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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

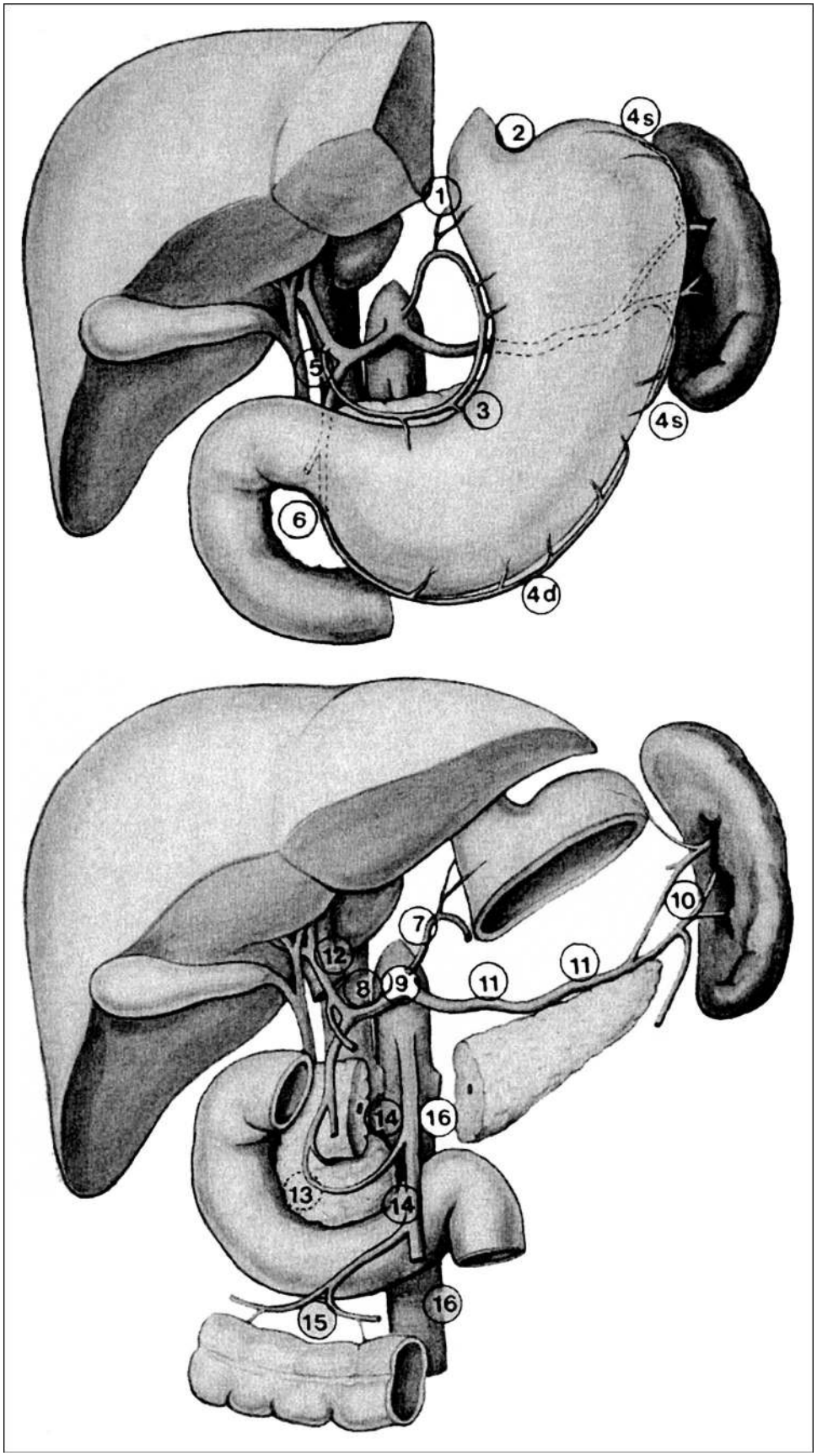

Fig 1. Lymph node stations surrounding the stomach. 1, right cardial nodes; 2, left cardial nodes; 3, nodes along the lesser curvature; 4, nodes along the greater curvature; 5, suprapyloric nodes; 6, infrapyloric nodes; 7, nodes along the left gastric artery; 8, nodes around the common hepatic artery; 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.

