**Randomized clinical trial comparing survival after D1 or D2 gastrectomy for gastric cancer**

# Randomized clinical trial comparing survival after D1 or D2 gastrectomy for gastric cancer

Degiuli M[1], Sasako M, Ponti A, Vendrame A, Tomatis M, Mazza C, Borasi A, Capussotti L, Fronda G, Morino M; Italian Gastric Cancer Study Group.

## Collaborators (7)

Ferri V, Rebecchi F, Garino M, Viganò L, Scaglione D, Locatelli L, Mello Teggia P.

## Author information


- [1]Division of Surgical Oncology, Azienda Ospedaliera Citta della Salute e della Scienza di Torino, Turin, Italy.
- the Italian Gastric Cancer Study Group


## Abstract


### Background

It is still unclear whether D2 lymphadenectomy improves the survival of patients with gastric cancer and should therefore be performed routinely or selectively. The aim of this multicentre randomized trial was to compare D2 and D1 lymphadenectomy in the treatment of gastric cancer.

### Methods

Between June 1998 and December 2006, patients with gastric adenocarcinoma were assigned randomly to either D1 or D2 gastrectomy. Intraoperative randomization was implemented centrally by telephone. Primary outcome was overall survival; secondary endpoints were disease-specific survival, morbidity and postoperative mortality.

### Results

A total of 267 eligible patients were allocated to either D1 (133 patients) or D2 (134) resection. Morbidity (12·0 *versus* 17·9 per cent respectively; $P = 0·183$) and operative mortality (3·0 *versus* 2·2 per cent; $P = 0·725$) rates did not differ significantly between the groups. Median follow-up was 8·8 (range 4·5–13·1) years for surviving patients and 2·4 (0·2–11·9) years for those who died, and was not different in the two treatment arms.

There was no difference in the overall 5-year survival rate (66·5 *versus* 64·2 per cent for D1 and D2 lymphadenectomy respectively; $P = 0·695$). Subgroup analyses showed a 5-year disease-specific survival benefit for patients with pathological tumour (pT) 1 disease in the D1 group (98 per cent *versus* 83 per cent for the D2 group; $P = 0·015$), and for patients with pT2–4 status and positive lymph nodes in the D2 group (59 per cent *versus* 38 per cent for the D1 group; $P = 0·055$).

Conclusion

No difference was found in overall 5-year survival between D1 and D2 resection. Subgroup analyses suggest that D2 lymphadenectomy may be a better choice in patients with advanced disease and lymph node metastases. Registration number: ISRCTN11154654 (http://www.controlled-trials.com).

## Introduction

D2 gastrectomy is considered the standard surgical treatment for locally advanced gastric cancer in Eastern countries[1][2][3][4][5]. In the Western world, this is still a matter of extensive debate[6-9]. Data from a previous Italian Gastric Cancer Study Group (IGCSG) phase II trial on D2 gastrectomy showed low morbidity and mortality rates, and good survival after pancreas-preserving D2 dissection when performed in high-volume, experienced centres with strict quality control[10, 11]. Following on from this phase II trial, a subsequent multicentre randomized clinical trial (RCT) (IGCSG-R01, registration number ISRCTN11154654) was designed to compare the effect of D2 *versus* D1 resection on long-term outcomes. Preliminary data[12, 13] from IGCSG-R01 have confirmed that, in specialized centres, morbidity and mortality rates following D2 procedures are much lower than those found in previously published RCTs[6, 7], and similar to Japanese figures[1][2][3][4][5], and that D2 dissection is a safe option for the radical management of gastric cancer in Western patients. The influence of extended lymph node (LN) dissection on long-term survival was also addressed in this study.

## Methods

The conduct of the IGCSG-R01 RCT has been reported previously[12, 13].

### Eligibility and assessment of curability

The trial was approved by the medical ethics committees of each participating hospital. Patients were enrolled if they had histologically proven gastric cancer, judged before surgery to be potentially curable, were aged less than 80 years, and were in an adequate physical condition with no serious co-morbid cardiorespiratory or renal disease precluding safe D2 dissection. Patients were excluded if they had undergone previous gastric surgery, or had previous or coexisting cancer outside the stomach. Emergency surgery was also an exclusion criterion.

