EXTENDED LYMPH-NODE DISSECTION FOR GASTRIC CANCER

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ABSTRACT

Background Curative resection is the treatment of choice for gastric cancer, but it is unclear whether this operation should include an extended (D2) lymph-node dissection, as recommended by the Japanese medical community, or a limited (D1) dissection. We conducted a randomized trial in 80 Dutch hospitals in which we compared D1 with D2 lymph-node dissection for gastric cancer in terms of morbidity, postoperative mortality, long-term survival, and cumulative risk of relapse after surgery.

Methods Between August 1989 and July 1993, a total of 996 patients entered the study. Of these patients, 711 (380 in the D1 group and 331 in the D2 group) underwent the randomly assigned treatment with curative intent, and 285 received palliative treatment. The procedures for quality control included instruction and supervision in the operating room and monitoring of the pathological results.

Results Patients in the D2 group had a significantly higher rate of complications than did those in the D1 group (43 percent vs. 25 percent, $P<0.001$), more postoperative deaths (10 percent vs. 4 percent, $P=0.004$), and longer hospital stays (median, 16 vs. 14 days; $P<0.001$). Five-year survival rates were similar in the two groups: 45 percent for the D1 group and 47 percent for the D2 group (95 percent confidence interval for the difference, −9.6 percent to +5.6 percent). The patients who had R0 resections (i.e., who had no microscopical evidence of remaining disease), excluding those who died postoperatively, had cumulative risks of relapse at five years of 43 percent with D1 dissection and 37 percent with D2 dissection (95 percent confidence interval for the difference, −2.4 percent to +14.4 percent).

Conclusions Our results in Dutch patients do not support the routine use of D2 lymph-node dissection in patients with gastric cancer. (N Engl J Med 1999; 340:908-14.)

THE overall incidence of gastric adenocarcinoma is declining despite the increasingly frequent occurrence of proximal gastric tumors. Nevertheless, stomach cancer remains an important cause of death worldwide. In the Netherlands, gastric cancer ranks fourth among all causes of death from cancer, with an annual mortality rate of approximately 20 per 100,000. In Japan, it is the most frequently diagnosed cancer.

Reported rates of survival after gastric resection are consistently higher in Japan than in the West.[1] Japanese and Western surgeons differ in their approach to lymph-node dissection during surgery for stomach cancer. D2 lymph-node dissection has never gained widespread popularity in the West, because of the associated morbidity and in-hospital mortality described in early studies.[2] The Southwest Oncology Group, in a recent study of adjuvant treatment for gastric cancer, found that even though the surgeons and pathologists participating in the study were required to document curative resection, only half of them reported dissection of the lymph nodes.[3]

The Japanese Research Society for the Study of Gastric Cancer (JRSGC) has standardized lymph-node dissection for gastric cancer. The JRSGC regards gastric resection without a formal clearance of the D2 lymph nodes as an insufficient procedure, except for palliation.[4] D2 lymph-node dissection is now performed more often in Western centers, and improved outcomes after the procedure have been reported.[5-8] To bring further evidence to the debate about D2 dissection, two major randomized trials comparing D1 with D2 dissection in patients undergoing potentially curative resection were conducted, one by the Medical Research Council in the United Kingdom[9] and the other by the Dutch Gastric Cancer Group in the Netherlands.[10,11]

Both trials found that the rates of short-term morbidity and in-hospital mortality were substantially higher among the patients who underwent D2 dissection. We now report the long-term survival rate and the cumulative risk of relapse in the Dutch trial and assess the overall value of D2 dissection in our patients with gastric cancer.

METHODS

Eligibility and Randomization

Subjects were enrolled in the study between August 1989 and July 1993. To be eligible for participation, patients had to have

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histologically confirmed adenocarcinoma of the stomach without evidence of distant metastasis. They had to be younger than 85 years and in adequate physical condition for D1 or D2 lymph-node dissection. Patients were excluded if they had previous or coexisting cancer or had undergone gastrectomy for benign tumors. Randomization was performed before surgery so as to allow scheduling for the presence of specially trained supervising surgeons. If a supervising surgeon could not attend a planned operation, the patient was considered ineligible. The 80 participating centers registered patients by means of telephone calls to the central office of the trial, where randomization in blocks of six and with stratification according to center was conducted.

