

Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial



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Background Historical data and recent studies show that standardised extended (D2) lymphadenectomy leads to better results than standardised limited (D1) lymphadenectomy. Based on these findings, the Dutch D1D2 trial, a nationwide prospectively randomised clinical trial, was undertaken to compare D2 with D1 lymphadenectomy in patients with resectable primary adenocarcinoma of the stomach. The aim of the study was to assess the effect of D2 compared with D1 surgery on disease recurrence and survival in patients treated with curative intent.

Methods Between August, 1989, and July, 1993, patients were entered and randomised at 80 participating hospitals by means of a telephone call to the central data centre of the trial. The sequence of randomisation was in blocks of six with stratification for the participating centre. Eligibility criteria were a histologically proven adenocarcinoma of the stomach without evidence of distance metastasis, age younger than 85 years, and adequate physical condition for D1 or D2 lymphadenectomy. Patients were excluded if they had previous or coexisting cancer or had undergone gastrectomy for benign tumours. Strict quality control measures for pathological assessment were implemented and monitored. Analyses were by intention to treat. This study is registered with the NCI trial register, as DUT-KWF-CKVO-8905, EU-90003.

Findings A total of 1078 patients were entered in the study, of whom 996 were eligible. 711 patients underwent the randomly assigned treatment with curative intent (380 in the D1 group and 331 in the D2 group) and 285 had palliative treatment. Data were collected prospectively and all patients were followed up for a median time of 15.2 years (range 6.9–17.9 years). Analyses were done for the 711 patients treated with curative intent and were according to the allocated treatment group. Of the 711 patients, 174 (25%) were alive, all but one without recurrence. Overall 15-year survival was 21% (82 patients) for the D1 group and 29% (92 patients) for the D2 group ($p=0.34$). Gastric-cancer-related death rate was significantly higher in the D1 group (48%, 182 patients) compared with the D2 group (37%, 123 patients), whereas death due to other diseases was similar in both groups. Local recurrence was 22% (82 patients) in the D1 group versus 12% (40 patients) in D2, and regional recurrence was 19% (73 patients) in D1 versus 13% (43 patients) in D2. Patients who had the D2 procedure had a significantly higher operative mortality rate than those who had D1 ($n=32$ [10%] vs $n=15$ [4%]; 95% CI for the difference 2–9; $p=0.004$), higher complication rate ($n=142$ [43%] vs $n=94$ [25%]; 11–25; $p<0.0001$), and higher reoperation rate ($n=59$ [18%] vs $n=30$ [8%]; 5–15; $p=0.00016$).

Interpretation After a median follow-up of 15 years, D2 lymphadenectomy is associated with lower locoregional recurrence and gastric-cancer-related death rates than D1 surgery. The D2 procedure was also associated with significantly higher postoperative mortality, morbidity, and reoperation rates. Because a safer, spleen-preserving D2 resection technique is currently available in high-volume centres, D2 lymphadenectomy is the recommended surgical approach for patients with resectable (curable) gastric cancer.

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Introduction

After several decades of debate on what the optimum surgical treatment of gastric cancer should be, it is now possible to treat patients using evidence-based principles established by well designed and conducted studies. Adequate surgery, the only treatment known to offer cure, is still the cornerstone of gastric-cancer treatment; however, local regional control remains an issue. In western Europe and the USA, optimum local control and survival seemed to be reached with surgery as a single-modality treatment, based mainly on two large European trials, the Dutch Gastric Cancer Trial (DGCT)¹ and the UK Medical Research Council (MRC) randomised trial.² In both trials, standardised extended (D2) lymph-

adenectomy did not improve survival, and was associated with significantly higher morbidity and mortality compared with standardised limited (D1) lymphadenectomy. The unfavourable outcomes were mostly associated with pancreatico-splenectomy, which was an integral part of the D2 resection in both trials. In 2004, results from a study by Degiuli and colleagues³ suggested a survival benefit after pancreas-preserving D2 resections, and in 2006, a Taiwanese single-institution trial⁴ found that extended lymph-node dissection (D2) led to better results (no postoperative mortality) than D1 lymphadenectomy. More extended resection (D2 plus para-aortic nodal dissection) was not found to be better than D2 resections in Japanese patients.⁵

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As a result of the INT0116 trial,⁶ a combination of surgery and postoperative chemoradiotherapy became the standard treatment for curable gastric cancer in the USA. In this trial, fluorouracil plus leucovorin given concomitantly with 45 Gy radiation after potentially curative surgery improved 3-year survival from 41% to 50%, compared with surgery alone. In Europe, following the results of the UK MAGIC trial,⁷ perioperative chemotherapy with the ECF (epirubicin, cisplatin, and fluorouracil) became the new treatment standard for gastric cancer. The MAGIC trial found that perioperative systemic chemotherapy improved 5-year survival from 23% to 36%, compared with surgery alone. Randomised controlled trials in Japanese patients have shown significant improvement in overall survival with postoperative adjuvant chemotherapy with S-1 (an orally active combination of tegafur, gimeracil, and oteracil) after D2 dissection.⁸ Therefore, S-1 after D2 surgery is becoming the standard treatment for patients with gastric cancer in Japan.

Early results from the DGCT showed significantly higher postoperative morbidity and mortality in the D2 group compared with the D1 group.⁹ With the 5-year follow-up results showing no significant survival benefit in the D2 group, a conclusion was drawn that D2 resection could not be advised in patients with curable gastric cancer.¹⁰ However, 11-year follow-up data showed better survival results in exploratory analyses in patients with stage II and IIIa disease who had D2 compared with D1 resections.¹¹ The current report is the 15-year follow-up data of the DGCT.

Methods

Patients

The DGCT was approved by the medical ethics committees of the Leiden University Medical Center and all participating hospitals. Written or oral informed consent was obtained according to the principles of the institution. 80 hospitals participated in the trial. Eligible patients had histologically proven adenocarcinoma of the stomach without evidence of distant metastasis, were younger than 85 years, and were in adequate physical condition for D1 or D2 lymphadenectomy. Patients were excluded if they had previous or coexisting cancer or had undergone gastrectomy for benign tumours. Randomisation was done before surgery to allow scheduling for the presence of specially trained supervising surgeons. If a supervising surgeon could not attend a planned surgery, the patient was considered ineligible. No patients received adjuvant chemotherapy, because at the time of the trial chemotherapy was not standard therapy.

