

Morbidity and mortality in the Italian Gastric Cancer Study Group randomized clinical trial of D1 versus D2 resection for gastric cancer

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Background: A randomized clinical trial was performed to compare D1 and D2 gastrectomy in specialized Western centres. This paper reports short-term results.

Method: A total of 267 patients with gastric cancer were randomly assigned to either a D1 or a D2 procedure in five specialized centres. Based on the findings of the phase II trial and published phase III trials, a prespecified non-inferiority boundary at 12 per cent difference between groups was set regarding total morbidity.

Results: In the intention-to-treat analysis, the overall morbidity rate after D2 and D1 dissections was 17.9 and 12.0 per cent respectively ($P = 0.178$), with a 95 per cent confidence interval of the difference of 0 to 13.0 per cent, slightly exceeding the prespecified non-inferiority limit. There was a single duodenal stump leak in the D2 arm (0.7 per cent). The postoperative 30-day mortality rate was 3.0 per cent after D1 and 2.2 per cent after D2 gastrectomy ($P = 0.722$).

Conclusion: In specialized centres the rate of complications following D2 dissection is much lower than in published randomized Western trials. D2 dissection, in an appropriate setting, can therefore be considered a safe option for the radical management of gastric cancer in Western patients. Registration number: ISRCTN11154654 (<http://www.controlled-trials.com>).

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Introduction

D2 gastrectomy is standard resection for locally advanced stomach cancer in most countries in the Far East^{1,2}. The evidence of survival benefit after D2 resection in Japan was based on observational studies^{1,3}. Although low morbidity and mortality rates have also been reported in retrospective studies in the West^{4–6}, high complication and death rates following surgery in two large European randomized clinical trials (RCTs)^{7–10} concluded that D2 dissection could not be recommended for Western patients¹¹. More recently in the Far East, a RCT¹² reported a survival benefit after extended dissection, and several critical appraisals^{13–15} of the two European RCTs concluded

that increased morbidity and mortality was related mostly to splenopancreatectomies performed routinely in D2 total gastrectomies in both trials, along with inadequate experience and low case volume of the hospitals and surgeons involved. In turn, this significant increase may have offset any long-term survival benefit. *Post hoc* analysis indicated that D2 dissection may benefit a subset of patients with n2 disease and that D2 gastrectomy may be of benefit if morbidity and mortality can be avoided¹⁶.

Based on these previous reports, the Italian Gastric Cancer Study Group (IGCSG) designed a multicentre phase II trial in 1994 to test the feasibility and safety of the extended procedure performed in Western patients undergoing pancreas-preserving splenectomy with

uniform, strict quality control. Postoperative morbidity and mortality rates were 20.9 and 3.1 per cent respectively, comparable with rates reported after standard D1 gastrectomy in the West^{17,18}.

As a result, a multicentre RCT was undertaken to compare the outcome and survival of D1 *versus* D2 resection (IGCSG-R01). This article reports the short-term results.

Methods

Eligibility

The trial was approved by the medical ethics committees of the participating hospitals.

Enrolment in IGCSG-R01 started in June 1998. Eligible patients had histologically proven potentially curable gastric adenocarcinoma, not requiring emergency surgery; they were aged less than 80 years and in adequate physical condition with no serious co-morbid cardiorespiratory disease that would preclude a safe D2 procedure. Patients were eligible for registration if they had not undergone previous gastric surgery and had no coexisting cancer. In accordance with ethics committee instructions an interim analysis was undertaken after the first half of the planned recruitment to ensure there was no excess mortality in the D2 group.

Staging laparotomy and randomization

After preoperative workup and informed consent, registered patients underwent staging laparotomy in order to exclude potentially non-curative cancer. This entailed abdominal lavage with 250 ml saline solution to exclude the presence of free neoplastic cells and exposure of the interaortocaval space below the left renal vein with a systematic biopsy and frozen section of lymph node station number 16b1¹⁹. Liver and/or peritoneal metastases, involvement of adjacent organs (T4), and macroscopic diffuse involvement of second-tier nodes and of the oesophagus, cardia or duodenum was excluded.