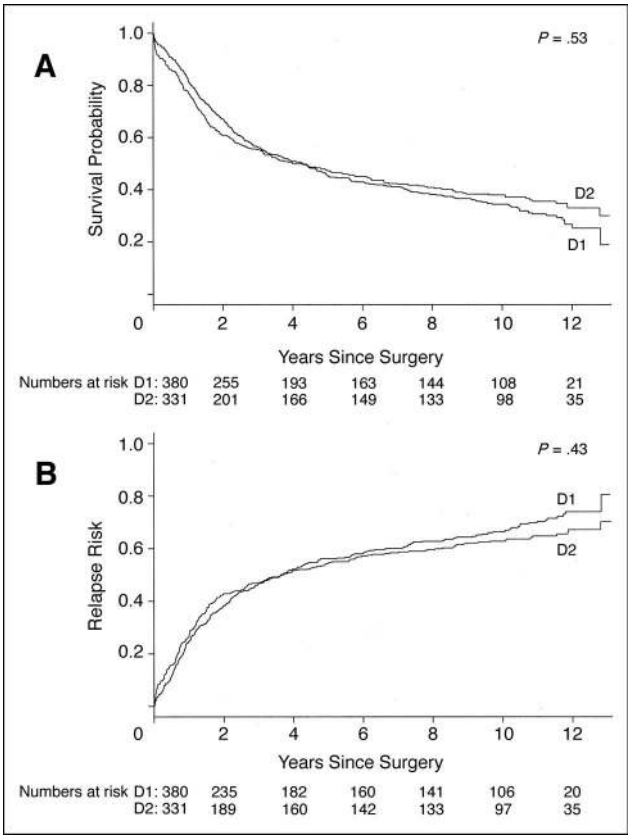

Fig 2. Survival probability (A) and relapse risk (B) of all patients treated with curative intent (n = 711). D1, limited lymph node dissection group; D2, extended lymph node dissection group.

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%.

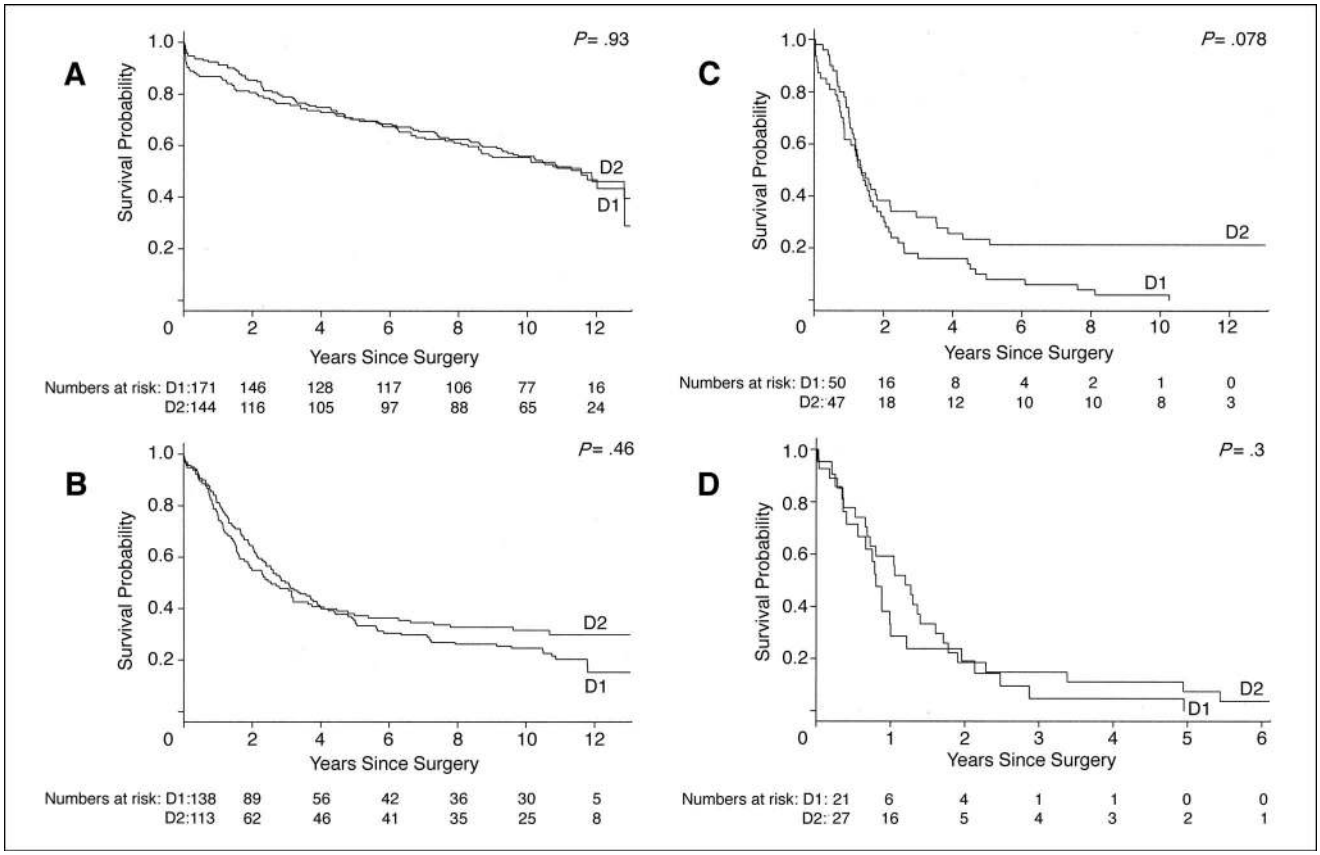

Fig 3. Survival of patients treated with curative intent according to N stage. (A), N0; (B), N1; (C), N2; (D), N3. D1, limited lymph node dissection group; D2, extended lymph node dissection group.

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

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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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