All patients were evaluated every three months during the first year and every six months thereafter. In accordance with common practice in the Netherlands, a clinical diagnosis was considered sufficient evidence of relapse; for the majority of patients, however, radiologic or endoscopic confirmation was sought. The trial was approved by the medical ethics committees of the Leiden University Medical Center and the other participating hospitals.

Surgery

The JRSGC has provided guidelines for the standardization of surgical treatment and pathological evaluation.[4] These guidelines, also recommended by the American Joint Committee on Cancer and the International Union against Cancer in the fourth edition of their manual for the staging of cancer,[12] formed the basis of our protocol. These guidelines recognize 16 different lymph-node compartments (stations), numbered 1 through 16, that surround the stomach.

In general, the perigastric lymph-node stations along the lesser curvature (stations 1, 3, and 5) and the greater curvature (stations 2, 4, and 6) of the stomach are grouped together as N1, and the nodes along the left gastric artery (station 7), the common hepatic artery (station 8), the celiac artery (station 9), and the splenic artery (stations 10 and 11) are grouped together as N2. These groupings can be modified slightly, depending on the location of the primary tumor. Researchers in Japan have described further lymph-node stations (12 through 16) and groups (N3 and N4), but these were outside the scope of our trial. A D1 dissection entails the removal of the involved distal part of the stomach or the entire stomach (distal or total resection), including the greater and lesser omenta. For a D2 dissection, the omental bursa is removed, along with the front leaf of the transverse mesocolon, and the mentioned arteries are cleared completely.

At the time the trial was designed, resection of the spleen and the tail of the pancreas was regarded as necessary for the adequate removal of D2 lymph-node stations 10 and 11 in proximal tumors; in a D1 dissection, the spleen and tail of the pancreas were resected only when removal was necessitated by tumor invasion. Our protocol followed these conventions. Assessment of the curability of the tumor was always performed by the supervising surgeon at laparotomy. Patients were regarded as able to undergo resection with curative intent and underwent the randomly assigned type of dissection (D1 or D2) if at laparotomy they had a tumor that was macroscopically completely removable, no peritoneal spread or liver metastases, and no distant lymph-node metastases. The fulfillment of these criteria had to be confirmed by examination of frozen sections of one or two para-aortic lymph nodes. The patients who met these criteria constituted the group treated with curative intent. To detect free abdominal tumor cells, analysis of abdominal fluid obtained by irrigation of the abdominal cavity immediately after laparotomy was recommended. The results were not used for immediate assessment of curability.[13]

The type of gastrectomy performed (distal or total) was independent of randomization. Distal gastrectomy was allowed if there was a tumor-free margin of 5 cm beyond the proximal resection line. All other patients underwent total gastrectomy. Reconstruction of the alimentary tract was done principally by the local surgeon, who used the method he or she preferred. Histologic examination of the resected specimens was performed by the local pathologist, and the results were reviewed by a panel of supervising pathologists. After the final pathological examination, the operation was classified as R0 if the microscopical evidence indicated complete tumor removal, if there was no involvement of distant lymph nodes, and if there were no malignant cells in the abdominal-washing fluid. None of the patients treated curatively underwent adjuvant radiotherapy or chemotherapy.

Patients who did not meet these criteria constituted the group not treated curatively. They underwent a palliative surgical procedure or exploratory laparotomy at the discretion of the surgeon and irrespective of the assigned treatment.

Quality Control

Participating surgeons received a videotape and booklet about the technique and were instructed in the operating room by an expert gastric-cancer surgeon from Japan. The expert was present during the first four months of the intake period, which served as an instruction period, and regularly thereafter. All operations involving D2 dissection were attended by one of eight surgeons, from eight regions, who had been specially trained in D2 dissection. The study coordinator attended nearly all D1 operations. These supervising surgeons monitored the technique and the extent of lymph-node dissection, and after the operation, they divided the perigastric tissue into the proper lymph-node stations. Regular meetings about the technique were held with the supervising surgeons, the study coordinator, and the instructing surgeon.

Quality control was carried out by relating the number and location of lymph nodes detected at pathological examination to the guidelines of our protocol.[14] If at pathological examination lymph nodes were detected in stations other than those specified by the protocol, this violation of the protocol was called "contamination." If the pathologist could not detect lymph nodes in stations that should have been dissected, this violation was called "noncompliance." These violations could occur in both D1 and D2 dissections, but contamination in the D1 group and noncompliance in the D2 group could theoretically blur the distinction between the two operative methods. There is considerable variation in the number of lymph nodes in each station, and the defined lymph-node stations may not contain any lymph nodes.[15] To account for this biologic variation, we allowed one missing station. If the discrepancies exceeded one lymph-node station, however, we considered this deviation from the protocol relevant.

