 3.91
Age, years									
≤ 70	481	152	32			20	4		
> 70	230	80	37	1.10	0.88 to 1.37	27	12	2.82	1.62 to 4.93

Abbreviations: RR, relative risk; D1, limited lymph node dissection group; D2, extented lymph node dissection group.

years. Differentiation between D1 and D2 dissections for the age groups younger and older than 70 years shows that the morbidity and hospital mortality is higher in the D2 dissection group compared with the D1 dissection group. Although some authors do not regard age as an important prognostic variable for survival, we believe that gastrectomies should not be withheld from elderly patients but that extended lymph node dissection should be avoided in Western patients older than 70 years.

The new (2002) tumor-node-metastasis system classification system[11] offers a better insight in subgroups with different prognosis.[26-28] Using this new classification system, we studied the effect of D1 and D2 dissections in the N0, N1, N2, and N3 groups and found what theoretically might be expected—that the largest advantage is for the N2 disease group if they had a D2 dissection. This advantage was less for the N0, N1, and N3 groups. So a D2 dissection probably is the only possible cure for N2 patients. Given that only 12% of all patients had N2 disease, it is not possible to find this difference through the randomized groups. We calculated that with exclusion of postoperative deaths, 21% of the population ought to have N2 disease to make an overall difference between D1 and D2 significant. Including postoperative death, no such percentage will make the difference between the D1 and D2 significant.

At this moment N classification can only be concluded postoperatively after histologic examination. Although we have tested many possible prognostic factors and their combinations, such as T stage, tumor location in the stomach, histologic characteristics (well *v* poorly differentiated, WHO classification, Lauren classification, and Goseki classification), oncogene markers (p53, Rb, Myc, and Nm23), adhesion molecules (Ep-CAM, E-Cadherin, CD44v5, and CD44v6), and sucrose maltase expression, we have so far not been able to identify any factor that can identify N2 patients preoperatively.[29,30] We hope that promising results from genomic profiling in the near future may help to discriminate between patients with a high risk of lymph node metastasis.[31]

The extent of surgery will especially be of influence on locoregional control. Relapse after curative surgery because of local recurrence or regional lymph node metastasis has been shown in up to 87.5% of patients.[32] In our trial, locoregional recurrence was registered in 58% of the D1 group and in 45% of the D2 group. In studies with extensive surgery (D2 or more) local recurrence rates of less than 1% are reported.[33] Another approach to improve locoregional control is postop-

Table 4. Impact of Age on Morbidity, Mortality, and Survival After Resection With Curative Intent (N = 711)

	Age (years)		
	≤ 70	> 70	*P*
Morbidity, %			
D1	20.4	31.7	.01
D2	41.1	46.4	NS
Mortality, %			
D1	1.7	7.6	.005
D2	5.9	17.0	.002
Mean survival, years			
D1	6.27	4.43	.0001
D2	6.13	4.73	.009

Abbreviations: D1, limited lymph node dissection group; D2, extended lymph node dissection group; NS, not significant.

erative chemoradiotherapy, which has recently been suggested as the standard of care treatment in the United States after a curative resection of gastric adenocarcinoma.[34] Because only 10% of these patients had the advised D2 lymph node dissection and 54% of the patients in that trial had a D0 lymph node dissection, the question has raised whether the adjuvant treatment given in that trial only compensates for inadequate surgery. Five-year survival rates of the group that received adjuvant chemoradiotherapy resemble those of the Dutch Gastric Cancer Trial, where no adjuvant treatment was given. Although the population of the INT 0116 trial[34] had more advanced stages of disease compared with our trial, we believe that this conclusion seems justified. Many comments on this trial support our opinion.[35-37] The effect of a limited lymph node dissection on survival was also reported by the study group itself.[38] It is therefore doubtful if any survival advantage of chemoradiotherapy would have been found if patients would have had adequate surgery.

We conclude that there is no long-term overall survival benefit from an extended lymph node dissection in Western patients with gastric cancer. The associated higher postoperative mortality offsets its long-term effect in survival. For patients with N2 disease, an extended lymph node dissection may offer cure, but it remains difficult to identify patients who have N2 disease. Morbidity and mortality are greatly influenced by the extent of lymph node dissection, pancreatectomy, splenectomy, and age. Extended lymph node dissections may be of benefit if morbidity and mortality can be reduced.

Acknowledgment

We are indebted to the participating surgeons and pathologists of the Dutch Gastric Cancer Group and to the data center of the Surgery Department at the Leiden University Medical Center for its contribution to this trial.

Appendix

The appendix is included in the full-text version of this article, available on-line at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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ORIGINAL REPORT

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

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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ABSTRACT

Purpose
Radical gastrectomy with regional lymphadenectomy is the only curative treatment option for gastric cancer. The extent of lymphadenectomy, however, is controversial. The two European randomized trials only reported an increase in operative morbidity and mortality, but failed to show survival benefit, in the D2 lymphadenectomy group. We conducted a randomized controlled trial to compare the Japanese standard D2 and D2 + para-aortic nodal dissection.