### Staging laparotomy and treatment groups

After preoperative investigation and informed consent, all registered patients underwent laparotomy and staging to exclude unresectable and/or potentially incurable gastric cancer. If no unresectable or incurable disease was found, a D1 or D2 procedure was done, with the operation determined by intraoperative randomization. The study was performed following the guidelines for standardization of surgical treatment and pathological evaluation of the Japanese Research Society for Gastric Cancer[14]. In addition, the Japanese Classification of Gastric Carcinoma (second English edition)[15] was adopted to provide a common language among participating centres for anatomical definition of LN stations and their grouping, and for the description of extent of LN dissection and gastric resection in both arms. *Table S1* (supporting information) summarizes the allocation of LN stations in D1 (removal of level 1) and D2 (removal of levels 1 and 2) procedures, according to gastric cancer location.
Splenopancreatectomy was not considered a standard part of D2 total gastrectomy; the pancreas was removed only when it was suspected to be invaded by the gastric cancer.
Distal gastrectomy was performed when the proximal edge of the tumour was more than 3 cm from the cardia in early gastric cancer and in Bormann type 1 and 2 locally advanced gastric cancer. Total gastrectomy was deemed appropriate when these conditions were not met and, in addition, when the tumour was located close to the greater curvature, beyond Demel's point, as well as in patients with linitis plastica[15].
The pathological classification used for all analyses was the fifth edition of the International Union Against Cancer/American Joint Committee on Cancer tumour node metastasis (TNM) staging system.
No patient received chemotherapy before or after surgery, until recurrence. Postoperative mortality was defined as death within 30 days after surgery or during the hospital stay.

## Quality control

Strict quality control measures for surgery, LN removal, pathology and patient follow-up were implemented and monitored.
Only surgeons who had already participated in the previous IGCSG phase II trial were allowed to recruit patients, to avoid bias generated by lack of experience with the D2 technique.
Regular meetings were organized by the study's principal investigator for discussion of eligibility, technical aspects and logistical problems.
Numbers and locations of LNs removed were monitored and compared as required by the International Gastric Cancer Association (IGCA) guidelines[15]. Contamination was defined as pathological proof of inclusion of more than two LN stations that should not have been removed. Non-compliance was defined as absence in the specimen of more than two LN stations that should have been excised[16].

## Statistical analysis

The trial was designed as a multicentre, parallel, individually randomized, superiority trial with balanced randomization. The size of the study was determined by the primary outcome – the overall survival rate. To detect (with 80 per cent power) an absolute increase in the 5-year survival rate of 15 per cent (from 30 per cent after D1 resection to 45 per cent after D2 resection), the sample size was originally set at 160 patients per arm[12]. Survival estimates were set according to the literature and based on the IGCSG phase II study of patients having D2 lymphadenectomy[7, 9, 10]. Enrolment was terminated because of slow accrual 8 years after trial inception. Taking into account the long accrual and duration of follow-up, the trial retained a statistical power of 83 per cent (two-sided $\alpha = 0{\cdot}05$, absolute survival difference 15 per cent). Treatment allocation was performed using random permuted blocks with fixed numbers ($n = 10$) per block, stratified by surgical unit, with the sequence generated by a random-number table. The randomization procedure was centralized and the size of the blocks concealed to the surgeons. Patients who fulfilled the eligibility criteria during laparotomy were registered by telephone contact with the randomization centre. Each surgical unit maintained a sequential register of randomized patients. Patients and care providers could not be blinded to the surgical treatment allocation. Outcome was assessed blind of treatment

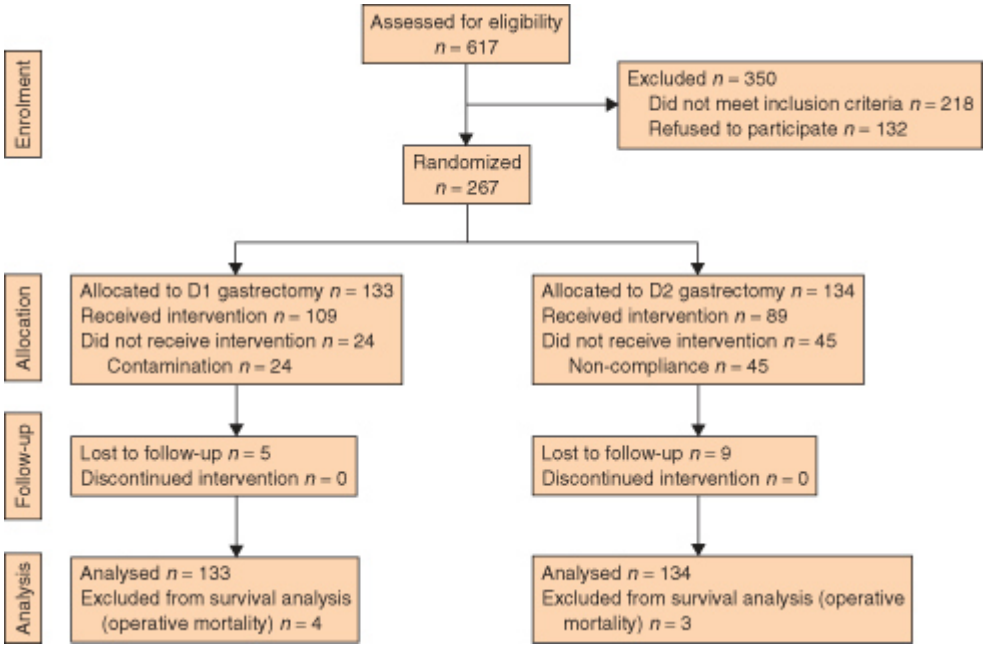
allocation by follow-up for mortality and cause of death, and was performed by the Piedmont Cancer Registry.