Patients fulfilling the above criteria were randomized to undergo either D1 or D2 gastrectomy. Intraoperative randomization, in blocks of ten and stratified by centre, was implemented centrally by telephone. The sequence was generated by the trial data centre (Centro Prevenzione Oncologica Piemonte) and concealed until interventions had been assigned. No blinding was applied after group assignment.

Surgery/treatment arms

The study was performed following the guidelines for the standardization of surgical treatment and pathological evaluation, first laid out by the Japanese Research Society for Gastric Cancer (JRS GC) in 1981²⁰. The Japanese Classification of Gastric Carcinoma, second English edition¹⁹, was also used to provide a common language for the anatomical description of lymph node stations and grouping, and the extent of gastric resection in the treatment arms (D1 and D2). In this classification¹⁹, the regional lymph nodes of the stomach were classified into stations 1–20, plus stations 110, 111 and 112. These regional lymph nodes were classified into three groups or levels (N1, N2 and N3), depending on the site of the primary tumour, following the JRS GC system. *Table 1* summarizes the allocation of lymph node stations in both D1 (removal of level 1) and D2 (removal of levels 1 and 2) procedures, according to the location of the primary tumour.

Splenopancreatectomy was not considered as a routine part of the D2 total gastrectomy in this trial; the spleen was removed (according to the Maruyama technique²¹) only when the tumour was in the left part of the upper stomach or located close to the greater curvature, beyond Demel's point. The spleen was also preserved in patients with clinical T1 tumours. The pancreas was removed only when tumour involvement was suspected.

The type of gastrectomy performed (distal or total) was not dependent on the randomization. Following the guidelines of the Japanese Gastric Cancer Association, distal gastrectomy was performed when the proximal edge of the tumour was more than 3 cm from the cardia in early cancers and well circumscribed (Borrmann type 1 and type 2) advanced cancers, or more than 6 cm in Borrmann type 3 advanced cancers. Total gastrectomy was performed when these conditions were not met, if the tumour was located close to the greater curvature and beyond Demel's point, and for linitis plastica^{19,22}.

Reconstruction of the alimentary tract was performed according to the normal practice of each institution.

Neither neoadjuvant nor adjuvant chemotherapy was administered to any patient.

Pathological examination of resected specimens was performed by local pathologists and results were reviewed by a supervising pathologist at the reference centre in Turin. The surgeon dissected the lymph node stations from the resection specimen at the end of the operation. The fifth edition of the International Union Against Cancer tumour node metastasis (TNM) classification²³ was used for staging cancers in the present trial.

Table 1 Lymph node groups¹⁹ required for D1 and D2 resection by location of tumour

	Lymph node station		
	Lower third	Middle third	Upper third
D1 gastrectomy	3, 4d, 4sb, 5, 6	1, 3, 4sb, 4d, 5, 6	1, 2, 3, 4sa, 4sb
D2 gastrectomy	1, 3, 4d, 4sb, 5, 6, 7, 8a, 9, 11p, 12a, 14v	1, 3, 4sb, 4d, 5, 6, 7, 8a, 9, 11p, 12a	1, 2, 3, 4sa, 4sb, 4d, 5, 6, 7, 8a, 9, 10, 11p, 11d