Statistical Analysis

The sample size was based on an expected five-year survival rate of 20 percent for the patients undergoing surgery with a D1 dissection with curative intent and 32 percent for those undergoing surgery with a D2 dissection with curative intent.[16] Using a significance level of 0.05 (two-sided) and a power of 0.90, and expecting 40 percent of the patients to be treated palliatively, we calculated that we needed to enroll 1100 patients. Survival rates were calculated from the time of enrollment in the study until death (event) or the last follow-up contact (if data were censored). For calculating the cumulative risk of relapse, the event was defined as relapse; data on a patient were censored when at the last follow-up contact the patient was alive with no evidence of disease or had died of diseases other than gastric cancer without evidence of a recurrence. Both survival and cumulative risk of recurrence were studied. The primary analysis of survival included all patients eligible for treatment (intention-to-treat analysis), including those who had undergone palliative treatment, whereas subsequent analyses focused on the patients operated on with curative intent. Because only the patients with an R0 resection who had not died in the hospital were at risk for recurrence, this group was used to study the cumulative risk of relapse. The effect of prognostic variables was studied in a univariate analysis. The log-rank test was used to evaluate the survival curves, although the assumption of proportional hazards was not always satisfied. The hazard ratios presented compare the results after D2 surgery with the results after the reference treatment, D1 surgery.

TABLE 1. RESULTS OF RANDOMIZATION AND ASSESSMENT OF ELIGIBILITY OF 1078 PATIENTS WITH GASTRIC CANCER.

PATIENTS	DISSECTION		TOTAL
	D1	D2	
	number of patients		
Randomly assigned to treatment	539	539	1078
Ineligible for participation*	26	56	82
No reference surgeon available	5	30	35
Metastases or second tumor	9	11	20
No adenocarcinoma	8	10	18
Inadequate physical condition	4	6	10
Eligible for participation	513	483	996
Incurable; treated with palliative intent	133	152	285
Treated with curative intent	380	331	711

*Some patients were ineligible for more than one reason.

TABLE 2. CHARACTERISTICS OF 711 PATIENTS AND TUMORS AFTER RESECTION WITH CURATIVE INTENT.*

CHARACTERISTIC	DISSECTION	
	D1 (N=380)	D2 (N=331)
Median age (yr)	67	65
Sex (M/F)	215/165	187/144
Median no. of lymph nodes investigated	17	30
	no. of patients (%)	
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)
Pathological 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)	126 (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	163 (43)	150 (45)
Without recurrence	159 (42)	147 (44)
With recurrence	4 (1)	3 (1)
Dead	217 (57)	181 (55)
Without recurrence†	48 (13)	61 (18)
With recurrence	169 (44)	120 (36)
Locoregional	49 (13)	37 (11)
Locoregional and distant	94 (23)	54 (16)
Distant	26 (7)	29 (9)

*Because of rounding, percentages may not total 100.

†These numbers include in-hospital deaths.

RESULTS

Between August 1989 and July 1993, we enrolled 1078 patients and randomly assigned them to either the D1 group or the D2 group (Table 1). Eighty-two patients (8 percent) were not eligible, 35 because no reference surgeon could attend the operation and the remainder because of secondary cancers, lack of adenocarcinoma, or inadequate physical condition. Of the 996 eligible patients, 285 (29 percent) were found to have peritoneal, hepatic, or distant lymph-node metastases or locally unresectable tumors at the time of surgery. These 285 patients with incurable disease underwent palliative gastrectomy (53 percent), gastric bypass (19 percent), or exploratory surgery only (28 percent). No gross evidence of metastatic disease was detected in 711 (71 percent) of the eligible patients, who underwent curative resection with D1 (380 patients) or D2 (331 patients) lymph-node dissection. Of these 711 patients, 632 fulfilled our criteria for an R0 resection. The D1 and D2 groups were well balanced, except in terms of associated pancreatectomy and splenectomy, a difference that was expected because of the protocol, and in terms of the type of gastrectomy ($P<0.05$) (Table 2). Pathological stage T1 tumors (defined as early gastric cancer) were found in 26 percent of the patients.