A safety interim analysis[12], foreseen in the protocol for assessment of postoperative morbidity, was performed on patients recruited until December 2002. The Kaplan–Meier method[17] was employed to estimate overall (OS) and disease-specific (DSS) survival, using the log rank test[18] to evaluate survival curves. Potential prognostic factors (age, pathological tumour (pT) category, pathological node (pN) category and type of resection) were entered into a Cox multivariable regression model[19]. Variables deemed clinically important were included in the model, with no exclusions on the basis of the results of the univariable analysis. All analyses were undertaken on an intention-to-treat basis. The Shapiro–Francia normality test was used to verify whether variables were normally distributed. Continuous and categorical outcome variables were analysed with Student's *t* test (or Mann–Whitney *U* test) and the $\chi[2]$ test (or Fisher's exact test) respectively. Statistical significance was set at the 0·050 level. The R environment (http://www.rproject.org) was used for statistical analyses. Planned analyses in the original trial protocol were the analyses of survival in the two trial arms. Subgroup analyses were performed later and should be interpreted with caution as no adjustment for multiple testing was applied.

The end of follow-up was set at 31 December 2010, when the predefined target would be met of at least 95 per cent of recruited patients having at least 5 years of follow-up. Data were collected prospectively and patients were followed up every 4 months until December 2010.

## Results

The Consolidated Standards of Reporting Trials (CONSORT) diagram is shown in *Fig*. 1. Between June 1998 and December 2006, 617 patients were assessed for eligibility by ten surgeons in five centres. Of these patients, 218 were ineligible and 132 did not provide informed consent, leaving 267 patients to be randomly assigned to treatment: 133 to the D1 and 134 to the D2 resection arm. The two groups were balanced with respect to age, sex, tumour site, extent of resection and pathology (*Table* 1). The median number of LNs removed was significantly higher in the D2 arm (25 *versus* 33 for D1; $P < 0{\cdot}001$).




## Figure 1.

- Open in figure viewer
- Download Powerpoint slide

CONSORT diagram for the study

Table 1. Characteristics of patients randomized to D1 or D2 resection

| | **D1 resection (*n* = 133)** | **D2 resection (*n* = 134)** | **Overall (*n* = 267)** | ***P*c** |
|---|---|---|---|---|
| Median (range) age (years) | 64 (30–81) | 62 (22–87) | 63 (22–87) | 0·187f |
| Patients aged ≥ 70 years | 45 (33·8) | 35 (26·1) | 80 (30·0) | 0·169 |
| Sex ratio (M : F) | 67 : 66 | 64 : 70 | 131 : 136 | 0·669 |
| Location of gastric cancer | | | | 0·946d |
| Lower third | 87 (65·4) | 90 (67·2) | 177 (66·3) | |
| Middle third | 32 (24·1) | 30 (22·4) | 62 (23·2) | |
| Upper third | 13 (9·8) | 13 (9·7) | 26 (9·7) | |
| Diffuse | 1 (0·8) | 0 (0) | 1 (0·4) | |
| Stump | 0 (0) | 1 (0·7) | 1 (0·4) | |
| Type of resection | | | | 0·547 |

1. Values in parentheses are percentages unless indicated otherwise. pT, pathological tumour; TNM, tumour node metastasis; pN, pathological node; LN, lymph node.
2. [a]pT1 *versus* other;
3. [b]stage IA *versus* other.
4. [c]$\chi^2$ test unless indicated otherwise;
5. [d]Fisher's exact test;
6. [e]Student's *t* test;
7. [f]Mann–Whitney *U* test.