Table 2 Characteristics of the two randomized groups

	D1 gastrectomy (n = 133)	D2 gastrectomy (n = 134)	P*
Sex ratio (M:F)	67:66	64:70	0.669
Median (range) age (years)	63.5 (30–81)	61.6 (22–87)	0.167†
Age > 70 years	45 (33.8)	35 (26.1)	0.169
Tumour location			0.946
Distal	87 (65.4)	90 (67.2)	
Mid	32 (24.1)	30 (22.4)	
Proximal	13 (9.8)	13 (9.7)	
Diffuse	1 (0.8)	0 (0)	
Stump	0 (0)	1 (0.7)	
Type of resection			
Total	35 (26.3)	31 (23.1)	0.547
Distal	98 (73.7)	103 (76.9)	
Splenectomy	9 (6.8)	12 (9.0)	0.507
Distal	2 (1.5)	2 (1.5)	0.992
pancreatectomy + splenectomy			
Tumour stage			0.224
pT1	49 (36.8)	39 (29.1)	0.191‡
pT2	42 (31.6)	55 (41.0)	
pT3	40 (30.1)	37 (27.6)	
Not known	2 (1.5)	3 (2.2)	
TNM stage			0.047
IA	41 (30.8)	25 (18.7)	0.021§
IB	20 (15.0)	31 (23.1)	
II	24 (18.0)	33 (24.6)	
IIIA	20 (15.0)	18 (13.4)	
IIIB	16 (12.0)	9 (6.7)	
IV	9 (6.8)	15 (11.2)	
Not known	3 (2.3)	3 (2.2)	
No. of lymph nodes dissected			
Mean	28.2	37.3	< 0.001†
Median (range)	25 (2–104)	33 (11–124)	
Node stage			
pN0	63 (48.1)	57 (43.5)	0.457
pN+	68 (51.9)	74 (56.5)	
pN1	32 (24.4)	43 (32.8)	0.293
pN2	28 (21.4)	20 (15.3)	
pN3	8 (6.1)	11 (8.4)	
Not known	2	3	

Values in parentheses are percentages unless indicated otherwise.
 (p)TNM, (pathological) tumour node metastasis. * χ^2 test unless indicated
 otherwise; †Wilcoxon test. ‡pT1 *versus* other; §stage IA *versus* other.

The postoperative course including all complications and reoperations was documented on forms specifically devised for the study and then recorded in the project database. In-hospital mortality was defined as death within 30 days of the procedure or during the patient's hospital stay.

Quality control

Only surgeons who had participated in the previous phase II trial^{17,18} were allowed to enter patients into this RCT to avoid bias generated by lack of experience among surgeons unfamiliar with the D2 technique.

Regular meetings were organized by the IGCSG coordinator (M.D.) to discuss issues around eligibility, technical or logistical problems at the participating centres.

The number and location of lymph nodes removed and detected during pathological examination was correlated to those required by International Gastric Cancer Association guidelines. Two types of protocol deviation were recognized: 'contamination' for D1 and 'non-compliance' for D2 gastrectomy. Contamination was the deviation with pathological proof of inclusion of more than two lymph node stations that were not supposed to be removed, and non-compliance was the absence of lymph nodes from more than two lymph node stations that were required²⁴.

Statistical analysis

The primary endpoint was overall survival, defined as the time from randomization to death. Secondary outcomes were recurrence-free survival (defined as the time from randomization to the first documentation of cancer recurrence or death from any cause), and procedure-related morbidity and mortality. Based on primary outcome, it was calculated that 160 patients per arm were required²⁵. From the phase II trial¹⁷ and published phase III trials^{7,9}, total morbidity was estimated at 20 per cent for both groups. A prespecified non-inferiority margin was selected for a 12 per cent difference between the groups (D2 minus D1) (α = 95 per cent, one tail, power = 80 per cent). To show equivalence between total morbidity in the two groups,