Patients and Methods
Only experienced surgeons in both procedures from 24 Japanese institutions participated in the study. Patients with potentially curable gastric adenocarcinoma (T2-subserosa, T3, or T4) who were surgically fit were intraoperatively randomized. Postoperative morbidity and hospital mortality were recorded prospectively in a fixed format and were compared between the two groups in this study.

Results
A total of 523 patients were randomized between July 1995 and April 2001. Postoperative complications were reported in 24.5% of all patients. Although the morbidity for the extended surgery group (28.1%) was slightly higher than the standard group (20.9%), there was no difference in the incidence of four major complications (anastomotic leak, pancreatic fistula, abdominal abscess, pneumonia) between the two groups. Hospital mortality was reported at 0.80%: one patient in each group died of operative complications, while one from each group died of rapid progressive cancer while inpatient.

Conclusion
Specialized surgeons could safely perform gastrectomy with D2 lymphadenectomy in patients with low operative risks. Para-aortic lymphadenectomy could be added without increasing major surgical complications in this setting.

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INTRODUCTION

Gastric cancer is the second most common malignancy in the world, and surgical resection remains the only curative treatment option. Lymph node metastases occur during the early stages of this disease, and regional lymphadenectomy is recommended as part of radical gastrectomy. However, the extent of lymphadenectomy to achieve the optimal result is controversial, and there is no worldwide consensus.

Japanese surgeons first introduced the extended lymphadenectomy procedure, known today as D2, in the 1960s.[1] This technique requires the systematic dissection of lymph nodes in the first tier (perigastric) and the second tier (along the celiac artery and its branches). Early studies have reported that between 30% to 40% of patients

Table 1. Eligibility Criteria of the Study

Before operation
Entry criteria
Histologically proven adenocarcinoma
75 years or younger
Forced expiratory volume in 1 second ≥ 50%
Arterial oxygen pressure in room air ≥ 70 mm Hg
Creatinine clearance ≥ 50 mL/min
Written consent
Exclusion criteria
Carcinoma in the remnant stomach
Borrmann type 4 (linitis plastica)
Synchronous or metachronous malignancy in other organs except for cervical carcinoma in situ and colorectal focal cancer in adenoma
Past history of myocardial infarction or positive results of exercise ECG
Liver cirrhosis or chronic liver disease with indocyanine green test ≥ 10%
During operation
Macroscopic T staging is T2-subserosa, T3, or T4
Potentially curative operation is possible
No gross metastasis in para-aortic nodes (frozen section diagnosis not allowed)
Peritoneal lavage cytology is negative for cancer cells

with positive lymph node metastases including the second tier lymph nodes, have survived longer than 5 years with D2 lymphadenectomy.[2] However, D2 gastrectomy has a steep learning curve,[3] and may be associated with a higher-than-expected operative morbidity and mortality.

Two European randomized controlled trials comparing D1 and D2 gastrectomy revealed a high operative mortality exceeding 10% in the D2 group.[4,5] Based on these reports, the British National Health Service Cancer Guidance discourages the use of D2 technique in routine clinical practice.[6] In contrast, D2 gastrectomy is considered a standard and safe procedure in Japan, where 100,000 cases of gastric cancers are diagnosed every year. General surgeons are taught this technique early during their surgical training.[7] The Japanese nationwide registry reported an operative mortality of less than 2%, and in specialized institutions, less than 1% for D2 gastrectomy.[8,9]

Since the eighties, even more radical extended lymphadenectomy procedures had been practiced in many Japanese specialized centers. It was reported that 20% to 30% of patients with nonearly gastric cancer had microscopic metastasis present in the para-aortic nodes.[10-13] The 5-year survival for these patients has reached 14% to 30% after extended systematic dissection. In addition to D2 lymphadenectomy, lymph nodes around the upper abdominal aorta were dissected, primarily for ultimate local tumor control. However, this extended dissection may not only increase operative morbidity but also may effect the function of other abdominal organs.

There has never been a prospective study to assess the perioperative morbidity and mortality in Japanese patients after D2 gastrectomy or more extended surgery. To evaluate the survival benefit and operative complications of D2 gastrectomy and extended para-aortic dissection in gastric cancer surgery, a multi-institutional randomized controlled trial was conducted on behalf of the Japan Clinical Oncology Group (JCOG). The accrual closed with 523 patients. We hereby present the data on the operative morbidity and mortality, which are the secondary end points of this trial. Survival analysis is scheduled to take place in August 2006.