All patients were assessed every 3 months during the first year and every 6 months thereafter. In accordance with common practice at that time, a clinical diagnosis was considered sufficient evidence of recurrence; however, radiological or endoscopic confirmation was

sought for most patients. Evidence of recurrent disease was accepted only if one of the following criteria were present: cytological puncture under CT scan or ultrasonography guidance; local recurrence found by endoscopy or with relaparotomy; peritoneal dissemination on ultrasonography or CT scan; liver metastasis on ultrasonography or CT scan; distant metastasis, including supraclavicular lymph-node involvement or metastases in the Douglas pouch; lung metastasis on chest radiography; or bone metastasis on radiography or bone scan. After recurrence, no data are available on additional treatments, and only the date of death was registered. Post-mortem examination was desired to confirm death due to disease, although not all patients had a post-mortem examination.

Randomisation and masking

After establishing the diagnosis and curative resectability, participating centres registered patients by means of a telephone call to the central data centre of the trial at the Leiden University Medical Center, Germany. The following information was requested: the institution's name, patient's name and date of birth, surgeon's name, and a check of inclusion and exclusion criteria. The sequence of randomisation was in blocks of six with stratification according to the participating centre. The surgical procedure (D1 or D2) was then assigned and a date for the surgery was agreed on. After registration, reference to the case was by a reference number, thus ensuring the privacy of the patient. Because of the nature of the treatment, concealment from the surgeons was not possible; the surgeons assessing outcomes or analysing data were not masked to group assignment.

Procedures

A D1 dissection entailed removal of the involved part of the stomach or the entire stomach (distal or total resection), including the perigastric lymph nodes (N1 level, station numbers 1–6) and the greater and lesser omenta. For a D2 dissection, both N1 and N2 lymph nodes (station numbers 7–11) were removed, along with omental bursa and the front leaf of the transverse mesocolon (figure 1). At the time of the trial, resection of the spleen and pancreatic tail were regarded as necessary for adequate removal of D2 lymph-node stations 10 and 11 in proximal tumours, and in D1 in the case of tumour invasion. Station numbers 12–14 were grouped as N3 and station numbers 15 and 16 as N4, but were outside the scope of our trial because involvement of N3 and N4 were considered distant metastases.

Assessment of curability was done by the supervising surgeon at laparotomy. Patients were regarded as able to undergo resection with curative intent and underwent the randomly assigned treatment (D1 or D2) if, at laparotomy, they had a macroscopically completely

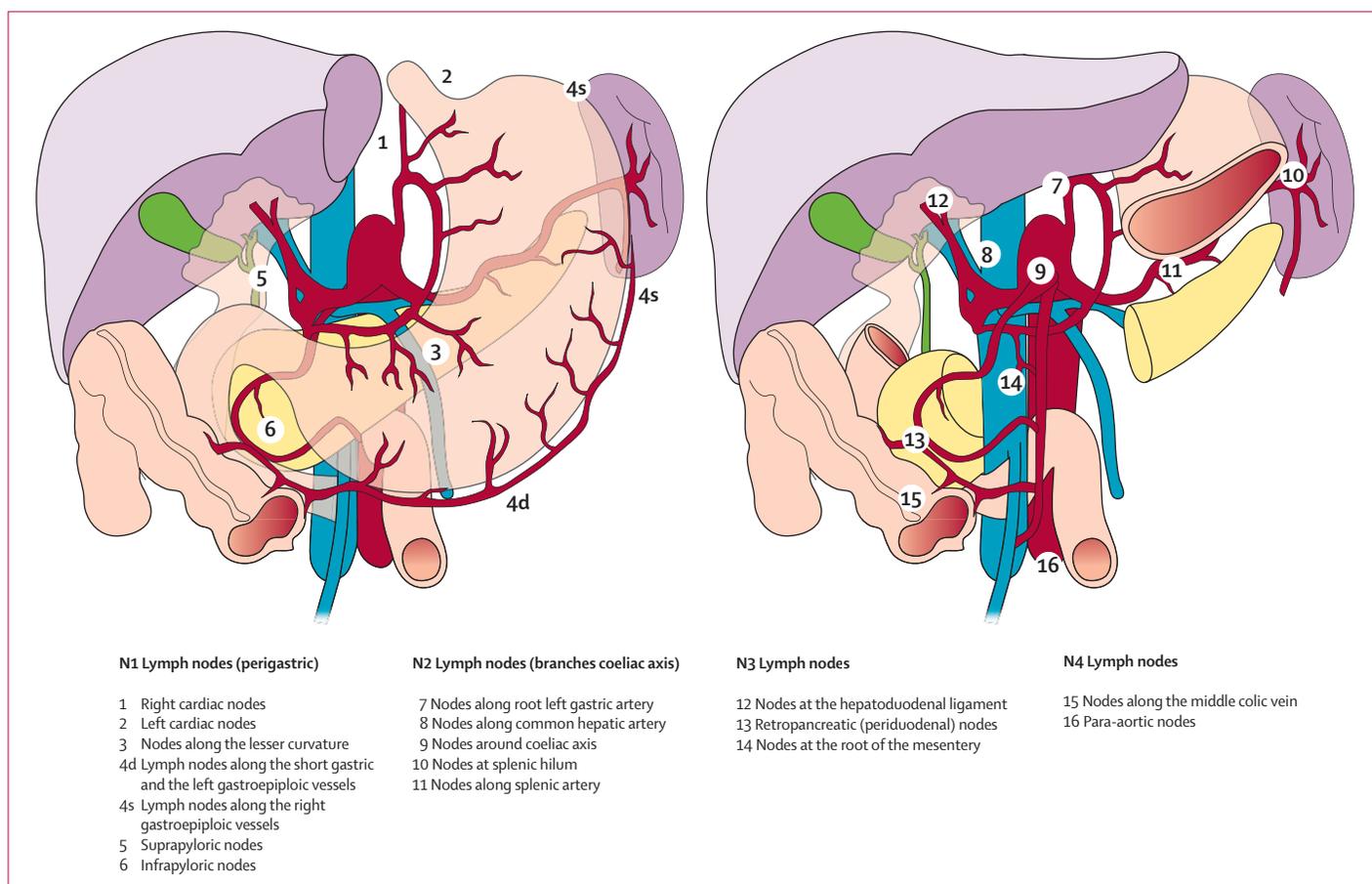


Figure 1: Location and grouping of the lymph nodes

D1 resection: removal of the N1 lymph nodes. D2 resection: removal of the N1 and N2 lymph nodes. Courtesy of Cornelis van de Velde.