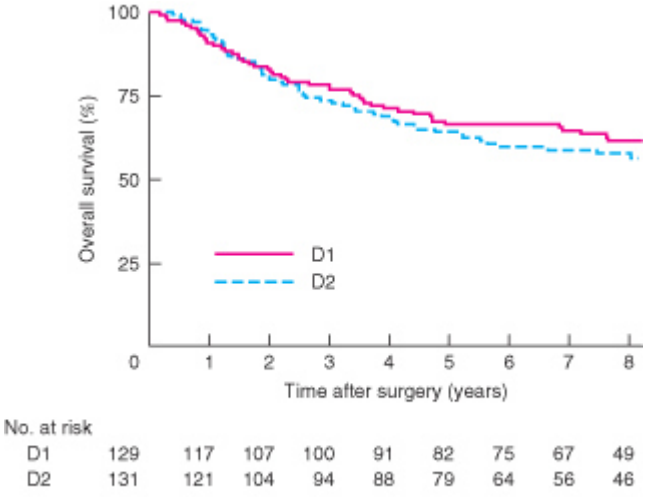
| | D1 resection (*n* = 133) | D2 resection (*n* = 134) | Overall (*n* = 267) | *P*c |
|---|---|---|---|---|
| Total gastrectomy | 35 (26·3) | 31 (23·1) | 66 (24·7) | |
| Distal gastrectomy | 98 (73·7) | 103 (76·9) | 201 (75·3) | |
| Splenectomy | 9 (6·8) | 12 (9·0) | 21 (7·9) | 0·507 |
| Distal pancreatectomy plus splenectomy | 2 (1·5) | 2 (1·5) | 4 (1·5) | 0·992d |
| pT category | | | | 0·224 |
| pT1 | 49 (36·8) | 39 (29·1) | 88 (33·0) | 0·191a |
| pT2 | 42 (31·6) | 55 (41·0) | 97 (36·3) | |
| pT3 | 40 (30·1) | 37 (27·6) | 77 (28·8) | |
| Unknown | 2 (1·5) | 3 (2·2) | 5 (1·9) | |
| TNM stage | | | | 0·047 |
| IA | 41 (30·8) | 25 (18·7) | 66 (24·7) | 0·021b |
| IB | 20 (15·0) | 31 (23·1) | 51 (19·1) | |
| II | 24 (18·0) | 33 (24·6) | 57 (21·3) | |
| IIIA | 20 (15·0) | 18 (13·4) | 38 (14·2) | |
| IIIB | 16 (12·0) | 9 (6·7) | 25 (9·4) | |
| IV | 9 (6·8) | 15 (11·2) | 24 (9·0) | |
| Unknown | 3 (2·3) | 3 (2·2) | 6 (2·2) | |
| pN category | | | | 0·457d |
| pN0 | 63 (47·4) | 57 (42·5) | 120 (44·9) | |
| pN+ | 68 (51·1) | 74 (55·2) | 142 (53·2) | |
| Unknown | 2 (1·5) | 3 (2·2) | 5 (1·9) | |
| pN1 | 32 (24·1) | 43 (32·1) | 75 (28·1) | |
| pN2 | 28 (21·1) | 20 (14·9) | 48 (18·0) | 0·293 |
| pN3 | 8 (6·0) | 11 (8·2) | 19 (7·1) | |
| No. of LNs dissected | | | | |
| Mean | 28 | 37 | 33 | < 0·001e |
| Median (range) | 25 (2–104) | 33 (11–124) | 30 (2–124) | < 0·001f |

Contamination occurred in 24 patients (18·0 per cent) undergoing D1 gastrectomy, and non-compliance was observed in 45 patients (33·6 per cent) having a D2 resection. There was no significant difference between the groups with regard to morbidity (16 (12·0 per cent) of 133 patients after the D1 procedure *versus* 24 (17·9 per cent) of 134 after D2; $P$ = 0·183) and operative mortality (4 (3·0 per cent) *versus* 3 (2·2 per cent) respectively; $P$ = 0·725) rates. Seven patients who died within 30 days of surgery were excluded from the survival analysis. Seventy-nine patients died from progression of gastric cancer and 25

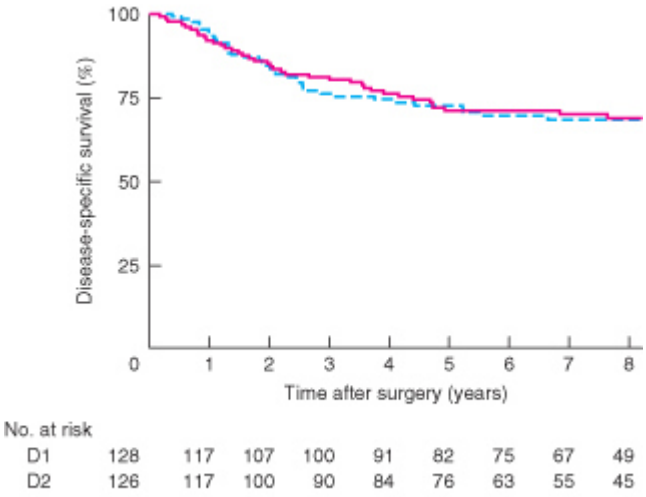
from causes unrelated to the cancer; 150 patients were alive at the end of follow-up without cancer relapse (*Table S2*, supporting information).

The median length of follow-up was 8·8 (range 4·5–13·1) years for surviving patients and 2·4 (0·2–11·9) years for patients who died, and was similar in the two arms (*Table S3*, supporting information).

Five-year OS and DSS rates for the whole cohort were 65·4 and 71·8 per cent respectively. The 5-year OS rate was 66·5 per cent for D1 and 64·2 per cent for D2 gastrectomy (difference −2·3 (95 per cent confidence interval (c.i.) −14·0 to 9·3) per cent; $P = 0·695$) (*Fig*. 2). The 5-year DSS rate was 71·0 per cent for D1 and 72·6 per cent for D2 gastrectomy (difference 1·6 (−9·8 to 12·9) per cent).