PATIENTS AND METHODS

Objectives and End Points of the Study

A prospective randomized controlled trial was designed to compare the two surgical techniques: the standard lymphadenectomy and the standard lymphadenectomy with the addition of para-aortic node dissection for gastric cancer. Only surgeons with sufficient experience of para-aortic dissection for gastric cancer participated in the trial. Since the role of neoadjuvant and adjuvant chemotherapy was not established, no patients received chemotherapy until recurrent disease was diagnosed.

The primary end point was the overall survival, while the secondary end points were the relapse-free survival, operative morbidity, hospital mortality, and quality of life. Randomization and data handling for this study was performed by the Data Centre of the JCOG, a government-sponsored organization for multi-institutional clinical trials.[14]

Eligibility Criteria

Eligibility criteria for this study are shown in Table 1. Patients with advanced gastric cancer deemed curable and fit for surgery were recruited into the trial following informed consent. Borrmann type 4 tumors (linitis plastica) were excluded because of their very poor prognosis after surgery. Liver cirrhosis and ischemic heart disease were important risk factors for mortality after surgery and hence were excluded from the study. Para-aortic lymph node metastasis is extremely rare in T1 (invasion confined

to the mucosa or submucosa) and T2-MP tumors (invasion confined to the muscularis propria); hence, these patients were not eligible for randomization. Only patients diagnosed with T2-SS (subserosal invasion) or deeper tumors at the time of laparotomy were included in the study. T2-SS is clinically recognized as a white discoloration on the serosal surface, without overt tumor serosal exposure.

During the operation, the para-aortic nodes were inspected to exclude patients with gross metastasis (enlarged and/or hard nodes) in this region. Frozen section diagnosis of the para-aortic nodes was forbidden to avoid technical contamination between the two groups of patients. Peritoneal lavage cytology was performed immediately after initial laparotomy, and absence of free cancer cells was confirmed before enrollment.

Random Assignment

While waiting for the result of lavage cytology, the surgeon examined the above eligibility criteria and started the D2 procedure. When the negative cytology result was obtained 30 to 60 minutes later, he informed the JCOG Data Centre for enrollment. Patients were then randomly assigned either to receive standard lymphadenectomy (group A) or extended lymphadenectomy (group B). The sizes of the groups were balanced according to T stage (T2 *v* T3/T4), tumor growth pattern (expansive *v* infiltrative growth), and institution. The randomization arm was notified to the surgeon immediately, who then completed the operation according to the allocated protocol.

Surgical Methods

Group A: Standard D2 gastrectomy. Patients were treated with gastrectomy and D2 lymphadenectomy. Depending on the location of the primary tumor, the surgeon performed either a total, proximal subtotal, or distal subtotal gastrectomy. D2 lymphadenectomy was a standard procedure for dissection of tumors located in the upper two thirds of the stomach as defined in the 12th edition of the Japanese Classification (1993)[15] when the study was initially designed. An extended D2 lymphadenectomy was performed for tumors located in the lower third of the stomach, which involves further dissecting the hepatoduodenal nodes (No.12a), retropancreatic nodes (No.13) and nodes along the superior mesenteric vein (No.14v). This technique was frequently performed as a standard procedure in the specialized centers, and thus adopted in this study (all except No.13 have been integrated as "D2" in the 13th edition of Japanese classification[16]).

In total or proximal subtotal gastrectomy for proximal tumors, the spleen was removed in principle for splenic hilar lymphadenectomy, while it was preserved in distal subtotal gastrectomy for distal tumors.

Group B: D2 gastrectomy combined with para-aortic lymphadenectomy. Patients in this group had similar procedure to group A, but with additional para-aortic lymph node dissection. The area to be dissected was defined in the Japanese classification (Fig 1). Proximal tumors were treated with the standard D2 lymphadenectomy, and also all "No.16-a2" (para-aortic nodes between the level of the celiac axis and the left renal vein) and "No.16-b1" (para-aortic nodes between the left renal vein and the inferior mesenteric artery) were removed. Standard distal subtotal gastrectomy was performed for the distal tumors including the "No.16-a2" and "No.16-b1" nodes; however, dissection of the left upper lateral nodes ("No.16-a2-lat") was optional.

Both group A and group B patients were followed up according to a fixed schedule, without receiving adjuvant chemotherapy.