removable tumour without peritoneal spread, liver metastases, or distant lymph-node metastases. For the latter criterion, a frozen-section examination of one or two para-aortic lymph nodes was required. Patients who met these criteria constituted the group treated with curative intent. To detect free abdominal tumour cells, abdominal fluid obtained by irrigation of the abdominal cavity immediately after laparotomy was recommended. The results were not used for immediate assessment of curability. The type of gastrectomy performed (distal or total) was independent of randomisation. Distal gastrectomy was allowed if there was a tumour-free margin of 5 cm beyond the proximal resection line. All other patients had total gastrectomy. Reconstruction of the alimentary tract was done mainly by the local surgeon, who used their preferred method. Histological examination of the resected specimens was done by the local pathologist, and the results were reviewed by a panel of supervising pathologists. After the final pathological examination, resections were considered R0 (radical resection, as opposed to R1, microscopic remnant tumour, and R2, macroscopic remnant tumour) when the cytology of the abdominal washing fluid was

tumour negative, the resection lines were microscopically tumour negative, no distant lymph-node stations (beyond N2) were involved, and there were no distant metastases. Patients who did not meet these criteria constituted the group treated non-curatively. These patients underwent a palliative surgical procedure or exploratory laparotomy at the discretion of the surgeon and irrespective of the assigned treatment. None of the patients treated curatively underwent adjuvant radiotherapy or chemotherapy.

The primary endpoint of the trial was overall survival, calculated from the day of randomisation until the day of death (event) or the day of last follow-up (censored) and recurrence, defined as the time from randomisation to disease recurrence; the data of a patient were censored when at last follow-up the patient was alive with no evidence of disease, or had died of diseases other than gastric cancer without evidence of a recurrence. Disease-free survival was defined as the time from randomisation to recurrence or death due to any cause. All analyses were based on patients treated with curative intent and were according to the group to which patients were randomised.

	D1 group	D2 group
Randomised	539	539
Ineligible	26	56
No supervising surgeon available	5	30
Metastases or second tumour	9	11
No adenocarcinoma	8	10
Physical condition	4	6
Eligible	513	483
Non-curative*	133	152
Remnant tumour	90	102
Peritoneal metastases	59	83
Distant lymph-node metastases	36	37
Liver metastases	27	22
Curative	380	331

D1=standardised limited lymphadenectomy. D2=standardised extended lymphadenectomy. *Patients may be included in more than one category.

Table 1: Numbers of patients in the Dutch Gastric Cancer Trial

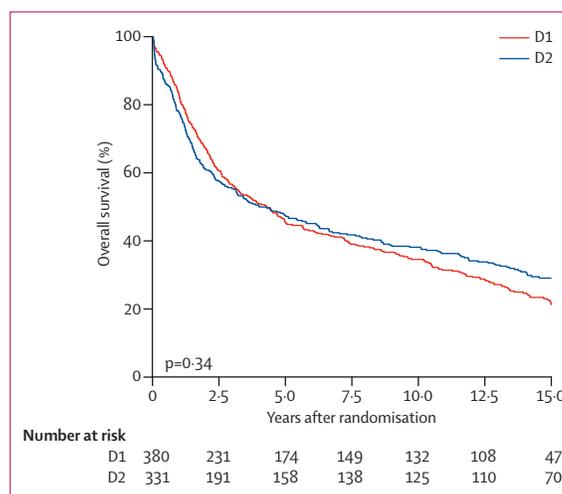


Figure 3: Overall survival in patients treated with curative intent (n=711)
D1=standardised limited lymphadenectomy. D2=standardised extended lymphadenectomy.

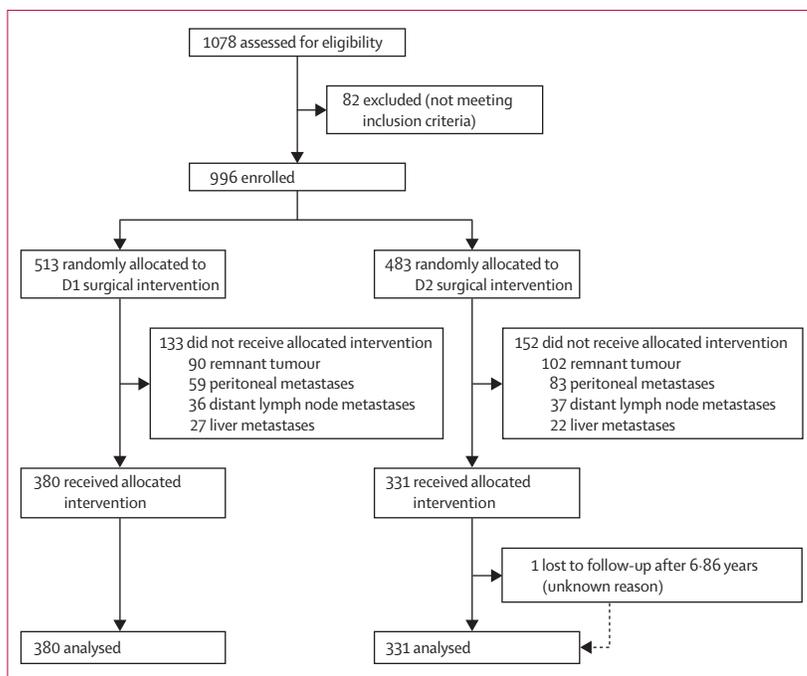


Figure 2: Trial profile

Strict quality control measures for surgery and pathology were implemented and monitored. Participating surgeons received a videotape and an instruction booklet about the technique and were instructed in the operating theatre by an expert gastric-cancer surgeon. The expert was present during the first 4 months of intake, which served as an instruction period, and regularly thereafter. All surgeries involving D2 dissection were attended by one of 11 surgeons who had been trained in D2 dissection. The study coordinator attended nearly all D1 procedures. The supervising

surgeons monitored the technique and the extent of lymph-node dissection. After the surgery, the perigastric tissue was divided into lymph-node stations and fresh specimens were sent to the pathologist. All locations dissected not en-bloc were prepared and labelled by the surgeon. Regular meetings about the technique were held with the supervising surgeons, the study coordinator, and the instructing surgeon. Quality control was done by relating the number and location of the lymph nodes detected at pathological examination to the guidelines of the study protocol.^{1,9,10}