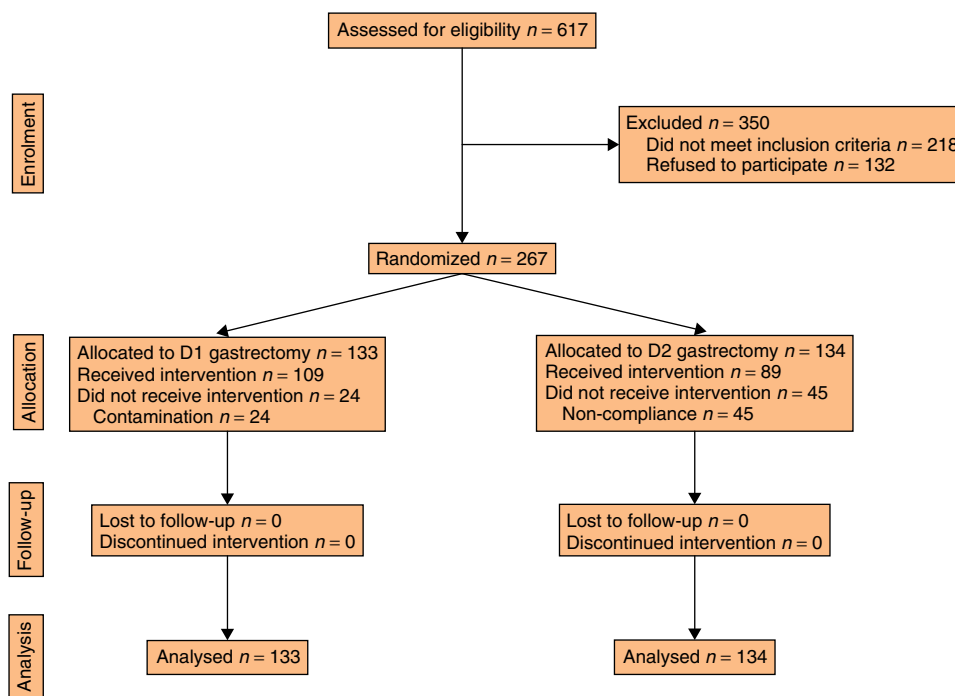


Fig. 1 CONSORT diagram for the trial

the 95 per cent confidence interval (c.i.) for the difference should not exceed the stated non-inferiority margin²⁶. All analyses were undertaken on an intention-to-treat basis, regardless of the treatment actually received.

Continuous variables were analysed by Student's *t* test or the Mann–Whitney test, and categorical variables by χ^2 test or Fisher's exact test. Statistical significance was set at the 0.050 level. The R environment (<http://www.r-project.org>) was used for all statistical analyses.

Results

Between June 1998 and December 2005, 617 patients were registered from five participating centres. Of these, 218 (35.3 per cent) were ineligible and excluded. A further 132 patients (21.4 per cent) were excluded because they did not accept the randomization and asked for extended surgery (Fig. 1).

Some 267 patients who fulfilled the eligibility criteria and gave informed consent were randomized to either D1 or D2 gastrectomy. Table 2 summarizes demographic, surgical and pathological characteristics of these patients. The groups were similar with respect to age, sex, tumour location and extent of resection.

About two-thirds of tumours were located in the distal part of the stomach. Only a quarter of patients required a total gastrectomy. Splenectomy was performed in only

12 of 31 patients assigned to a D2 total gastrectomy. The pancreas was removed in four of 66 D2 total gastrectomies.

The mean number of nodes removed from each patient was 32.8 (median 30), with a mean of 28.2 (median 25) nodes harvested during D1 gastrectomy and 37.3 (median 33) during a D2 procedure ($P < 0.001$). Lymph nodes were involved by tumour in 74 patients (56.5 per cent) in the D2 arm and 68 (51.9 per cent) in the D1 arm ($P = 0.457$) (Table 2). Contamination occurred in 23 (17.3 per cent) of 133 patients with a D1 resection, and non-compliance in 45 (33.6 per cent) of the 134 patients submitted to a D2 dissection.

Surgical and non-surgical complications were documented (Table 3). The overall morbidity rate was 15.0 per cent (40 of 267 patients). Morbidity was higher in the D2 than in the D1 group (17.9 versus 12.0 per cent), but not significantly so ($P = 0.178$). The absolute risk difference (D2 minus D1) was 5.9 (95 per cent one-tail c.i. 0 to 13.0) per cent. The upper limit of the 95 per cent c.i. for this difference exceeded the predetermined non-inferiority boundary of 12 per cent.

Table 4 summarizes postoperative complications. Major cardiorespiratory complications were observed more often in the D2 arm, although the difference was not significant ($P = 0.507$, χ^2 test). There was a single duodenal stump leak (0.7 per cent) in the D2 arm.