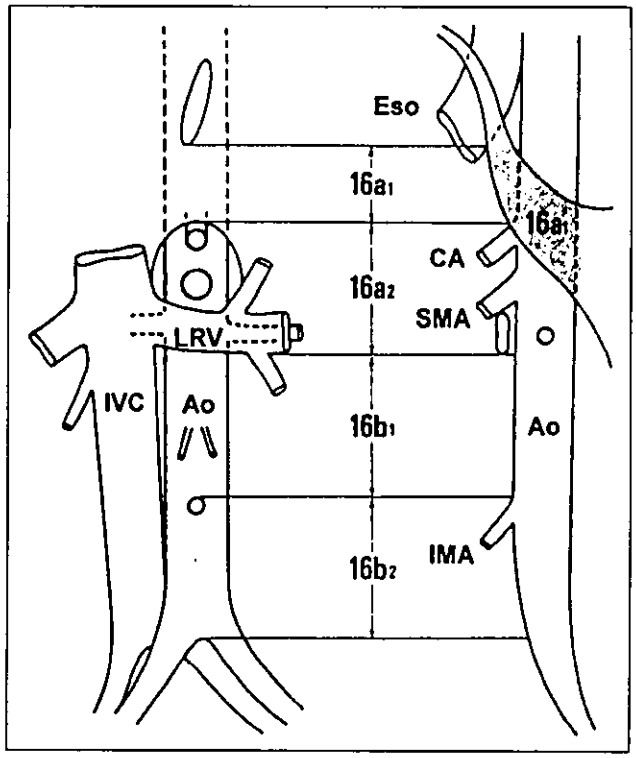

Fig 1. Anatomic definitions of para-aortic lymph nodes.[15] The nodes No.16a2 and No.16b1 are defined as "regional nodes" and were dissected in the extended surgery group. Ao, aorta; CA, celiac artery; Eso, esophagus; IMA, inferior mesenteric artery; IVC, inferior vena cava; LRV, left renal vein; SMA, superior mesenteric artery.

Evaluation of Operative Morbidity and Mortality

Operative methods and pathology results were recorded according to the 12th edition of the Japanese Classification of Gastric Carcinoma.[15] The following information was included on the case report form for prospective data collection concerning the four major groups of operative morbidity: presence or absence of anastomotic leak, pancreatic fistula, abdominal abscess, and pneumonia. Anastomotic leak was diagnosed radiologically either on routine postoperative contrast swallow or based on clinical suspicion, and was recorded regardless of its clinical significance. Pancreatic fistula was usually diagnosed when fluid with a high amylase concentration drained from the peripancreatic area for more than 7 days.

Other complications were recorded on a free format. The duration of surgery, blood loss, blood transfusion requirement and reoperation details were also recorded. Hospital mortality was defined as postoperative death of any cause within 30 days, or death within the same hospitalization.

Sample Size

The projected 5-year survival rates for groups A and B patients were 50% and 62%, respectively, and we initially planned to recruit 412 patients (206 each group) to detect this difference with one-sided α error of .05 and statistical power of 80%. At first, the recruitment was slow, but it improved as the study progressed. When the planned recruitment was almost achieved, the JCOG Clinical Trial Review Committee approved the amendment to increase the number of patients to 520 (260 each group) to

Table 2. Patients' Demographics and Tumor Characteristics

	Group A (n = 263)	Group B (n = 260)	Total (N = 523)
Male-female ratio	176/87 = 2.02	182/78 = 2.33	358/165 = 2.17
Age, years			
Median	60	61	61
Range	25-75	27-75	25-75
Tumor diameter, cm			
Median	5.5	5.5	5.5
Range	2-17	2-15.2	2-17
T-stage (macroscopic)			
T2-SS	99	93	192
T3	150	159	309
T4	14	8	22
Tumor location			
Upper 1/3	53	47	100
Middle 1/3	103	103	206
Lower 1/3	107	110	217

NOTE. All data are numbers of patients except where otherwise indicated.
Abbreviation: SS, subserosal invasion.

enforce the statistical power to detect 8% difference in the 5-year survival rates, with a 5.5-year accrual period and an additional 5-year follow-up.

Institutions and Quality Control of Surgery

The approval of the institutional review board from all participating institutions was obtained. Initially, the 12 institutions of the Gastric Cancer Surgical Study Group of the JCOG participated in the trial. Twelve institutions were added to increase patient recruitment before February 1999.

All participating surgeons agreed to the technical details for surgery during the planning stages of this trial. Significant experience in gastric cancer surgery, especially experience in extended lymphadenectomy, was a prerequisite for a surgeon's participation in the trial. Surgeons with experience of more than 100 D2 gastrectomies, or institutions with a specialized unit with annual gastrectomy volume of 80 cases or more were selected.

During the recruitment period, participating surgeons and Data Centre representatives met three times per year to monitor the study. In each meeting, videos of para-aortic dissection were presented for critique from four or five institutions, and the technical details were discussed. To assess compliance with lymphadenectomy, dissection, node recovery status in all nodal "stations," and the number of dissected nodes in the para-aortic area were recorded in the case report form, and the results were monitored.

Statistical Methods

The operative morbidity and mortality rates were based on the proportion of the number of cases divided by all registered patients based on the intention-to-treat principle. The differences in proportion between groups were evaluated using Fisher's exact test. Differences in length of hospital stay and blood loss were compared by Wilcoxon test. All P values are two-sided, and statistical analysis was done using SAS (SAS Institute, Cary, NC) version 8.12.