Statistical analysis

The study size was based on an expected 5-year survival of 20% for patients undergoing D1 dissection with curative intent and 32% for those undergoing D2 dissection with curative intent. Using a two-sided significance level of 5%, a power of 90%, and an expected curability rate of 40%, 1062 patients had to be randomised.

The SPSS program (SPSS Inc, Chicago, IL, USA) and R version 2.9.1 were used for statistical analysis. A two-sided p value of 0.05 was considered statistically significant. Logistic regression was used to assess the influence of prognostic factors on postoperative mortality. The χ^2 test was applied to assess differences in proportions, and the log-rank test was used to assess the difference in survival and recurrence rates between groups, although the assumption of proportional hazards was not always satisfied.¹¹ The Kaplan-Meier method was used to estimate survival curves for overall and disease-free survival. For the analysis of death due to gastric cancer and due to other causes, a competing-risks analysis was done. Cumulative incidences were calculated and Gray's test was done to test between treatment groups.¹² Hazard ratios reported for these competing-risks analyses are based on the Fine and Gray model.¹³

	D1 group (n=380)	D2 group (n=331)
R0 resection	339	297
Cytology tumour-positive	15	10
Resection-line involvement		
Proximal	10	13
Distal	15	9
Distant metastases	8	3
Distant lymph-node involvement		
Station # 12	1	3
Station # 13	2	4
Station # 14	2	0
Station # 16	8	0
Total number of patients excluded	41	34

Patients may be included in more than one category. D1=standardised limited lymphadenectomy. D2=standardised extended lymphadenectomy. R0=radical resection. R1=microscopic remnant tumour.

Table 2: Reasons for R1 rather than R0 resections

Risk of recurrence is also reported as cumulative incidence, accounting for death due to other causes as a competing risk.

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 should be viewed as hypotheses that require validation in subsequent studies. A p value of 0.05 might not be strict enough for these subgroups. Cox proportional-hazards model was used to test for interaction between prognostic factors and lymph-node dissection.

This study is registered with the NCI trial register, identifier DUT-KWF-CKVO-8905, EU-90003.

Role of the funding source

The funding source had no role in the study design, collection, analysis, or interpretation of data, or writing of the report. The corresponding author had full access to all data and the final responsibility to submit for publication.

Results

Between August, 1989, and July, 1993, 1078 patients with gastric adenocarcinoma were entered and randomised (539 to each group) in the DGCT. 996 patients met the eligibility criteria and were randomly assigned to have a D1 or D2 lymph-node dissection. Because of peritoneal, hepatic, or distant lymph-node metastasis or locally irresectable disease, 285 patients (29%) underwent palliative surgery without a formal lymph-node dissection, according to the discretion of the surgeon. Of these 285 patients, 156 (55%) had a palliative resection, 51 (18%) had a bypass, and 78 (27%) had exploration only. Characteristics of the patients judged ineligible and non-curative are summarised in table 1 and patient flowchart in figure 2. The remaining 711 patients underwent a D1

	D1 group		D2 group		HR (95% CI)	Log-rank p value	Interaction p value
	N	15-year overall survival (95% CI)	N	15-year survival overall (95% CI)			
Total	380	21% (17–26)	331	29% (24–34)	0.92 (0.78–1.09)	0.34	..
Sex							
Male	215	21% (15–27)	186	24% (18–30)	1.08 (0.86–1.35)	0.50	0.04
Female	165	21% (15–28)	145	35% (27–43)	0.75 (0.58–0.98)	0.03	
Age, years							
≤70	252	30% (25–36)	229	36% (30–42)	0.93 (0.75–1.16)	0.54	0.89
>70	128	3% (0–6)	102	13% (6–20)	0.88 (0.67–1.16)	0.36	
Pathological stage*							
T1	98	39% (29–49)	85	53% (42–63)	0.79 (0.53–1.18)	0.25	0.79
T2	181	21% (14–27)	152	25% (18–32)	0.95 (0.75–1.22)	0.70	
T3	94	5% (1–10)	82	15% (7–22)	0.94 (0.68–1.28)	0.68	
Lymph nodes							
Negative	171	35% (27–42)	144	39% (31–47)	0.98 (0.74–1.30)	0.88	0.33
Positive	209	10% (6–14)	187	22% (16–27)	0.87 (0.70–1.08)	0.20	
N stage							
N0	171	35% (27–42)	144	39% (31–47)	0.98 (0.74–1.30)	0.88	0.15
N1	138	15% (9–21)	113	28% (19–36)	0.87 (0.66–1.15)	0.33	
N2	50	0% (0)	47	19% (8–30)	0.68 (0.44–1.04)	0.07	
N3	21	0% (0)	27	0% (0)	0.73 (0.40–1.25)	0.28	
TNM stage (UICC, 1997)†							
IA	75	41% (29–52)	69	53% (42–65)	0.79 (0.50–1.25)	0.32	0.14
IB	97	36% (26–45)	72	27% (17–38)	1.29 (0.89–1.85)	0.18	
II	93	15% (7–22)	77	33% (23–44)	0.68 (0.48–0.97)	0.03	
IIIA	60	3% (0–8)	54	19% (8–29)	0.84 (0.57–1.25)	0.39	
IIIB	24	0% (0)	20	10% (0–23)	0.81 (0.44–1.51)	0.51	
IV	28	0% (0)	36	3% (0–8)	0.71 (0.42–1.18)	0.18	
Gastrectomy							
Total	115	15 (9–22)	126	19 (12–26)	1.00 (0.76–1.32)	0.99	0.35
Partial	265	24 (18–29)	205	35 (29–42)	0.82 (0.66–1.02)	0.08	

D1=standardised limited lymphadenectomy. D2=standardised extended lymphadenectomy. HR=hazard ratio. TNM=tumour, node, metastasis. UICC=International Union Against Cancer. *Does not include two patients with missing data, two patients with T0 stage tumours, and three patients with T4 stage tumours in the D1 group, and three patients with T0 stage tumours and nine patients with T4 stage tumours in the D2 group. †Does not include one patient with missing data and two patients with TNM0 in the D1 group, and three patients with TNM0 in the D2 group.