Follow-up continued until January 1998. In all eligible patients the median follow-up period was 72 months (range, 47 to 98 months). Of the 711 patients who were treated with curative intent, 398 died. Forty-seven patients died of complications soon after surgery and never left the hospital (Table 3). During follow-up, 47 patients died of cardiopulmonary disease, and the remaining 304 died of infections not related to the operation or of secondary cancers. Death with recurrence of gastric cancer occurred in 289 patients. Of the 313 surviving patients in the curative group, 7 had recurrence. D2 dissection was associated with substantially more complications, more in-hospital deaths, and a longer median hospital stay than was D1 dissection (Table 3).[10,11]

Figure 1 summarizes the long-term survival of all patients eligible for participation in the study and of the patients who were treated with curative intent. According to a proportional-hazards analysis, the hazard ratio comparing the risk of death within five years after D2 surgery with the risk of death within five years after D1 surgery for the eligible patients was 1.09 (95 percent confidence interval, 0.94 to 1.27). For the patients in the curative group, this hazard ratio was 1.00 (95 percent confidence interval, 0.82 to 1.22). The mean (±SE) five-year survival rates for all eligible patients were 34±2.1 percent in the D1 group and 33±2.2 percent in the D2 group (difference in five-year survival rates, 1 percent; 95 percent confidence interval, −5 percent to +7 percent). For the patients in the curative group, these

TABLE 3. SHORT-TERM OUTCOME AFTER RESECTION WITH CURATIVE INTENT IN 711 PATIENTS.*

OUTCOME	DISSECTION		P VALUE
	D1 (N=380)	D2 (N=331)	
Median duration of hospital stay — days	14	16	<0.001
Complications — no. (%)	94 (25)	142 (43)	<0.001
In-hospital death — no. (%)	15 (4)	32 (10)	0.004

*Data have previously been reported.[10]

figures were 45±2.6 percent for the D1 group and 47±2.8 percent for the D2 group (difference, −2 percent; 95 percent confidence interval, −9.6 percent to +5.6 percent).

The cumulative risk of relapse, calculated for the cohort of 589 patients who had an R0 resection but did not die in the hospital, was lower for patients with D2 dissections than for those with D1 dissections (hazard ratio 0.84; 95 percent confidence interval, 0.65 to 1.09). The risks of relapse by five years after surgery were 43 percent for the D1 group and 37 percent for the D2 group (Fig. 2). The curves for the cumulative risk of relapse diverged two years after surgery, but the difference did not reach statistical significance (P=0.22). The estimated difference of 6 percent at seven years had a standard error of 4.2 percent and was associated with a 95 percent confidence interval of −2.4 percent to +14.4 percent.

In the univariate analysis, none of the prognostic variables shown in Table 4 changed the overall results in the two groups. Patients who needed resection of the spleen or the tail of the pancreas had a lower survival rate than those who did not require these resections, but the difference between the D1 and D2 groups was not significant. Univariate analysis of the cumulative risk of relapse among patients with R0 resections showed a marginally significant difference for patients who did not require splenectomy or pancreatectomy (cumulative risk of relapse at five years, 41 percent for the D1 group and 29 percent for the D2 group; P=0.02).

The degree of adherence to the protocol is shown in Table 5. The quality-control system effectively prevented dissection beyond the limits of the protocol (contamination) in nearly all cases, but in 36 percent of the patients in the D1 group and in 51 percent of the patients in the D2 group, the pathologist could not detect lymph nodes in stations that should have been dissected (noncompliance).

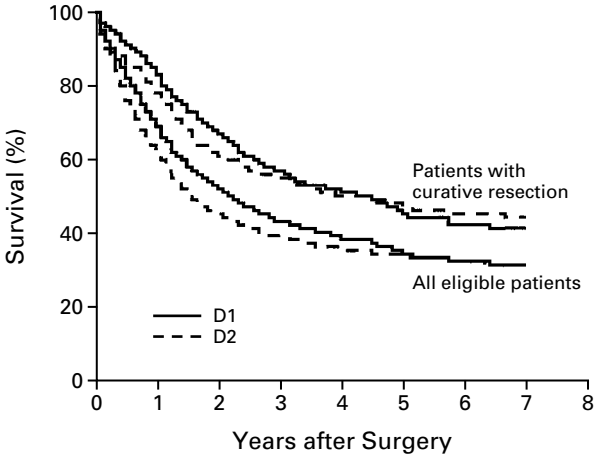

Figure 1. Survival among All Eligible Patients and Those Treated with Curative Intent.