**a** Overall survival




**b** Disease-specific survival

**Figure 2.**

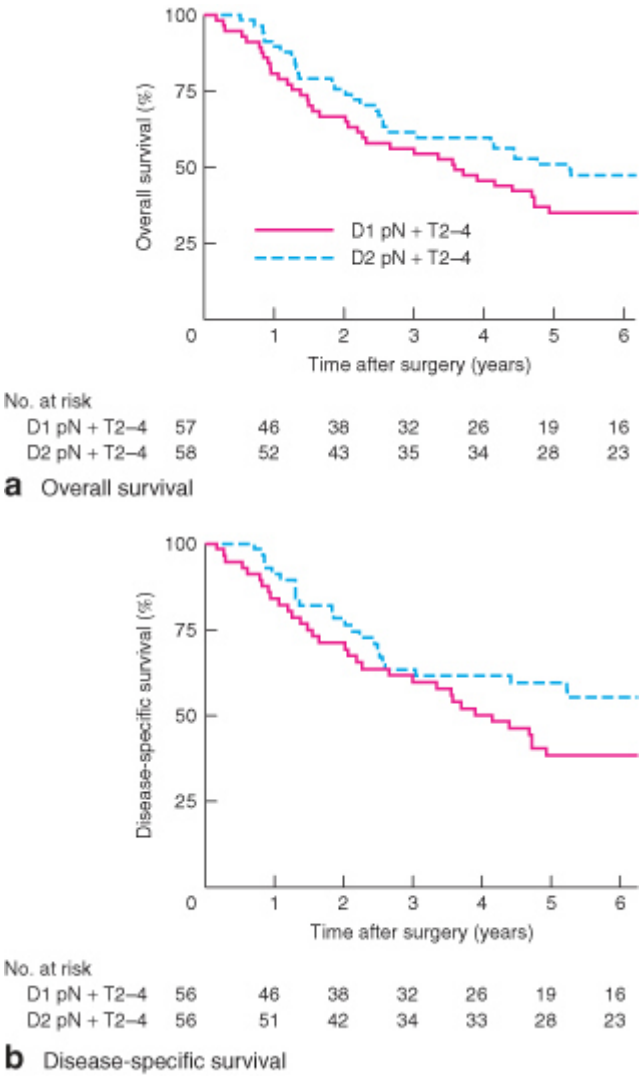
- Open in figure viewer
- Download Powerpoint slide

Kaplan–Meier curves of **a** overall and **b** disease-specific survival for patients treated by D1 or D2 gastrectomy with curative intent. **a** Hazard ratio (HR) 1·19, 95 per cent confidence interval 0·82 to 1·73 ($P$ = 0·358, log rank test). **b** HR 1·02, 0·66 to 1·59 ($P$ = 0·916, log rank test)

Tumours were stratified by depth of invasion into two subgroups, pT1 and pT2–4 categories (*Table S4*, supporting information). For pT1, the 5-year OS rate was 92 per cent in the D1 and 81 per cent in the D2 arm (difference −11 (95 per cent c.i. −26 to −4) per cent). For pT2–4 tumours, 5-year OS rates were 51 and 59 per cent respectively (difference 8 (−8 to 22) per cent) in the D1 and D2 arms. For pT1 tumours, the 5-year DSS rate was 98 per cent after D1 and 83 per cent after D2 gastrectomy, with a statistically significant difference (−15 (−28 to −2) per cent) in favour of D1 resection ($P$ = 0·015). For patients with pT2–4 tumours, the 5-year DSS rate was 55 and 69 per cent respectively (difference 14 (−1 to 29) per cent; $P$ = 0·143), with a non-significant survival advantage in favour of D2 resection (*Fig. S1*, supporting information).

LN status was not known for five of the 267 patients enrolled in the trial. Of the 255 patients with known LN status (seven patients who died within 30 days were excluded), 138 (54·1 per cent) had pathologically confirmed node involvement. In patients with N+ tumours, the 5-year OS rate was 43 per cent in the D1 and 54 per cent in the D2 arm. The 95 per cent c.i. of the 11 per cent difference (−5 to 28 per cent) suggests a non-significant survival advantage of up to 28 per cent for D2 resection. Similarly, for the 5-year DSS rate (46 and 61 per cent for D1 and D2 respectively), the difference was 15 (−2 to 32) per cent (*Fig. S2*, supporting information).

In 115 patients with pT2–4 tumours with LN involvement, the 5-year OS rate was 35 per cent in the D1 arm and 51 per cent in the D2 arm (difference 16 (95 per cent c.i. −2 to 34) per cent) (*Fig*. 3). The 5-year DSS rate was 38 per cent for D1 and 59 per cent for D2 gastrectomy, with a nearly significant difference of 21 (3 to 40) per cent; $P$ = 0·055).




## Figure 3.

- Open in figure viewer
- Download Powerpoint slide

Kaplan–Meier curves of **a** overall and **b** disease-specific survival for patients with pathological tumour (pT) 2–4 status and positive pathological lymph node status (pN+) treated by D1 or D2 gastrectomy. **a** Hazard ratio (HR) 0·74, 95 per cent confidence interval 0·47 to 1·17 ($P$ = 0·193, log rank test). **b** HR 0·63, 0·36 to 1·06 ($P$ = 0·078, log rank test) Univariable analysis of the 5-year DSS rate showed a survival benefit for patients aged 70 years or more who had a D1 gastrectomy (75 *versus* 51 per cent for D2 resection; $P$ = 0·018). Although not statistically significant, univariable analysis suggested a benefit in 5-year survival for patients with positive LNs (difference 15 per cent), pN1 category (17 per cent), pathological TNM stage II (14 per cent) and IIIA (32 per cent) who had D2 resection (*Table* 2).