Table 3: Univariate analysis of overall survival at 15 years (median) follow-up

or D2 resection with curative intent, according to random assignment. Data were collected prospectively and all patients were followed up: median follow-up for all eligible patients was 15.2 years (range 6.9–17.9). The lower limit is 6.9 years because one patient was lost to follow-up at that point. The trial is now closed. This analysis focuses on the 711 patients (71%) who had a curative resection with D1 (n=380) or D2 (n=331) lymphadenectomy. The characteristics of the 711 curative patients are well balanced between the two treatment groups, except for pancreatico-splenectomy, which was expected because of the protocol and type of gastrectomy (webappendix pp 1^{9,10}).

At last follow-up, 217 patients (31%) died without recurrence (110 in the D1 group and 107 in the D2 group)

See Online for webappendix

	D1 group (n=380)	D2 group (n=331)	p value
Alive	82 (22%)	92 (28%)	0.34*
Deaths from gastric cancer	182 (48%)	123 (37%)	0.01†
Deaths from other causes	116 (31%)	116 (35%)	0.12†
Other diseases	94 (25%)	77 (23%)	..
Toxicity treatment	15 (4%)	32 (10%)	..
Unknown	7 (2%)	7 (2%)	..

Data are number of patients (%) or p value. D1=standardised limited lymphadenectomy. D2=standardised extended lymphadenectomy. *Log-rank p value. †Gray's test p value.

Table 4: Causes of death

and 320 patients (45%) died with recurrence (188 in D1 and 131 in D2). 173 patients (24%) were alive without recurrence (82 in D1 and 91 in D2), and one patient was alive with recurrence in the D2 group. 15-year overall survival for patients who had curative resections was 21% (85 of 380, 95% CI 17–26) for D1 and 29% (98 of 331, 24–34) for D2 (log-rank $p=0.34$; figure 3).

D2 patients had significantly higher operative mortality than D1 patients (32 of 331 [10%] vs 15 of 380 [4%], 95% CI for the difference 2–9%, $p=0.004$), higher complication rate (142 of 331 [43%] vs 94 of 380 [25%], 11–25%, $p<0.0001$), and higher reoperation rate (59 of 331 [18%] vs 30 of 380 [8%] 5–15%, $p<0.00016$; previously published^{9,10}). Significant risk factors for postoperative mortality in logistic regression analysis were: age >70 versus ≤ 70 years (overall risk [OR] 3.55, 95% CI 1.91–6.61, $p<0.0001$), D2 versus D1 lymphadenectomy (OR 2.64, 1.38–5.04, $p=0.003$), male versus female (OR 2.50, 1.25–4.99, $p=0.01$) and total versus partial

gastrectomy (OR 2.04, 1.01–3.79, $p=0.02$; data not shown). Other factors included in the analysis but that had no significant association with postoperative mortality were T stage, lymph-node involvement (N-negative vs N-positive and N0–N3), and TNM stage. Overall survival for patients who had an R0 resection was 25% (85 of 324, 95% CI 20–30) for D1 and 35% (97 of 268, 30–41) for D2, when postoperative deaths (15 of 380 [4%] in D1 and 32 of 331 [10%] in D2) are excluded (log-rank $p=0.08$). The reasons for no R0 resection are reported in table 2.

The following analyses are based on the 711 patients who had curative resections. Table 3 shows the results of univariate analyses of 15-year overall survival and hazard ratios (HR), according to subgroups based on several prognostic variables. Overall survival was significantly higher for female patients who had D2 versus D1 dissection (35% vs 21%, $p=0.03$), and for patients with TNM stage II disease (33% in D2 vs 15% in D1, $p=0.03$). Patients with N2 disease had better survival after a D2 dissection (19% in D2 vs 0% in D1, $p=0.07$), as did those who had partial gastrectomy (35% in D2 vs 24% in D1, $p=0.08$), however this was not statistically significant.

Cause of death was analysed for all patients and the distribution for the D1 and D2 groups is summarised in table 4. Gastric-cancer-related death was significantly higher in the D1 group compared with the D2 group (HR 0.74 for D2 vs D1, 95% CI 0.59–0.93, $p=0.01$), whereas death due to other causes was not different between groups (HR 1.22 for D2 vs D1, 0.95–1.58, $p=0.12$; figure 4). Five patients in the D1 group had recurrence at the time of death (two patients with locoregional recurrence, two patients with local and distant recurrence,