RESULTS

Recruitment

Recruitment commenced in July 1995, and closed in April 2001. A total of 523 patients were enrolled: 263 in group A and 260 in group B. A large variance was observed for the number of patients recruited between the institutions. Fifty-three percent of all patients were recruited by the five major hospitals.

The JCOG site-visit audit reported that written consent was available for all except nine patients from one institution. In another institution, an additional six patients had informed consent submitted by a family member.

Patients and Surgery

Patient demographics and tumor characteristics are presented in Table 2. The two groups were well balanced, as there were no significant differences in their baseline data.

The operative details are shown in Table 3. Total gastrectomy was performed in 38% of all patients, and the vast majority of total gastrectomies (186 of 199 cases) were accompanied by splenectomy. Pancreatectomy was confined to those patients whose pancreas was involved by tumor, accounting for 11% of all total gastrectomies. In four cases, proximal subtotal gastrectomy with splenectomy was performed instead of total gastrectomy. Para-aortic lymphadenectomy required longer operation time (median, 63 minutes) and resulted in greater blood loss (median, 230 mL) than the standard D2. Blood transfusion was required approximately twice as often.

Protocol Violation and Ineligible Cases

There were 10 cases of protocol violation (1.9%). In one case, the para-aortic nodes were examined by frozen

Table 3. Operative Details

	Group A (n = 263)	Group B (n = 260)	Total (N = 523)	P
Gastrectomy, No. of patients				.62
Total	102	97	199	
Distal subtotal	160	160	320	
Proximal subtotal	1	3	4	
Splenectomy, No. of patients	98	93	191	.79
Pancreatectomy, No. of patients	9	13	22	.39
Operation time, minutes				< .001
Median	237	300	270	
Range	127-625	153-600	127-625	
Blood loss, mL				< .001
Median	430	660	530	
Range	32-1,810	60-2,885	32-2,885	
Blood transfusion				< .001
No. of cases	37	78	115	
%	14.1	30.0	22.0	
No. of retrieved nodes				< .001
Median	54	74	61	
Range	14-161	30-235	14-235	

section before registration. In another case, the surgeon performed para-aortic dissection despite the allocation to group A because after randomization, he found a positive node behind the common hepatic artery, believed to be strongly suggestive of metastasis in the para-aortic area. The postoperative course of this patient, who was allocated to group A but treated as group B, was uneventful, and analyzing this patient as either group A or group B had no effect on the results in this study. We left this case in group A based on intention-to-treat analysis. In the other eight patients, nodal stations No.13 and/or No.14v were not dissected in distal third tumors.

In another case, the initial histological diagnosis following endoscopic biopsy was poorly differentiated adenocarcinoma but the final histology of the resected stomach revealed gastric lymphoma. We included this patient in the morbidity/mortality analysis, but will exclude their data from the final survival analyses.

Operative Morbidity

The overall operative morbidity rate was 24.5%. The morbidity for group B patients was higher than group A (28.1% and 20.9%, respectively), but the difference did not reach statistical significance ($P = .067$). The incidence of the four major surgical complications was not different between the two groups (Table 4).

There were various other complications reported, and the incidence was significantly higher in group B than group A patients. Paralytic ileus causing significant delay of recommencement of oral feeding, abdominal and/or left pleural lymphorrhea requiring prolonged drainage for more than 1 week, and severe diarrhea, were specific to the extended para-aortic dissection group (Table 4). Reoperation was needed in 12 patients (2.3%), and there was no difference in the reoperation rate between the two groups. Median hospital stay after surgery was 21 days in group A, and 24 days in group B ($P < .01$).

Hospital Mortality

There were four hospital deaths (0.8%)—two in each group. Each group had one patient who died of postoperative complications, and one died of rapidly progressive cancer. All other patients recovered from surgery and were discharged from hospital.

DISCUSSION

In this randomized controlled trial, the role of para-aortic dissection will be evaluated in terms of survival benefit,

Table 4. Operative Morbidity and Hospital Mortality

	Group A (n = 263)		Group B (n = 260)		
	No. of Patients	%	No. of Patients	%	P
Any complication	55	20.9	73	28.1	.067
Anastomotic leak	6	2.3	5	1.9	.99
Pancreatic fistula	14	5.3	16	6.2	.71
Abdominal abscess	14	5.3	15	5.8	.85
Pneumonia	12	4.6	4	1.5	.072
Others	24	9.1	52	20.0	< .001
Obstruction or ileus	5		11		
Lymphorrhea	0		10		
Left pleural effusion	1		6		
Severe diarrhea	0		3		
Reoperation	5	1.9	7	2.7	.57
Hospital death	2	0.8	2	0.8	.99

operative morbidity/mortality, and quality of life. The results will provide important information and should guide decision making regarding the choice of operative methods. The quality of life and survival among these patients are still in the follow-up phase, and the analyses will take place in 2004 and 2006, respectively. This report compares the morbidity and mortality rates of D2 plus para-aortic node dissection with standard D2 dissection.