Table 2. Univariable analysis of survival rates

| | Total no. of patients | D1 resection (*n* = 129) | | D2 resection (*n* = 131) | | *P*b |
|---|---|---|---|---|---|---|
| | | No. of patients | 5-year DSS (%) | No. of patients | 5-year DSS (%) | |
| Age (years) | | | | | | |
| 0–69 | 183 | 87 | 69 | 96 | 79 | 0·208 |
| ≥ 70 | 77 | 42 | 75 | 35 | 51 | 0·018 |
| pT category | | | | | | |
| pT1 | 87 | 49 | 98 | 38 | 83 | 0·019 |
| pT2 | 96 | 41 | 63 | 55 | 76 | 0·399 |
| pT3 | 72 | 37 | 44 | 35 | 57 | 0·310 |
| Unknown | 5 | 2 | 0 | 3 | 0 | – |
| LN status | | | | | | |
| Negative | 117 | 62 | 97 | 55 | 90 | 0·162 |
| Positive | 138 | 65 | 46 | 73 | 61 | 0·192 |
| Unknown | 5 | 2 | 0 | 3 | 0 | – |
| pN category | | | | | | |
| pN0 | 117 | 62 | 97 | 55 | 90 | 0·162 |
| pN1 | 74 | 31 | 63 | 43 | 80 | 0·233 |
| pN2–3 | 64 | 34 | 30 | 30 | 37 | 0·655 |
| Unknown | 5 | 2 | 0 | 3 | 0 | – |
| TNM stage | | | | | | |
| IA | 65 | 41 | 98 | 24 | 95 | 0·554 |
| IB | 50 | 19 | 100 | 31 | 83 | 0·066 |
| II | 56 | 24 | 71 | 32 | 85 | 0·601 |
| IIIA | 37 | 19 | 39 | 18 | 71 | 0·118 |
| IIIB + IV | 47 | 24 | 22 | 23 | 26 | 0·773 |
| Unknown | 5 | 2 | 0 | 3 | 0 | – |
| Type of resection | | | | | | |
| Distal | 198 | 97 | 81 | 101 | 76 | 0·180 |
| Total | 62 | 32 | 41 | 30 | 63 | 0·131 |
| Overall | 260a | 129 | 71·0 | 131 | 72·6 | 0·916 |

1. [a]Seven patients who died within 30 days of operation were excluded from the analysis. DSS, disease-specific survival; pT, pathological tumour; LN, lymph node; pN, pathological node; TNM, tumour node metastasis.
2. [b]Log rank test.

In multivariable analysis, D2 dissection was not an independent prognostic factor (hazard ratio (HR) 0·90, 95 per cent c.i. 0·56 to 1·43; $P = 0·647$). A significantly worse survival was

observed in patients aged 70 years or more ($P$ = 0·033), with pT category greater than 2 ($P$ = 0·029) and LN metastases ($P$ < 0·001). Multivariable analysis also showed that total gastrectomy was associated with a poorer DSS than distal gastrectomy (HR 1·93, 1·19 to 3·13; $P$ = 0·008) (*Table* 3).

Table 3. Cox multivariable regression analysis of survival rates

| | **Hazard ratio** | ***P*** |
|---|---|---|
| D1 (reference) *versus* D2 gastrectomy | 0·90 (0·56, 1·43) | 0·647 |
| Age 0–69 (reference) *versus* ≥ 70 years | 1·03 (1·00, 1·05) | 0·033 |
| pT category | | |
| pT1 | 1·00 (reference) | |
| pT2 | 1·67 (0·75, 3·72) | 0·207 |
| pT3 | 2·49 (1·10, 5·64) | 0·029 |
| pN category | | |
| pN0 | 1·00 (reference) | |
| pN1 | 3·74 (1·77, 7·88) | < 0·001 |
| pN2 | 6·84 (3·14, 14·90) | < 0·001 |
| pN3 | 18·60 (7·71, 44·87) | < 0·001 |
| Distal (reference) *versus* total gastrectomy | 1·93 (1·19, 3·13) | 0·008 |

1. Values in parentheses are 95 per cent confidence intervals. pT, pathological tumour; pN, pathological node.

## Discussion

The present findings, based on 5-year follow-up data from the IGCSG-R01 RCT, show that D2 gastrectomy is not associated with improved overall survival. Subgroup analyses suggest that a benefit may exist for extended surgery in patients with locally advanced gastric cancer and positive nodes. In this trial, overextensive node dissection (contamination) during D1 and a higher rate of stage IA disease in the D1 arm, and of stage IV in the D2 arm, seem to have nullified the effect of correct extended node removal. Japanese authors[1, 2] have reported impressive 5-year survival rates after extended LN dissection for gastric cancer, although these results have often been criticized, mainly because they were not obtained from RCTs. The first RCT[3] reporting a significant survival benefit for extended LN dissection was from Taiwan. In this single-institution RCT comparing 110 D1 with 111 D3 procedures, intention-to-treat analysis showed the 5-year overall survival rate to be 59·5 per cent for D3 and 53·6 per cent for the D1 arm ($P$ = 0·002).