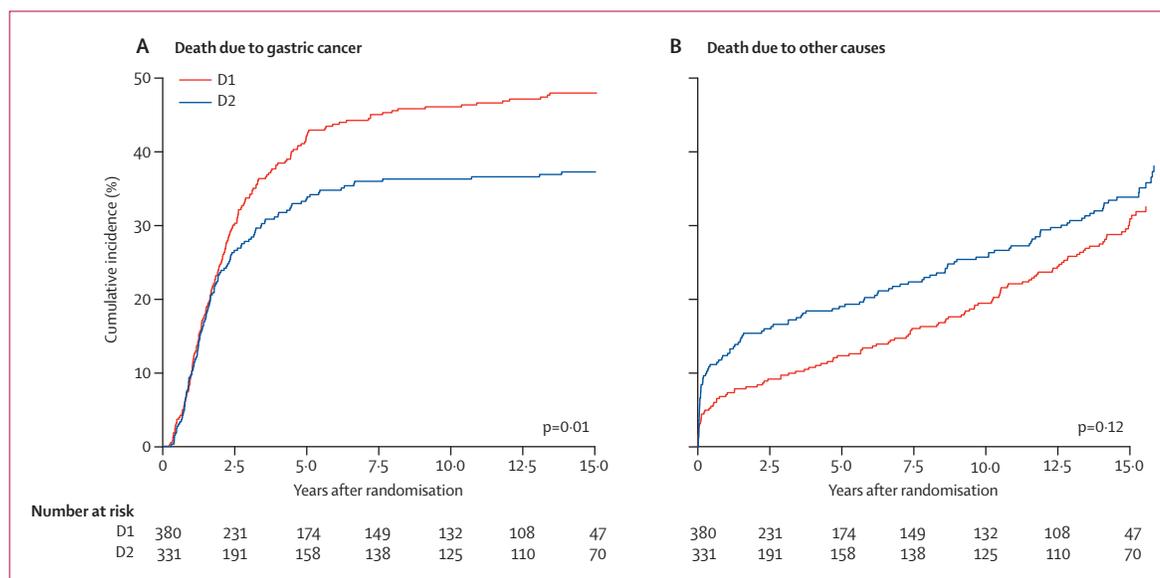


Figure 4: Cumulative risk of death due to gastric cancer and due to other causes in patients treated with curative intent (n=711)
D1=standardised limited lymphadenectomy. D2=standardised extended lymphadenectomy.

	D1 group (n=380)	D2 group (n=330)*
Alive, no recurrence†	82 (22%)	91 (28%)
Dead, no recurrence†	110 (29%)	107 (32%)
Dead, with recurrence‡	188 (49%)	131 (40%)
Local	82	40
Regional	73	43
Adjacent organs	37	26
Liver metastasis	65	37
Lung metastasis	12	6
Other organs	48	38
Dead, local+regional†	58 (15%)	42 (13%)
Dead, local+distant†	100 (26%)	56 (17%)
Dead, distant†	30 (8%)	34 (10%)

Data are number of patients (%). D1=standardised limited lymphadenectomy. D2=standardised extended lymphadenectomy. *One patient is alive with recurrence. †Overall p value for recurrence pattern is 0.015. ‡Patients may be included in more than one category.

Table 5: Recurrence sites and patterns at time of death

and one patient with distant recurrence) and seven patients in the D2 group (three patients with locoregional recurrence, three patients with local and distant recurrence, and one patient with distant recurrence), although they died of other causes. In the group of patients who died from gastric cancer, postmortem examinations were done for ten patients in the D1 group and in 18 patients in the D2 group. Except for 31 patients in the D1 group and 25 patients in the D2 group, all recurrences were established by means of additional investigations (CT scan or ultrasonography, or both, biopsy or cytology, chest radiography or bonescan) depending on the recurrence.

Local recurrence was significantly higher in the D1 versus D2 group (82 of 380 [22%] vs 40 of 330 [12%]). Regional recurrence (73 of 380 [19%] in D1 vs 43 of 330 [13%] in D2) and liver metastases (65 of 380 [17%] in D1 vs 37 of 330 [11%] in D2) were also more common in the D1 group (table 5). Locoregional, distant, and distant-only recurrence are reported in table 5. Results for disease-free survival ($p=0.31$) and risk of recurrence ($p=0.10$) are shown in figure 5. Most patients had recurrence within 2–2.5 years, and after 5 years recurrence occurs less frequently. The difference in recurrence rates between the D1 and D2 group seems to present between 2.5 and 5 years of follow-up.

Patients older than 70 years had significantly lower overall survival in both the D1 and the D2 treatment groups, male patients had significantly lower survival compared with female patients in the D2 group (mean 7.07 years vs 8.73 years, $p<0.0001$), and patients undergoing splenectomy and pancreatectomy had significantly lower overall survival in both D1 and D2 (table 6). Subgroup analysis of patients without pancreatico-splenectomy (339 patients in D1 and 206 in D2, data not shown) shows a significantly higher overall survival in those who had D2 lymphadenectomy, with 15-year survival of 22% (75 of 339, 95% CI 17–26) in D1 and 35% (71 of 206, 29–42) in D2 (HR 1.34, 95% CI 1.09–1.65; log-rank $p=0.006$).

Discussion

Our findings based on 15-year follow-up data of the DGCT show that D2 lymphadenectomy is associated with lower locoregional recurrence and fewer gastric-cancer-related deaths than D1. The drawback of a D2 resection is its association with significantly higher

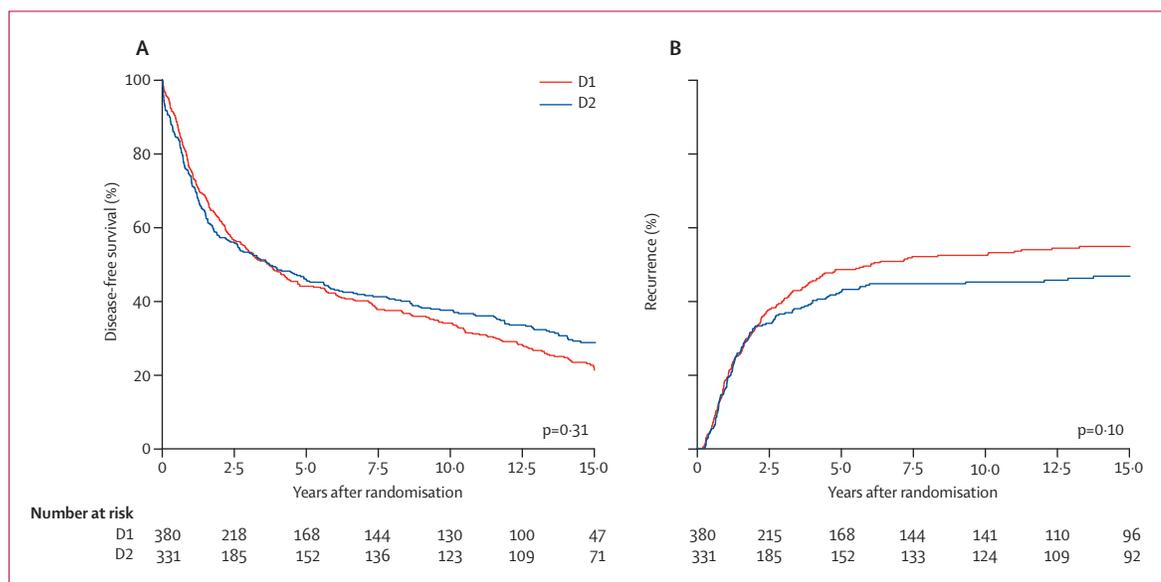


Figure 5: Disease-free survival and risk of recurrence in patients treated with curative intent (n=711)
D1=standardised limited lymphadenectomy. D2=standardised extended lymphadenectomy.