There is a wide variation in operative morbidity and mortality following gastric cancer surgery among countries and institutions. The presence of comorbid disease that affects patient fitness for surgery, surgical experience of the operator, and the workload volume seem to be important factors.[17,18] The mortality for gastrectomy in Western countries often exceeds 5% and approaches 16% in some series.[19-21] Conversely, Japanese studies have consistently reported a mortality rate of lower than 2% in retrospective observations. To date, the present study is the first large-scale prospective randomized controlled trial in Japan to compare surgical techniques under strict quality control and data management. The extremely low hospital death rate after extended para-aortic lymphadenectomy (0.8%) in this multi-institutional setting confirms the findings from previous retrospective reports.

This trial is a striking contrast to the the Dutch[4] and British[5] D1/D2 trials, in which D2 lymphadenectomy was associated with operative mortality rates of 10% and 13%, respectively. One important criticism of the European randomized trials was the issue of learning curve, as many British and Dutch surgeons participating in the trials were new to the D2 procedure. Surgical experience, specific anatomic knowledge, and careful postoperative managements by experienced teams are crucial to the success of this type of surgery. An Italian group appropriately carried out a phase 2 study of D2 lymphadenectomy in selected institutions[22] until an acceptable operative mortality rate was achieved, before conducting a randomized controlled trial comparing D1 and D2 gastrectomies.

The D2 gastrectomy procedure is known as "extended lymphadenectomy" in Western countries, while Japanese surgeons employ D2 as a standard technique, and reserve the term "extended" for para-aortic dissection. Lymphatic drainage from the stomach flows to the perigastric nodes and then to the nodes around the celiac axis and its main branches. From here it enters the para-aortic nodes before joining the systemic circulation via the thoracic duct. Hence, the para-aortic nodes may be regarded as the final station of nodes that can be dissected to remove the threat of systemic metastases originating from the lymphatic system. Many Japanese surgeons in specialized centers who performed para-aortic dissection found microscopic metastases in this region, and believe that this type of surgery may be potentially worthwhile. However, the risk associated with para-aortic dissection dictates advanced operative skills and intensive postoperative care. Therefore, scientific evidence supporting a survival benefit must be obtained before employing this technique in routine gastric cancer surgery.

The very low operative morbidity and mortality achieved in this JCOG trial can be attributed to several factors: (1) we selected a group of fit patients who could tolerate para-aortic dissection in the study. (2) Only specialist surgeons with an established track record of extended lymphadenectomy participated in the trial. (3) High-throughput centers were selected for their operative skills and standardized postoperative management. (4) Pancreatectomy was avoided whenever possible, while splenectomy accompanied total gastrectomy in most cases. We report that there was no significant difference in the overall complications between the two groups; however, the para-aortic dissection group had significantly higher "other" complications (on free format) compared with standard D2. Lymphorrhea and paralytic ileus were more specific to this operation. This observation may be biased because of the surgeon's awareness of the patient's randomization arm of para-aortic dissection.

In the British and Dutch trials, splenectomy with or without distal pancreatectomy was highlighted as a major risk factor for operative morbidity and mortality.[5,23] Total gastrectomy for proximal tumor requires more advanced surgical skill and is associated with a higher morbidity compared to distal gastrectomy. Proximal gastric tumors are rapidly increasing in number in the western countries,[24,25] while the incidence remains stable in Japan,[26] and this may partly explain the superior results obtained in Japanese studies. However, no difference was observed in the distribution of the primary tumor location between the Dutch[4] and the Japanese cohort. The proportion of total to distal gastrectomy was also very similar. Therefore, variation in tumor location and type of gastrectomy could not account for the difference in morbidity/mortality, at least between these trials. JCOG recently launched a randomized controlled trial to evaluate the role of splenectomy combined with total gastrectomy in proximal tumors.[27]

Gastric cancer, though decreasing in incidence worldwide, remains a major health problem in many countries. R0 (no residual disease) resection is the only curative measure; but the more extended the surgery, it is believed the greater is the risk of operative morbidity and mortality. The type of gastrectomy and the extent of lymphadenectomy must be carefully planned for each individual patient with gastric cancer. The Japanese guidelines clearly define D2 gastrectomy as standard surgery[28] based on the excellent results in Japanese studies, while the British cancer guidance[6] discourages D2 based on the poor results of their randomized trial. This contrast should be addressed by surgeons' efforts, such as establishment of specialized standard training systems or production of evidence by high-quality randomized trials in specialized centers.

