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Abstract

Background

The extended lymphadenectomy (D2) was recently introduced in several guidelines as the optimal treatment for gastric cancer, based only on the 15-year follow-up results of the Dutch randomised trial, while the British Medical Research Council (MRC) study failed to demonstrate a survival benefit over the more limited D1 dissection. The Italian Gastric Cancer Study Group randomised controlled trial (RCT) was also undertaken to compare D1 versus D2 gastrectomy, and a tendency to improve survival in patients with advanced resectable disease (pT > 1N+) was documented despite negative results in the entire patient population. Now we present the 15-year follow-up results of survival and gastric cancer-related mortality.

Methods

Between June 1998 and December 2006, eligible patients with gastric cancer who signed the informed consent were randomised at 5 centres to either D1 or D2 gastrectomy. Intraoperative randomisation was implemented centrally by phone call. Primary outcome was overall survival (OS); secondary end-points were disease-specific survival, postoperative morbidity and mortality. Analyses were by intention to treat. Strict quality control measures for surgery, lymph node removal, pathology and patient follow-up were implemented and monitored. Registration number: ISRCTN11154654 (http://www.controlled-trials.com).

Findings

A total of 267 eligible patients were assigned to either D1 (133 patients) or D2 (134) procedure. Median follow-up time was 16.76 years. Analyses were done both in overall patient population and in pT > 1N+. One hundred patients (38.5) were alive without recurrence. OS and disease-specific survival (DSS) were very high in both arms. In overall population, they were not different between D1 and D2 arm (51.3% vs. 46.8% and 65% vs. 67% respectively, p = 0.31 and p = 0.94). DSS was significantly higher after D2 in pT > 1N+ patients (29.4% vs. 51.4%, p = 0.035). OS and DSS were better after D1 in patients older than 70 years (p = 0.003 and p = 0.006). DSS was higher after D1 also in early stages (p = 0.01).

Interpretation

After 15-year follow up, despite no relevant difference in overall population, DSS and gastric cancer-related mortality of patients with advanced disease and lymph node metastases are improved by D2 procedure. Further data available from this trial suggest that D1 procedure should be preferably used in older patients and in early disease. As accurate detection of advanced diseases can be currently provided by adequate preoperative workup in referral centres, D2 procedure should be recommended in these cases.

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Keywords

Gastric cancer

Lymphadenectomy

D2 lymph node dissection

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Survival

Disease Specific Survival

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1 Introduction

Worldwide there has been a long period of debate on what the optimal surgical treatment of gastric cancer should require. Once the Japanese guidelines suggesting the adequate type of gastrectomy (distal vs. total) according with tumour location and Borrmann classification have been globally adopted, this debate focused on the lymph node (LN) dissection required for an adequate oncologic procedure [1,2]. Exceptional survival results from Far East (mostly from Japan and later from Korea) suggested that a dissection extended to the second LN tier (D2 lymphadenectomy) was required for an optimal dissection [3–6]. This entailed the removal of the perigastric nodes (nodes along the lesser and greater curvature, stations 1–6) (N1 level), together with nodes along the left gastric artery (station 7), common hepatic artery (station 8), celiac trunk (station 9), splenic hilum and splenic artery (stations 10, 11p and 11d) (N2 level), although much recently stations 11d and 10 are no longer included [7].

These extended resections provided eastern patients with 5-year overall survival (OS) higher than 70%, while reports after D1 resections were extremely unfavourable in western world (about 20% at 5 years) [8–10]. After a first educational time period spent to learn the technique of D2 dissection, two randomised studies were carried out in Great Britain [11] and in the Netherlands [12] in the late 1980s, to assess the safety and efficacy of D2 dissection as compared to the traditional D1. A third RCT was started in Italy (Italian Gastric Cancer Study Group [IGCSG]) in the middle of the 1990s with the same end-points [13].