Table 3 Short-term outcome

	D1 gastrectomy	D2 gastrectomy	<i>P</i> ‡	Total	<i>P</i> §
Non-surgical complications	10 of 133 (7.5)	16 of 134 (11.9)	0.223	26 of 267 (9.7)	
Surgical complications	9 of 133 (6.8)	10 of 134 (7.5)	0.825	19 of 267 (7.1)	
Total morbidity	16* of 133 (12.0)	24† of 133 (17.9)	0.178	40 of 267 (15.0)	
Total gastrectomy	6 of 35 (17)	6 of 31 (19)	0.186	12 of 66 (18)	0.401
Distal gastrectomy	10 of 98 (10)	18 of 103 (17.5)	0.137	28 of 201 (13.9)	
N0	8 of 63 (13)	12 of 57 (21)	0.220	20 of 120 (16.7)	0.563
N+	8 of 68 (12)	12 of 74 (16)	0.446	20 of 142 (14.1)	
< 70 years	10 of 88 (11)	15 of 99 (15)	0.447	25 of 187 (13.4)	0.259
≥ 70 years	6 of 45 (13)	9 of 35 (26)	0.159	15 of 80 (19)	
In-hospital mortality	4 of 133 (3.0)	3 of 134 (2.2)	0.722¶	7 of 267 (2.6)	
Total gastrectomy	3 of 35 (9)	2 of 31 (6)	1.000¶	5 of 66 (8)	0.011¶
Distal gastrectomy	1 of 98 (1)	1 of 103 (1.0)	1.000¶	2 of 201 (1.0)	
N0	1 of 63 (2)	1 of 57 (2)	1.000¶	2 of 120 (1.7)	0.459¶
N+	3 of 68 (4)	2 of 74 (3)	0.670¶	5 of 142 (3.5)	
< 70 years	2 of 88 (2)	2 of 99 (2)	1.000¶	4 of 187 (2.1)	0.431¶
≥ 70 years	2 of 45(4)	1 of 35 (3)	1.000¶	3 of 80 (4)	

Values in parentheses are percentages. *Three and †two patients had both surgical and non-surgical complications. ‡D1 *versus* D2 (χ^2 test except where indicated); §*versus* other variable in total group (χ^2 test except where indicated); ¶Fisher's exact test.

Table 4 Categorization of postoperative complications

	D1	D2
Non-surgical complications	10	16
Cardiac	3*	4
Pulmonary	6†	8
Ascites		1
Systemic infections		1*
Urinary retention	1	
Other		2*
Surgical complications	9	10
Pancreatic leakage	1	2
Peritoneal haemorrhage	2*§	2*§
Bleeding from anastomosis	1	
Duodenal leakage		1‡
Colonic perforation	1	
Abdominal abscess	3†‡	2*
Intestinal ischaemia	1	
Acute pancreatitis		2§
Gastric atonia		1

*One and †two of whom had both surgical and non-surgical complications; ‡one and §two of whom required operation.

Three patients in the D1 group and four in the D2 group required reoperation ($P = 1.000$).

For D1 resections, patients who had a contaminated procedure experienced higher total morbidity (four (17.4 per cent) of 23) than those who had an uncontaminated procedure (12 (10.9 per cent) of 110), whereas for D2 resections morbidity was lower in patients with compliance (15 (16.9 per cent) of 89) than in those with non-compliance (nine (20.0 per cent) of 45 patients).

The overall in-hospital mortality rate was 2.6 per cent (seven of 267 patients), 3.0 per cent (four of 133 patients)

in the D1 arm and 2.2 per cent (three of 134 patients) in the D2 arm ($P = 0.722$) (Table 3). The level of lymph node dissection did not adversely affect postoperative morbidity and mortality even after stratification by extent of resection (total *versus* distal), nodal involvement and age.

There was a higher in-hospital mortality rate after total gastrectomy compared with distal gastrectomy (8 *versus* 1.0 per cent; $P = 0.011$) (Table 3).

The mean hospital stay after surgery was 12.8 (median 12, range 8–78) days for patients in the D1 group and 13.1 (median 11, range 7–39) days for those in the D2 group ($P = 0.732$). Splenectomy also had no effect on length of hospital stay: median 11 (range 8–78) days in the group without splenectomy *versus* 12 (range 9–22) days with splenectomy ($P = 0.413$).