European trials[6, 7] to detect a survival benefit for D2 over D1 resection were undertaken by British and Dutch groups in the late 1990 s. Unfortunately, both trials documented increased morbidity and mortality after the extended procedure while failing to demonstrate a survival benefit for D2 resection at 5 years[6, 7] and 11 years[8]. However, in subgroup analysis, patients with N2 status submitted to D2 resection tended to have better survival (19 *versus* 0 per cent for D1 resection)[8]. Further, after a median follow-up of 15 years, D2 resection was associated with lower locoregional relapse and gastric cancer-related mortality rates than D1[9].

In the present trial, the 5-year OS rate was 65·4 per cent and the DSS rate was 71·8 per cent. This high OS rate is probably related to the unexpectedly high proportion of pT1 and pT2 tumours, and may also result from refined staging due to extensive LN dissection in the D1 arm. The absolute number of LNs harvested during a D1 procedure was excessive, compared with that in previous reports[4, 6-9, 20, 21]. Thus, although the difference in harvested LNs between the D1 and D2 arms was still significant, this may have confounded the outcome. A correct D1 dissection usually collects about 15 LNs, and a D2 procedure should harvest at least 25 nodes. Thus, the mean of 28 LNs removed after D1 resection reflects the problem of contamination. Contamination occurred as a result of incorrect harvesting of LN station numbers 7 and 8 during the D1 procedure; as all participating surgeons had acquired sufficient experience in D2 dissection in the previous phase II trial[10], they may have had difficulty in keeping to the D1 rules. In addition, all surgeons should have dissected the LN stations from the fresh specimen at the end of the operation, but detailed quality control over this procedure was missing, and some surgeons confirmed they had not done this routinely[20-22].

This trial did not use preoperative or postoperative chemotherapy and was, in fact, conducted before medical treatment became standard practice.

In the intention-to-treat analysis in the present trial, no long-term overall survival advantage was documented after extended LN dissection. Contamination may explain the absence of benefit of the more extended dissection. Moreover, the presence of more early tumours in the D1 arm and more advanced tumours in the D2 arm may explain the observed findings. The absence of a survival benefit after D2 dissection was also observed for DSS (HR 1·02, 95 per cent c.i. 0·66 to 1·59).

For locally advanced gastric cancer (pT2–4), a trend towards improvement in both OS and DSS was observed for the more extensive dissection. This trend was confirmed in further subgroup analyses of tumours with positive LNs. Patients in the D2 resection group with

both pT2–4 status and LN metastases (pN+) had a fairly pronounced tendency to improved DSS (almost a statistically significant difference of 21 per cent compared with D1 resection at 5 years).

Preoperative staging of early and advanced gastric cancer is now possible in most institutions. Therefore, a population at high risk for relapse can be identified before surgery, and may benefit subsequently from more extensive dissection.

The results of subgroup analyses in this trial should be interpreted with caution as it was not powered for such analyses; the outcomes should be taken as hypothesis-generating.

The main factor influencing the survival of patients with pT1 status after D1 and D2 resection was probably the difference in LN metastasis in the two trial arms. In fact, there was a major difference in LN metastases between the two groups of 23 per cent (16 *versus* 39 per cent in the D1 and D2 arms respectively) in patients with pT1 status. The LN metastasis rate of 39 per cent in the D2 arm was unusually high in the early gastric cancer subgroup.

Irrespective of the type of dissection performed (D1 or D2), the present data show an increased HR for patients aged 70 years or above, for those with advanced tumour stage (pT3) and with metastasis in regional nodes. The data also suggest that total gastrectomy is associated with a worse prognosis than distal resection, perhaps because of the risk of serious postoperative complications. Anastomotic leakage and abdominal infection, as well as postoperative mortality, are more common after oesophagojejunal anastomosis compared with gastrojejunal anastomosis, as has been observed previously by the present authors[13]. In addition, patients undergoing total gastrectomy in the present trial had more advanced disease, and this may also have contributed to their worse progress.

Current IGCA guidelines for the extent of resection are clear, and surgeons should follow these indications strictly and avoid total gastrectomy whenever it is not mandatory. The results of this trial are consistent with worldwide changes in the management of gastric cancer, of targeting the treatment to the tumour and the individual patient.

## Collaborators

Members of the Italian Gastric Cancer Study Group are: V. Ferri, F. Rebecchi (Digestive, Colorectal and Oncological Surgery, University of Turin, Turin, Italy), M. Garino (Division of General Surgery, Ospedale E. Agnelli, Pinerolo, Italy), L. Viganò (Hepato-Pancreato-Biliary and Digestive Surgery, Ospedale Mauriziano Umberto I, Turin, Italy), D. Scaglione

(Division of General Surgery, Ospedale Martini, Turin, Italy), L. Locatelli (Division of General Surgery, Maria Pia Hospital (GMV), Turin, Italy), P. Mello Teggia (Division of General Surgery, Ospedale S Luigi Gonzaga, Orbassano, Italy).