Short-term outcomes of these trials were contradictory. Both the MRC and Dutch trials showed morbidity and mortality rates significantly increased after D2 procedures and these unfavourable results were mostly referred to the spleno-pancreatectomy routinely performed during a total D2 gastrectomy. Avoiding this procedure, results of our RCT documented the safety and feasibility of D2 gastrectomy also in western patients' setting.

Mostly due to the increased postoperative mortality, after 5 years both the MRC and the Dutch trials failed to demonstrate a survival benefit of D2 over D1 technique, and Authors' recommendation was that 'D2 resection could not be advised in patients with curable gastric cancer' [14,15]. Only after a median follow-up of 15 years the Dutch trial could report a significant advantage in locoregional recurrence and in gastric cancer-related death associated to D2 resection [16]. Five-year survival results of the Italian RCT documented only a tendency to improved survival in advanced disease (pT > 1) with positive nodes [17].

Therefore, the very late survival results of the Dutch trial actually represent the only evidence to recommend D2 resection in western populations.

Additionally, also a Taiwanese Trial, which enrolled eastern patients, documented a significant OS advantage in the experimental arm, which was a D2 plus (LNs in the hepatoduodenal ligament, retropancreatic region and surrounding the superior mesenteric

vein were added to proper D2 nodes) for antral tumours and a proper D2 for other locations. Despite the limitation due to a long accrual and other disadvantages related to any single centre trial, it remains the only RCT that could meet the original hypothesis in terms of significant benefit in 5-year OS after extended dissection.

The findings of the IGCSG after a median follow-up time of 15 years are detailed below.

2 Methods

The setting and early outcomes of the IGCSG-R01 D1 versus D2 randomised surgical trial are summarised shortly as the details have been reported in previous publications [13,17].

2.1 Eligibility and patients

The medical ethics committees of each participating facility approved the IGCSG-R01 trial.

Written informed consent was obtained according to the ethical rules of these hospitals. Five centres responding to requirements of the study quality control participated in the trial.

Patients were recruited if they had histologically proven gastric cancer preoperatively staged as potentially resectable with curative intent, were aged less than 80 years and did not carry any severe comorbidities involving cardiorespiratory, renal or metabolic system which could preclude safe D2 resection.

Patients were excluded from the enrolment in case they had been submitted to previous gastric surgery, harboured previous or coexisting cancer outside the stomach or required emergency surgery for any complications (bleeding, perforation or obstruction).

2.2 Staging laparotomy and details of treatment arms

After preoperative assessment and formal informed consent, enrolled patients were submitted to staging laparotomy to exclude unresectable and/or incurable disease. In case of resectable and/or curable cancer (macroscopically removable disease without peritoneal spread, liver metastases or distant LN metastases [metastases in 3rd and 4th tier LNs or N3 and N4 LNs, station numbers 12–14 and 15–16 respectively]), patients were intraoperatively randomised either to a D1 or a D2 dissection.

The study was conducted adopting the Japanese Classification of Gastric Carcinoma (second English edition) to provide a common language among participating facilities for anatomical descriptions of LN stations and their grouping in tiers (1st to 4th or N1 to N4), and for the definition of the extent of LN dissection and gastric resection in both arms.

Unlike MRC and Dutch trials, hemipancreatico-splenectomy was not an integral part of D2 resection for middle and upper third disease. The pancreas was removed only in case it was suspected to be involved by the tumour.

Following the Japanese guidelines, a distal gastrectomy was done when the proximal edge of the tumour was more than 3 cm from the cardias in early gastric cancer (EGC) and in Bormann type 1 and 2 locally advanced gastric cancer (AGC). Otherwise, and in case the tumour was located close to the greater curvature, beyond Demel's point, as well as in patients with linitis plastica, a total gastrectomy was recommended.

The fifth edition of the International Union Against Cancer/American Joint Committee on Cancer tumour node metastasis (TNM) staging system was used in the analyses for the Pathologic Classification.

No neoadjuvant nor adjuvant chemotherapy was administered to any registered patients until recurrence.