In conclusion, this study has shown that specialized surgeons could safely perform gastrectomy with D2 lymphadenectomy in patients with low operative risks. Extending the surgery to para-aortic lymphadenectomy did not increase the major operative complications and hospital deaths. However, compared with the D2 procedure, para-aortic dissection requires a longer operation time, leads to a larger volume of blood loss, and longer hospital stay. Until survival benefits are clarified when the data mature sufficiently, para-aortic lymphadenectomy for gastric cancer should be regarded as experimental surgery[28] and only performed in specialized institutions within the context of a well-designed clinical trial.

Appendix

The appendix is included in the full-text version of this article, available on-line at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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Morbidity and mortality after D1 and D2 gastrectomy for cancer: Interim analysis of the Italian Gastric Cancer Study Group (IGCSG) randomised surgical trial☆

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KEYWORDS
Gastric cancer; Extended lymph node dissection; Randomised trial; D1 resection; D2 resection

Summary *Background.* The disadvantages of D2 gastrectomy have been mostly related to splenopancreatectomy. Unlike two large European trials, we have recently showed the safety of D2 dissection with pancreas preservation in a one-arm phase I-II trial. This new randomised trial was set up to compare post-operative morbidity and mortality and survival after D1 and D2 gastrectomy among the same experienced centres that participated into the previous trial.

Methods. In a prospective multicenter randomised trial, D1 gastrectomy was compared to D2 gastrectomy. Central randomisation was performed following a staging laparotomy in 162 patients with potentially curable gastric cancer.

Findings. Of 162 patients randomised, 76 were allocated to D1 and 86 to D2 gastrectomy. The two groups were comparable for age, sex, site, TNM stage of tumours, and type of resection performed. The overall post-operative morbidity rate was 13.6%. Complications developed in 10.5% of patients after D1 and in 16.3% of patients after D2 gastrectomy. This difference was not statistically significant ($p < 0.29$). Reoperation rate was 3.4% after D2 and 2.6% after D1 resection. Post-operative mortality rate was 0.6% (one death); it was 1.3% after D1 and 0% after D2 gastrectomy.

☆ For the IGCSG (T. Allone, D. Andreone, M. Calgaro, F. Calvo, L. Capussotti, M. Degiuli, G. R. Fronda, M. Garino, L. Locatelli, P. Mello Teggia, M. Morino, A. Ponti, F. Robecchi, D. Scaglione)

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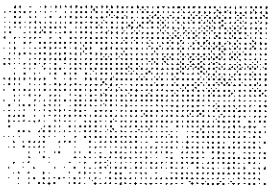

Interpretation. Our preliminary data confirm that in very experienced centres morbidity and mortality after extended gastrectomy can be as low as those showed by Japanese authors. They also suggest that D2 gastrectomies with pancreas preservation are not followed by significantly higher morbidity and mortality than D1 resections.

Introduction

Large retrospective Japanese series have shown impressive survival results after D2 gastrectomy (gastric resection together with the removal of level-2 lymph nodes as standardized by the Japanese Society for Research in Gastric Cancer–JSRGC) for potentially curable gastric cancer.[1,2]

Although some non-Japanese series have also reported favourably,[3,4] these extended lymphadenectomies are still mostly avoided in western countries due to the related increase of postoperative morbidity and mortality.

During the last decade, two European prospective randomised trials have reported that D2 gastric resections are followed by higher morbidity and mortality than D1 resections, and offer no survival benefit over D1 procedures.[5,6]

The disadvantages of D2 resections have been mostly related to pancreatico-splenectomy, which had been described as an integral part of D2 gastrectomy for all proximal tumours by the JRSGC until the 1990s, and consequently was routinely adopted for middle and upper third tumours in the D2 arm of European trials.[7]

Unlike these two European trials, we have recently shown that D2 dissection with pancreas preservation is safe in a one-arm phase I-II trial with a very strict quality control system.[8]

There is not yet evidence from randomised controlled trials that D2 resections give better long-term survival results than standard D1. For this reason our new IGCSG phase III multicentre randomised trial was set up involving the same centres that had already participated into the previous phase 1-2 trial, in order to maintain a homogeneous level of experience among all surgeons.

Patients and methods

Design of the Italian gastric cancer trial

Goals of the trial

- To evaluate whether extending the lymph node dissection to N2 level can improve the survival rate.
- To evaluate whether extending the lymph node dissection to N2 level can decrease the recurrence rate.
- To evaluate morbidity and mortality rates after surgery in both groups of patients.
- To determine the prognostic value of D2 dissection.

Patient selection

Patients less than 80-year-old with histologically proven and potentially curable gastric cancer were eligible for enrolment in the IGCSG trial. Patients undergoing emergency surgery or with severe cardio respiratory, renal or metabolic disease (ASA ≥ 4) precluding extended resections were excluded, as were those with a co-existing cancer or distant metastases at preoperative staging. ASA assessment was performed by an experienced consultant anaesthetist in all cases.