Of the 996 patients eligible for participation, 513 underwent D1 dissection and 483 underwent D2 dissection. Of the 711 patients treated with curative intent, 380 underwent D1 dissection and 331 underwent D2 dissection.

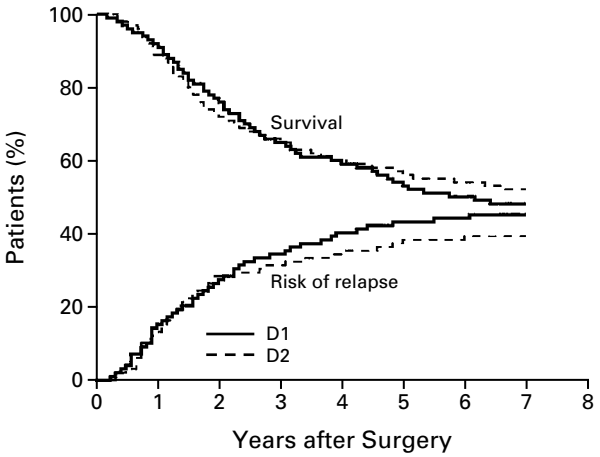

Figure 2. Survival and Cumulative Risk of Relapse among the Patients with R0 Resection, Excluding In-Hospital Deaths.

Of these 589 patients, 324 underwent D1 dissection and 265 underwent D2 dissection.

DISCUSSION

For most solid tumors, en bloc removal of regional lymph nodes is part of the surgical treatment, although it is unclear whether this procedure improves survival or merely refines staging.[18] For gastric cancer, the JRSGC has consistently recommended extended (D2) lymph-node dissection. In most countries outside Asia this procedure is performed less often, however, mainly because the morbidity associated with D2 dissection is higher than in Japan. Furthermore, the evidence of better survival after D2 surgery in Japan is based solely on observational studies. Large Western institutions tend to perform

TABLE 4. UNIVARIATE ANALYSIS OF SURVIVAL RATES AMONG 711 PATIENTS FIVE YEARS AFTER RESECTION WITH CURATIVE INTENT, ACCORDING TO SELECTED PROGNOSTIC VARIABLES.

VARIABLE	DISSECTION				P VALUE*
	D1		D2		
	no.	% surviving	no.	% surviving	
Age					
≤65 yr	178	54	168	55	0.90
>65 yr	202	38	163	40	0.87
Pathological stage†					
T1	98	75	85	77	0.69
T2	181	45	152	44	0.87
T3	94	16	82	22	0.93
Tumor–node–metastasis (TNM) stage‡					
IA	76	81	69	81	0.88
IB	97	60	64	61	0.65
II	105	38	66	42	0.29
IIIA	70	11	72	28	0.07
IIIB	16	13	39	13	0.61
IV	12	0	18	28	0.09
Lymph nodes					
Negative	175	69	146	69	0.84
Positive	205	26	185	30	0.72
Gastrectomy					
Partial	265	53	205	56	0.63
Total	115	28	126	32	0.84
All patients	380	45	331	47	0.99

*P values were derived by the log-rank test for the difference between the D1 and D2 groups.

†Stages T0 and T4 (total, 5 patients in the D1 group and 12 in the D2 group) have been omitted.

‡These stages are given according to the fourth edition of the TNM classification manual[17]; stage 0 (4 patients in the D1 group and 3 in the D2 group) has been omitted.

D2 dissections, but the justification for this operation also rests solely on retrospective evidence.[5-8]

The results of our randomized trial comparing limited (D1) and extended (D2) lymph-node dissections do not confirm the experience with these dissections in Japan. Our earlier report of increased short-term morbidity and in-hospital mortality among patients who underwent D2 dissection[10] has been confirmed in a separate trial performed by the Medical Research Council.[9] There was no long-term improvement in survival or decrease in the risk of relapse among patients in our trial who had a D2 dissection. For these reasons, we cannot recommend extended lymph-node dissection for Western patients.

TABLE 5. ADHERENCE TO THE PROTOCOL FOR LYMPH-NODE DISSECTION IN THE 711 PATIENTS WHO UNDERWENT RESECTION WITH CURATIVE INTENT.