Discussion

A variety of problems were encountered during patient enrolment to this trial. One-fifth of registered patients did not accept the randomization because of a perception that D2 gastrectomy might be associated with better survival. Several surgeons who participated in the authors' first trial¹⁷, having improved their skills in D2 gastrectomy, did not join this RCT owing to reluctance to perform a less radical operation that might have less chance of cure, even though evidence at the time was inconclusive¹⁶. Of the nine centres (18 surgeons) from the previous trial, only five (ten surgeons) joined the new randomized study. With accumulating evidence, increasing reluctance on the part of the surgeons to randomize patients slowed recruitment

such that the study was stopped after 6 years of recruitment, slightly below the accrual target.

The finding that D2 resection did not significantly increase the rate of complications compared with D1 gastrectomy is not in accordance with the outcome of either the Dutch Gastric Cancer Group⁷ or the UK Medical Research Council⁹ trials, or with the recent RCT from Taiwan²⁷. All three reported higher complication rates after D2 compared with D1 resection. Overall, the rate of complications after D2 dissections was much lower than that in European series and close to those reported from Japanese reference centres²⁸.

The rate of suture-line leakage was also low in the present series, with only one duodenal stump leak in a patient having a D2 resection and no anastomotic dehiscence in either group. These results are similar to those reported from Japan in a recent RCT^{2,28}. These figures are substantially better than those in the two earlier European randomized trials, of 9 per cent⁷ and 13 per cent⁹. More than 50 per cent of cancers in the present study were distal and only 10 per cent were proximal gastric cancers. Consequently, total gastrectomy was performed in only one-quarter of patients. As distal gastrectomy is reported to have fewer complications and reduced mortality compared with total resection, this and the avoidance of routine splenopancreatectomy during total D2 gastrectomy, may partly explain the low morbidity.

Despite strict quality control, contamination (see definitions in Methods) was identified in 17.3 per cent of D1 and non-compliance in 33.6 per cent of D2 procedures. These protocol violations may potentially be responsible, in the intention-to-treat analysis, for an underestimation of the difference in morbidity between the two arms. However, significant underestimation appears unlikely because, although patients having D1 gastrectomy with contamination had a higher total morbidity rate than those without contamination (17.4 *versus* 10.9 per cent), for D2 gastrectomy the morbidity rate was lower for patients with compliance than for those with non-compliance (16.9 *versus* 20.0 per cent).

Mortality rates associated with radical resection of stomach cancer have improved greatly owing to more rigorous patient selection and developments in surgical technique and postoperative care^{3,13}. The growing surgical interest in gastric cancer in Western countries has resulted in an increase in the numbers of surgeons trained in specialist Far East centres, as well as centralization of this type of surgery in high-volume hospitals^{29–31}.

In the present trial, the mortality rate after D2 resection was 2.2 per cent, similar to that of D1 gastrectomy (3.0 per cent; $P = 0.722$) and much lower than values of

10 and 13 per cent in the previous European randomized trials^{7,9}.

The short-term and survival results of the UK⁹ and Dutch⁷ RCTs did not support the routine use of D2 gastrectomy for Western patients. Although the observed difference in total morbidity between groups was small and not statistically significant in the present series, the upper limit of the 95 per cent c.i. for this difference marginally exceeded the predetermined non-inferiority boundary of 12 per cent, possibly due to the lower than anticipated statistical power (75 per cent rather than 80 per cent). The results suggest that in specialized centres morbidity and mortality rates following D2 procedures are much lower than shown in previously published RCTs and similar to Japanese figures. D2 dissection, in an appropriate setting, is a safe option for the radical management of gastric cancer in Western patients.

Collaborators

Members of the IGCSG are: Maurizio Degiuli, Mitsuru Sasako, Alessandro Vendrame, Mariano Tomatis, Dario Andreone, Mauro Garino, Fabrizio Rebecchi, Donatella Scaglione, Luca Viganò, Lorenzo Capussotti, Gian Ruggero Fronda, Locatelli Luigi, Paolo Mello Teggia, Mario Morino, Fabio Calvo and Antonio Ponti.

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