Written informed consent was required.

Criteria of curability at laparotomy included:

- Absence of macroscopic involvement of liver and peritoneum (HO, PO).
- Absence of macroscopic involvement of adjacent organs ($T < 4$).
- Absence of macroscopic massive involvement of N2 nodes (enlarged nodes at celiac area).
- Absence of malignant cells in para-aortic nodes (16B1) at biopsy and frozen section.
- Absence of malignant cells in peritoneal washing fluid, during intraoperative fresh examination.
- Absence of macroscopic residual tumour (RO).
- No involvement of the oesophagus, cardia or duodenum.

Surgical definitions

The study was performed according to the rules of the JRGC as regards the extent of stomach removal and the technique of lymph-node dissection,[9] and to the Japanese Classification of Gastric Carcinoma–second English Edition by the Japanese Gastric Cancer Association,[12] particularly as concern the definitions of classifications and grouping of regional lymph nodes, the extent of lymph node metastasis (N) and the curative potential of gastric resection (Resection A, B or C). In this new classification the regional lymph nodes are

classified into three groups (compartments or levels 1-3), depending upon the location of the primary tumour.

Treatment details

The operative details of the two procedures respected the general rules for gastric cancer study, as described by the Japanese Research Society for Gastric Cancer in 1981. D1 resection entailed removal of the nodes usually defined as perigastric nodes 'en bloc' with the specimen, according to the JGCA. In the D2 arm, during total gastrectomy, the pancreas was removed only when it was suspected to be involved by the tumour. When required (clinical $T > 1$ on the greater curvature of the proximal and middle thirds of the stomach), splenectomy was performed with the pancreas preservation technique as described by Maruyama.[10]

Quality control

Only surgeons who participated in the previous one-arm phase 1-2 study on D2 gastrectomy were allowed to participate in this new randomised trial. This restriction permitted maintenance of an homogeneous level of acquired experience among all participating surgeons, as in our previous trial a strict system for quality control had been set up and documented.[8] Since there is evidence that the learning curve for D2 gastrectomy may be between 20 and 25 cases,[11] the randomised part of the study was restricted to the five centres at which more than 25 D2 dissections had been performed during the earlier study. A minimum number of 25 retrieved nodes were required for definition of proper D2 dissection.

Data about post-operative course (hospital stay, blood transfusions, bowel transit, drainage) and early or late morbidity (< or >30 days) and treatment were reported on patient-cards. Hospital mortality (not 30 days mortality) was reported.

Registration and treatment data were regularly collected and sent to the Reference Centre within 30 days of compilation. Follow-up data were sent every 6 months.

Registration and randomisation

Centralised randomisation was performed from the Department of Oncology, Division of Surgery, San Giovanni Antica Sede Hospital, Turin.

The randomisation was performed using random permuted blocks, stratified according to the different operative units. Patients who fulfilled the eligibility criteria during laparotomy were registered by phone call to the randomisation centre. The operator at the randomisation centre completed the patient-form data on the patient operative unit, time and date of randomisation, then opened the envelope with the randomisation code and immediately communicated it to the operative unit.

In order to document strict adhesion to the recruitment procedures, and to prove the absence of selection bias, all patients with a gastric cancer undergoing surgery in each operative unit (eligible or non-eligible) were registered.

Size of the study

The size of the study was calculated on the basis of the effects D1 and D2 surgery on 5 year survival rate. To detect an increase in survival of 15% (from 30% after D1 to 45% of D2 group) 5 years after curative surgery, 160 patients will have to be randomised to each arm (alpha = 0.05 one-sided, power = 0.80).

Results

From January 1999 to December 2002, 296 patients were registered from five participating centres out of the nine centres which participated in our previous trial. Of these, 134 were found not to be eligible for randomisation. Causes of non-eligibility are shown in Table 1. One hundred and sixty-two patients were randomised either to D1 (76) or D2 (86). The two groups were comparable with respect to median age, sex and location of the tumour, as reported in Table 2. They were also similar as regard the extent of gastric resection and stage of disease. Early gastric cancer accounted for 33 per cent of the tumours. The spleen was removed in only 16 patients, four times during a D1 and 12 times during a D2 gastrectomy. A distal pancreatectomy was required in only four patients, when the pancreas was suspected of being involved by the

Table 1 Reasons for exclusion

	No. of patients (%)
Total patients registered	296 (100)
Patients randomised	162 (54.7)
Patients non-eligible	134 (46.3)
No informed consense	8 (6.0)
Metastases/secons tumour	14 (10.4)
Nodal spread (N2, N3)	34 (25.2)
Peritoneal spread	26 (19.3)
T4	25 (18.4)
Physical conditions/age	26 (19.3)
No adenocarcinoma (lymphoma)	1 (1.4)