TYPE OF PROTOCOL VIOLATION	DISSECTION	
	D1 (N=380)	D2 (N=331)
	no. of patients affected (%)	
Contamination (proof of lymph nodes from more than two lymph-node stations that were not supposed to be harvested)	22 (6)	23 (7)
Noncompliance (absence of lymph nodes from more than two lymph-node stations that were supposed to be harvested)	137 (36)	169 (51)

When our results are compared with historical data, it can be seen that long-term survival has improved. At the start of the trial, we had expected the five-year survival rates to be 20 percent for the patients who had D1 dissection and 32 percent for the patients who had D2 dissection with curative intent.[1,16] The observed five-year survival rates were 45 percent and 47 percent, respectively. This improvement is certainly related to the unexpectedly high proportion of pathological stage T1 tumors (26 percent) and pathological stage T2 tumors (47 percent), which have a relatively good prognosis, but it is also a reflection of more refined staging. Before the trial, N4 (distant) lymph-node involvement was not evaluated, and the criteria for defining a potentially curative resection were less restrictive. In this trial, 89 of the 996 eligible patients were regarded as having incurable disease because of N4 lymph-node involvement.

The incidence of gastric cancer in any Western country is so low that a randomized trial requires

the cooperation of many surgeons. To make sure that the surgeons understood the sometimes fine distinction between D1 and D2 dissections, and to ensure the quality of surgery, we implemented a strict quality-control system, in which supervising surgeons were required to attend the operations.[14] We had hoped that this system would reduce the risk of complications, but D2 dissection was nevertheless associated with relatively high morbidity and in-hospital mortality. As compared with patients in Japan, even our patients who underwent D1 dissection had more complications. These differences might result from the Western habitus, which diminishes accessibility of the abdomen, and from the amount of intraabdominal fatty tissue. Western patients also frequently have underlying diseases. For instance, of the 109 patients who died after curative resection without signs of recurrence, more than half died of cardiovascular and pulmonary diseases.

To guarantee that the assigned D1 and D2 dissections were carried out, supervising surgeons in the operating room prevented crossover to the alternative treatment, with a degree of success that is evidenced by the mean number of lymph nodes harvested. However, because the JRSGC protocol describes in detail which lymph-node stations have to be dissected for each tumor location, we felt that additional measures of adherence to the protocol were needed. These measures, contamination and noncompliance, have never been used in the context of a surgical trial, so our results cannot be directly compared with those of other trials.

In earlier reports on protocol adherence, the number and site of the lymph nodes detected at pathological investigation were related to the protocol of the JRSGC.[14] However, our study protocol differed slightly from that of the JRSGC, because we did not perform proximal gastrectomy and we required a different indication for pancreaticosplenectomy. As a consequence, the indicated lymph-node stations in all proximal tumors differ between the JRSGC and Dutch protocols. Furthermore, we did not account for the biologic variation in the numbers of lymph nodes per station.[15] The data presented here, adjusted for these variables, show that surgeons did confine the operation to the indicated dissection. Noncompliance seems serious, but it is merely a reflection of suboptimal division of the fatty tissue into lymph-node stations and incomplete detection of lymph nodes by the pathologist.[19]

Performing splenectomy and distal pancreatectomy as part of surgery for gastric cancer has been criticized, mainly because of the immunologic properties of the spleen.[20] To dissect the D2 lymph nodes along the tail of the pancreas and in the hilum of the spleen, resection of these organs was required in the protocol for proximal tumor sites with invasion beyond the muscularis propria (stage T3 or T4). We found that resection of the spleen was an independent risk factor for surgical complications[11] and was associated with reduced survival in both the D1 and the D2 groups. Although this conclusion rests on an independent observation based on a subgroup analysis outside the scope of the trial, we concur with reports that splenic resection (and concomitant pancreatic resection) should not be part of standard gastrectomy for cancer.[11,20,21]

It is difficult to compare our results with the results obtained in Japan. In our patients, lymph-node dissection was clearly defined and depended solely on the involved area of the stomach. In Japan, however, the approach is much more individualistic, with lymph-node dissection tailored according to various preoperative selection criteria. Furthermore, the outcome of curative resections in Japanese patients may have been modified by the frequent use of adjuvant chemotherapy; in Western patients, adjuvant chemotherapy after gastric resection is given only in clinical trials. In our trial, adjuvant therapy was not used in patients in the curative group.