	N	D1 group mean OS (95% CI)	D2 group mean OS (95% CI)
Age			
≤70 years	481	8.23 (7.38–9.09)	8.69 (7.71–9.66)
>70 years	230	4.97 (4.10–5.82)	5.35 (4.21–6.49)
p value*	..	<0.0001	<0.0001
Sex			
Male	401	7.19 (6.33–8.05)	6.75 (5.75–7.74)
Female	310	7.07 (6.06–8.08)	8.73 (7.53–9.93)
p value*	..	0.83	0.02
Splenectomy			
Yes	165	5.14 (3.16–7.12)	5.19 (4.07–6.31)
No	546	7.37 (6.68–8.06)	9.09 (8.09–10.08)
p value*	..	0.02	<0.0001
Pancreatectomy			
Yes	108	2.34 (0.00–5.23)	4.85 (3.64–6.07)
No	603	7.27 (6.61–7.93)	8.81 (7.87–9.73)
p value*	..	0.0007	<0.0001

D1=standardised limited lymphadenectomy. D2=standardised extended lymphadenectomy. OS=overall survival. *Log-rank p value.

Table 6: Effect of age, sex, splenectomy, and pancreatectomy on mean overall survival

postoperative mortality and morbidity. However, at the time of the trial, resection of the spleen and pancreatic tail were regarded as necessary for adequate removal of D2 lymph-node stations 10 and 11 in proximal tumours, and in D1 in case of tumour invasion. Considering that a safer, spleen-preserving D2 resection is currently available in high-volume centres, and our findings of better recurrence and gastric-cancer-related survival rates, D2 resection now seems likely to be the recommended surgical approach for patients with resectable (curable) gastric cancer, despite the earlier follow-up results.

The extent of lymphadenectomy for curative resections in patients with gastric cancer has been debated for several decades. Better survival results reported for extended lymphadenectomy in Asian countries and better results with D2 in historical controls in western Europe and the USA were the reasons for the DGCT investigation. The MRC trial² in the UK addressed the

same issue—eg, whether standardised D2 leads to better survival than D1 in patients with resectable gastric cancer. In both the MRC trial and the DGCT, no adjuvant chemotherapy was given. Both trials showed similar results: significantly increased morbidity and postoperative mortality after D2 surgery, without improvement in 5-year overall survival.^{9,10} Long-term follow-up analysis of the DGCT after 11 years also showed no overall survival benefit with D2 lymphadenectomy.¹ In subgroup analysis, patients with N2 disease in the D2 group had higher survival than those in the D1 group (19% vs 0%, p=0.07). Since N2 disease is difficult to identify preoperatively, the conclusion was that extended lymph-node dissections might be beneficial if morbidity and mortality can be avoided. Meanwhile, it was reported that D2 lymphadenectomy can also be done safely in western Europe and the USA, without increased morbidity and mortality and after an adequate learning period, when routine pancreatico-splenectomy is avoided.^{3,14}

After a median follow-up of 15 years after randomisation, these data show a more favourable recurrence pattern and a cancer-related survival benefit for patients who had a D2 rather than D1 lymphadenectomy. Patients older than 65 years, male sex and type of gastrectomy, splenectomy, and pancreatectomy were identified as important risk factors for the increased morbidity seen in the D2 group.¹⁵ The increased mortality in this group of the pancreatico-splenectomy probably offset the survival benefit of D2 compared with D1 lymphadenectomy in the earlier analysis of the DGCT.

Current practice for treatment of patients with gastric cancer in Europe has become surgery with perioperative chemotherapy after the promising results of the MAGIC trial.⁷ However, in the MAGIC trial, both D1 and D2 resections were done according to the discretion of the physician and 68% of the gastrectomies were D2 resections. A French trial¹⁶ provided additional evidence for improved disease-free survival (DFS) and overall survival in resectable adenocarcinoma of the stomach and lower oesophagus with preoperative chemotherapy. Continuous infusion of fluorouracil and cisplatin resulted in a significantly higher R0 resection rate

	Time period	Surgery only			Multimodality treatment		
		N	RFS	OS	N	RFS	OS
MacDonald et al (2001) ⁶	1991–1998	275	31% (3-year)	41% (3-year)	281 CRT	48% (3-year)	50% (3-year)
Cunningham et al (2006) ⁷	1994–2002	253	NA	23% (5-year)	250 ECF	NA	36% (5-year)
Sakuramoto et al (2007) ⁸	2001–2004	530	60% (3-year)	70% (3-year)	529 S-1	72% (3-year)	80% (3-year)
Boige et al (2007) ¹⁶	1995–2003	111	21% (5-year)	24% (5-year)	113 FP	34% (5-year)	38% (5-year)

RFS=relapse-free survival. OS=overall survival. NA=not available. CRT=postoperative chemoradiotherapy (fluorouracil plus leucovorin followed by 45 Gy radiotherapy). ECF=Three preoperative and three postoperative cycles of epirubicin, cisplatin, and fluorouracil. S-1=cycles of S-1 (orally active combination of tegafur, gimeracil, and oteracil) for 1 year postoperatively. FP=2–3 cycles of preoperative fluorouracil and cisplatin; postoperative FP was recommended for patients with a response or stable disease with pN+.