## REFERENCES


- 1*Kinoshita T, Maruyama K, Sasako M, Okajima K. Treatment results of gastric cancer patients: Japanese experience. In Gastric Cancer, Nishi M, Ichikawa H, Nakajima T, Maruyama K, Tahara E (eds). Springer: Tokyo, 1993; 319–330.*

- 2*Fujii M, Sasaki J, Nakajima T. State of the art in the treatment of gastric cancer: from the 71st Japanese Gastric Cancer Congress. Gastric Cancer 1999; 2: 151–157.*

- 3*Wu CW, Hsiung CA, Lo SS, Hsieh MC, Chen JH, Li AF et al. Nodal dissection for patients with gastric cancer: a randomised controlled trial. Lancet Oncol 2006; 7: 309–315.*

- 4*Sasako M, Sano T, Yamamoto S, Kurokawa Y, Nashimoto A, Kurita A et al.; Japan Clinical Oncology Group. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. N Engl J Med 2008; 359: 453–462.*

- 5*Gotoda T, Iwasaki M, Kusano C, Seewald S, Oda I. Endoscopic resection of early gastric cancer treated by guideline and expanded National Cancer Centre criteria. Br J Surg 2010; 97: 868–871.*

- 6*Bonenkamp JJ, Sasako M, Hermans J, van de Velde CJ, Welvaart K, Songun I et al.; Dutch Gastric Cancer Group. Extended lymph-node dissection for gastric cancer. N Engl J Med 1999; 340: 908–914.*

- 7*Cuschieri A, Weeden S, Fielding J, Bancewicz J, Craven J, Joypaul V et al. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. Br J Cancer 1999; 79: 1522–1530.*

- 8*Hartgrink HH, van de Velde CJ, Putter H, Bonenkamp JJ, Klein Kranenbarg E, Songun I et al. Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized Dutch Gastric Cancer Group trial. J Clin Oncol 2004; 22: 2069–2077.*

- 9*Songun I, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol 2010; 11: 439–449.*

- 10*Degiuli M, Sasako M, Ponti A, Calvo F. Survival results of a multicentre phase II study to evaluate D2 gastrectomy for gastric cancer. Br J Cancer 2004; 90: 1727–1732.*

- 11*Maruyama K, Sasako M, Kinoshita T, Sano T, Katai H, Okajima K. Pancreas-preserving total gastrectomy for proximal gastric cancer. World J Surg 1995; 19: 532–536.*

- 12*Degiuli M, Sasako M, Calgaro M, Garino M, Rebecchi F, Mineccia M et al.; Italian Gastric Cancer Study Group. Morbidity and mortality after D1 and D2 gastrectomy for cancer: interim analysis of the Italian Gastric Cancer Study Group (IGCSG) randomised surgical trial. Eur J Surg Oncol 2004; 30: 303–308.*

- 13*Degiuli M, Sasako M, Ponti A; Italian Gastric Cancer Study Group. Morbidity and mortality in the Italian Gastric Cancer Study Group randomized clinical trial of D1 versus D2 resection for gastric cancer. Br J Surg 2010; 97: 643–649.*

- 14*Kajitani T. The general rules for the Gastric Cancer Study in Surgery and Pathology. Part 1. Clinical classification. Jpn J Surg 1981; 11: 127–139.*

- 15*Japanese Gastric Cancer Association. Japanese Classification of Gastric Carcinoma – 2nd English edition. Gastric Cancer 1998; 1: 10–24.*

- 16*Bunt TM, Bonenkamp HJ, Hermans J, van de Velde CJ, Arends JW, Fleuren G et al. Factors influencing noncompliance and contamination in a randomized trial of 'Western' (r1) versus 'Japanese' (r2) type surgery in gastric cancer. Cancer 1994; 73: 1544–1551.*

- 17*Bland JM, Altman DG. Survival probabilities (the Kaplan–Meier method). BMJ 1998; 317: 1572.*

- 18*Bland JM, Altman DG. The logrank test. BMJ 2004; 328: 1073.*

- 19*Cox DR. Regression models and life-tables. J R Stat Soc Ser B 1972; 34: 187–220.*

- 20*Siewert JR, Böttcher K, Roder JD, Busch R, Hermanek P, Meyer HJ. Prognostic relevance of systematic lymph node dissection in gastric carcinoma. German Gastric Carcinoma Study Group. Br J Surg 1993; 80: 1015–1018.*

- 21*Cozzaglio L, Doci R, Celotti S, Roncalli M, Gennari L. Gastric cancer: extent of lymph node dissection and requirements for a correct staging. Tumori 2004; 90: 467–472.*

- 22*Wagner PK, Ramaswamy A, Rüschoff 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: 825–827.*