It is well known that stage migration, in which diagnostic information leads to refined staging without actually altering the prognosis of patients with cancer, is one of the reasons for the discrepancy between the long-term results of surgery for gastric cancer in Japan and the results in the West, because additional information on lymph nodes is available only for patients with D2 dissection. Stage migration occurred in our trial in 30 percent of the D2 group.[22] If we use the observed five-year survival rates, we can calculate that stage migration in the D2 group led to a drop in the patients' stage-specific survival rates of 3 percent for International Union against Cancer (UICC) stage I disease, 8 percent for stage II, 6 percent for stage IIIA, and 12 percent for stage IIIB. For comparisons of limited and extended lymph-node dissections, therefore, we recommend the use of pathological tumor staging. The subgroup analyses of five-year survival rates for pathological stage T1, T2, and T3 tumors are shown in Table 4. The five-year cumulative risks of relapse (restricted to patients who underwent R0 resections and not including in-hospital deaths) for patients with pathological stage T1, T2, and T3 tumors, respectively, were 14 percent, 48 percent, and 83 percent for D1 dissection and 11 percent, 40 percent, and 72 percent for D2 dissection.

One of the arguments for D2 dissection is its ability to reduce rates of local recurrence, thereby increasing the quality of life. The distressing finding of local recurrence, usually in a terminal phase of the disease, often leads to second operations to restore gastrointestinal continuity. In our trial, there was a tendency toward a reduced cumulative risk of relapse after D2 dissection, but the rate of relapse remained high and the difference from D1 dissection

was not significant. A subgroup analysis indicated a significant or marginally significant difference for patients with disease in UICC stages II and IIIA, but this difference was attributable largely to stage migration.

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APPENDIX

The following centers took part in the study: Medisch Centrum Alkmaar, Rijnoord Alphen, De Lichtenberg Amersfoort, Ziekenhuis Amstelveen, Academisch Medisch Centrum Amsterdam, Academisch Ziekenhuis Vrije Universiteit Amsterdam, Antoni van Leeuwenhoekhuis Amsterdam, St. Lucas Amsterdam, Bovenij Amsterdam, Slotervaart Amsterdam, Gooi Noord Blaricum, Ziekenhuis Centrum Apeldoorn, Rijnstate Arnhem, Diaconessenhuis Arnhem, Wilhelmina Assen, Rode Kruis Beverwijk, St. Ignatius Breda, St. Gregorius Brunssum, Reinier de Graaf Gasthuis Delft, Delfzicht Delfzijl, Geertruiden Deventer, Nij Smellinghe Drachten, Catharina Eindhoven, Diakonessenhuis Eindhoven, Dr. Jansen Emmeloord, Scheperziekenhuis Emmen, St. Anna Geldrop, Bleuland Gouda, Bronovo 's-Gravenhage, Westeinde 's-Gravenhage, Rode Kruis 's-Gravenhage, Leyenburg 's-Gravenhage, Academisch Ziekenhuis Groningen, Martini Groningen, Johannes de Deo Haarlem, Elisabeth Gasthuis Haarlem, Röpcke Zweers Hardenberg, Oranjeoord Harlingen, Spaarne Heemstede, Tjongerschans Heerenveen, Elkerliek Helmond, Streekziekenhuis Midden Twente Hengelo, Groot Ziekengasthuis 's-Hertogenbosch, Bethesda Hoogeveen, Westfries Gasthuis Hoorn, Zeeweg IJmuiden, Medisch Centrum Leeuwarden, Diaconessenhuis Leiden, Academisch Ziekenhuis Leiden, St. Antoniushove Leidschendam, IJsselmeerziekenhuizen Lelystad, Academisch Ziekenhuis Maastricht, Diaconessen Inrichting Meppel, Canisius-Wilhelmina Nijmegen, Academisch Ziekenhuis Nijmegen, St. Laurentius Roermond, Academisch Ziekenhuis Dijkzigt Rotterdam, St. Franciscus Gasthuis Rotterdam, St. Clara Rotterdam, Antonius Sneek, Ruwaard van Putten Spijkenisse, Rivierenland Tiel, St. Elisabeth Tilburg, Academisch Ziekenhuis Utrecht, Diakonessen Utrecht, Overvecht Utrecht, St. Joseph Veghel, St. Elisabeth Venray, Streekziekenhuis Walcheren Vlissingen, Diaconessenhuis Voorburg, St. Jans Gasthuis Weert, St. Lucas Winschoten, Streekziekenhuis Koningin Beatrix Winterswijk, 't Lange Land Zoetermeer, 't Nieuwe Spittaal Zutphen, Sophia Zwolle, and De Weezenlanden Zwolle.