Table 7: Randomised trials of surgery only versus surgery combined with chemotherapy or chemoradiotherapy

	Time period	Group 1				Group 2			
		N	Morbidity	Mortality	5-year overall survival	N	Morbidity	Mortality	5-year overall survival
Cuschieri et al (1999) ²	1987–1994	200 (D1)	28%	6.5%	35%	200 (D2)	46%	13%	33%
Bonenkamp et al (1999) ⁹ and Hartgrink et al (2004) ¹	1989–1993	380 (D1)	25%	4%	45% and 30% (11-year)	331 (D2)	43%	10%	47% and 35% (11-year)
Degiuli et al (2004) ¹⁴	1999–2002	76 (D1)	10.5%	1.3%	NA	86 (D2)	16.3%	0%	NA
Wu et al (2006) ⁴	1993–1999	110 (D1)	7.3%	0%	53.6%	111 (D3)	17.1%	0%	59.5
Sasako et al (2008) ⁵	1995–2001	263 (D2)	20.9%	0.8%	69.2%	260 (D2+PAND)	28.1%	0.8%	70.3

D1=standardised limited lymphadenectomy. D2=standardised extended lymphadenectomy. NA=not available. D3=referred to as D3 in this trial, but the same as D2. PAND=para-aortic nodal dissection.

Table 8: Randomised trials comparing the extent of lymphadenectomy

(73% vs 84%, $p=0.04$), a 13% improvement in 5-year DFS (21% vs 34%, $p=0.003$), and a 14% improvement in overall survival (24% vs 38%, $p=0.02$).¹⁶ The INT0116 trial⁶ found a significant improvement in 3-year overall survival, from 41% to 50%, with postoperative chemoradiotherapy in patients with adenocarcinoma of the stomach or gastro-oesophageal junction; only 10% of the patients had D2 resections, most had gastrectomy with D0 or D1 lymph-node dissection. The significant improvement in survival seemed to be merely a compensation of inadequate surgery. Nevertheless, as a result of this trial, a combination of surgery and postoperative chemoradiotherapy became the standard treatment for curable gastric cancer in the USA. A randomised controlled trial in Japanese patients with gastric cancer showed a significant improvement in 3-year overall survival with postoperative adjuvant chemotherapy with S-1 after D2, from 70.1% to 80.1%, compared with D2 dissection alone⁸ (table 7). In non-Asian patients, however, meta-analyses of adjuvant chemotherapy showed only a small advantage in survival, insufficient to be considered standard of care.^{17–21}

The results of these studies suggest that D2 surgery alone results in much better survival than limited surgery plus adjuvant CRT, as shown by the INT0116 trial, and that (neo)adjuvant therapy improves results even after D2 resection. Promising results from the Maruyama Index^{22–24} and nomograms^{25–27} that predict disease-specific survival might also help distinguish between patients with a high risk of relapse, and select those who will most likely benefit from tailored multimodality treatment. Because there are no other studies with such long-term follow-up data, including the MRC trial with similar design, the results of the DGCT are unique and of paramount clinical relevance. The main outcomes of the surgical trials discussed in this paper are summarised in table 8.

In selecting patients with gastric cancer for surgery, we do not think that elderly patients should be denied surgery. However, we cannot advocate extensive surgery, especially in elderly male compared with female patients. In this study, patients treated without curative intent were excluded from the analyses, according to the study protocol, and analyses were by intention to treat.

Postoperative deaths were excluded from the analyses in one example as an illustration of whether patients would benefit from a D2 resection if excessive postoperative mortality could be prevented. Nowadays, surgery for gastric cancer can be done with a spleen-preserving and pancreas-preserving D2 resection technique (unless removal is indicated because of tumour invasion into these organs).^{15,28–30} This technique is safer and is applicable in experienced, high-volume hospitals, where the outcome of patients with gastric cancer has been shown to be better.^{31–33} Several countries (eg, Scandinavian countries) have already implemented a high-volume hospital setting and centralisation for gastric-cancer treatment, because it is recognised as high-risk surgery. Bilimoria and colleagues³⁴ studied the effect of differences in hospital surgical volume on perioperative mortality and long-term survival using the National Cancer Data Base. When comparing low-volume hospitals with high-volume hospitals, hazard ratios for perioperative mortality were substantially larger than for long-term survival. The effect of hospital volume in the DGCT has also been analysed and published,⁹ and no association was noted between the number of patients randomised at centres (five vs five–14 vs ≥ 15 patients per centre) and complication, hospital death, or reoperation rates (webappendix pp 2). However, the importance of standardisation and surgical training is shown in a population-based study from the Netherlands.³⁵ The 5-year overall and relative survival of patients with curatively resected non-cardia gastric cancer was evaluated over time on a regional basis. The evaluation periods were before, during, and after the DGCT. Survival improved over time, most likely because of the standardisation and surgical training in D1 and D2 resection during the national DGCT, with extensive quality control measures for surgery and pathology implemented and monitored. With 5-year survival of 45% and 47% and 11-year survival of 30% and 35% for D1 and D2, respectively,¹ the results are the best recorded survival rates in western Europe and the USA.

Our results suggest that a D2 resection provides better locoregional control and significantly better cancer-specific survival compared with limited D1 surgery. Still, the significantly better gastric-cancer-specific survival

after D2 has to be interpreted carefully; a p value of <0.01 could be considered appropriate, since not all patients had post-mortem examinations (this was not mandatory according to the trial protocol) to confirm death due to gastric cancer.

Since a D2 resection can now be done safely with the spleen-preserving method, and more extended resections (D2 plus para-aortic nodal dissection) do not further improve survival outcome,⁵ we believe D2 resection should be recommended as the standard surgical approach to resectable gastric cancer. With the surgical standard determined, a logical next step for investigation is whether patients with low Maruyama Index derive a survival benefit and improved locoregional control from chemoradiotherapy combined with gastrectomy and optimum standardised lymphadenectomy—ie, D2 resection without splenectomy—since treatment of gastric cancer requires a multidisciplinary approach. These issues are currently being addressed in the CRITICS trial (participating countries: the Netherlands, Sweden, and Denmark), a multicentre randomised phase 3 trial investigating whether chemoradiotherapy (45 Gy in 5 weeks with daily cisplatin and capecitabine) after preoperative chemotherapy (3×ECC [epirubicin, cisplatin, capecitabine]) and standardised D2 surgery without splenectomy leads to improved survival compared with postoperative chemotherapy (3×ECC).

Contributors

CJHV conceived and designed the trial. MS instructed surgeons during the first 6 months of the trial. Data collection was done by EM-KK. HP and IS did the statistical analyses. IS wrote the report with revisions from all other authors.

Conflicts of interest

The authors declared no conflicts of interest.

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