REFERENCES

1. Akoh JA, Macintyre IMC. Improving survival in gastric cancer: review of 5-year survival rates in English language publications from 1970. Br J Surg 1992;79:293-9.
2. McNeer G, Lawrence W Jr, Ortega LG, Sunderland DA. Early results of extended total gastrectomy for cancer. Cancer 1956;9:1153-9.
3. Estes NC, MacDonald JS, Touijer K, Benedetti J, Jacobson J. Inadequate documentation and resection for gastric cancer in the United States: a preliminary report. Am Surg 1998;64:680-5.
4. Kajitani T, Japanese Research Society for the Study of Gastric Cancer. The general rules for gastric cancer study in Surgery and Pathology. Jpn J Surg 1981;11:127-45.
5. Pacelli F, Doglietto GB, Bellantone R, Alfieri S, Sgadari A, Crucitti F. Extensive versus limited lymph node dissection for gastric cancer: a comparative study of 320 patients. Br J Surg 1993;80:1153-6.
6. Roder JD, Böttcher K, Siewert JR, et al. Prognostic factors in gastric carcinoma: results of the German Gastric Carcinoma Study 1992. Cancer 1993;72:2089-97.
7. Smith JW, Shiu MH, Kelsey L, Brennan MF. Morbidity of radical lymphadenectomy in the curative resection of gastric carcinoma. Arch Surg 1991;126:1469-73.
8. Sue-Ling HM. Radical surgery is essential for treating gastric cancer. Eur J Surg Oncol 1994;20:179-82.
9. 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.
10. 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.
11. Sasako M. Risk factors for surgical treatment in the Dutch Gastric Cancer Trial. Br J Surg 1997;84:567-71.
12. Beahrs OH, Henson DE, Hutter RVP, Kennedy BJ, eds. Manual for staging of cancer. 4th ed. Philadelphia: J.B. Lippincott, 1992.
13. Bonenkamp JJ, Songun I, Hermans J, van de Velde CJH. Prognostic value of positive cytology findings from abdominal washings in patients with gastric cancer. Br J Surg 1996;83:672-4.
14. Bunt AMG, Hermans J, Boon MC, et al. Evaluation of the extent of lymphadenectomy in a randomized trial of Western- versus Japanese-type surgery in gastric cancer. J Clin Oncol 1994;12:417-22.
15. Wagner PK, Ramaswamy A, Ruschoff J, Schmitz-Moormann P, Rothmund M. Lymph node counts in the upper abdomen: anatomical basis for lymphadenectomy in gastric cancer. Br J Surg 1991;78:825-7.
16. Bonenkamp JJ, van de Velde CJH, Kampschöer GHM, et al. Comparison of factors influencing the prognosis of Japanese, German, and Dutch gastric cancer patients. World J Surg 1993;17:410-5.
17. Hermanek P, Hutter RVP, Sobin LH, Wagner G, Wittekind C, eds. TNM atlas. 4th ed. Berlin, Germany: Springer-Verlag, 1997.
18. Cady B. Lymph node metastases: indicators, but not governors of survival. Arch Surg 1984;119:1067-72.
19. Bonenkamp JJ, Hermans J, Sasako M, van de Velde CJH. Quality control of lymph node dissection in the Dutch randomized trial of D1 and D2 dissection for gastric cancer. Gastric Cancer (in press).
20. Griffith JP, Sue-Ling HM, Martin I, et al. Preservation of the spleen improves survival after radical surgery for gastric cancer. Gut 1995;36:684-90.
21. Wanebo HJ, Kennedy BJ, Winchester DP, Stewart AK, Fremgen AM. Role of splenectomy in gastric cancer surgery: adverse effect of elective splenectomy on longterm survival. J Am Coll Surg 1997;185:177-84.
22. Bunt AMG, Hermans J, Smit VTH, van de Velde, Fleuren GJ, Bruijn JA. Surgical/pathologic-stage migration confounds comparisons of gastric cancer survival rates between Japan and Western countries. J Clin Oncol 1995;13:19-25.