Postoperative mortality was defined as death within 30 d after surgery or within postoperative hospitalisation.

2.3 Quality control setting

A strict quality control setting for adequacy of surgery, LN retrieval and pathologic definitions was set up and implemented. The most striking restriction was that only surgeons with proved skill on D2 resection, based on their previous participation in the IGCSG phase II trial, were allowed to enrol patients in this phase III RCT.

Regular meeting to debate indications, eligibility and technical aspects of LN tier grouping and surgical treatment arms were also implemented.

Moreover, numbers and site of LNs removed were monitored as required by the International Gastric Cancer guidelines, with the supervision of the Independent data centre. Contamination and non-compliance were documented as relevant bias. The first was defined as the pathologic proof of inclusion of more than two LN stations that should not have been removed during LN dissection. Non-compliance was the absence in the specimen of more than two LN stations, which were required according to the allocated surgery.

2.4 Follow-up

All patients were assessed every 4 months during the first 2 years and every 6 months thereafter or whenever they required a consultation for a supposed emergency. Although in accordance with common practice at that time a clinical diagnosis was considered sufficient evidence of recurrence, a radiologic (ultrasonography and computed tomography [CT] scan) or endoscopic confirmation was deemed mandatory for the acceptance of the evidence of recurrence.

Post-mortem examination was not a routine part of patients' follow-up and was required only in selected cases in which the cause of death was not clear.

For drop out patients who left the follow-up program due to change of residence, other personal causes or death, the update at 15 years from surgery was done by phone call to patients relatives or by official mail enquires to Register Offices to obtain their vital status (dead or alive) and the eventual cause of death.

2.5 Randomisation and statistics

This study was conceived as a multicentre, parallel, individually randomised, superiority trial with balanced randomisation.

Treatment allocation was implemented by blocks randomisation with fixed numbers (n = 10) per block, and stratified by surgical unit, with the sequence generated by a random number

table. The randomisation program was centralised, and the size of the blocks blinded to the surgeons. Patients who fulfilled the inclusion criteria during laparotomy were registered by telephone call to the randomisation centre. Each centre maintained a sequential register of randomised patients. Patients and care providers could not be blinded to the 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. The Cancer Epidemiology Unit of the S Giovanni Hospital acted as Independent data centre, handling the data and overseeing recruitment and randomisation. The study sample size was originally set up at 160 patients per treatment arm, to find out an increase in the 5-year OS rate of 15% (from 30% after D1 to 45% after D2 dissection) with 80% power, two-sided $\alpha = 0.05$. These survival estimates were consistent with data from literature and mostly based on the results of the IGCSG feasibility Phase II study on D2 LN dissection. Taking into account the long accrual (8 years) and duration of follow-up and the lower-than-expected recruitment, the trial retained a post hoc statistical power of 71.8% (two-sided $\alpha = 0.05$, absolute survival difference 15%).

All the analyses of this trial were performed on an intention-to-treat basis. Quantitative and qualitative variables were described using means and standard deviations and frequencies and percentages, respectively. Differences were tested using the Student's t test, Mann–Whitney U test, $\chi 2$ test and Fisher's exact test as appropriate. OS, disease-free survival, and disease-specific (DSS) survival were estimated with the Kaplan–Meier method, and survival curves evaluated using the log-rank test. Supposed prognostic factors (age, pT [pathological Tumor] stage, pN [pathological Nodal] stage, type of LN dissection [D1 or D2] and extent of resection [distal or total gastrectomy]) were evaluated as potential risk factors through univariate analysis and those variables that appeared statistically significant and clinically relevant were included in a Cox multivariable regression model. All the analyses were performed using R, V 4.0.2 and statistical significance was set at the 0.050 level.

The survival analyses in the two trial arms had been planned in advance and specified as such in the original trial protocol. Subgroup analyses were conceived and performed at a later time and should be interpreted with caution as no adjustment for multiple testing was applied.

The end of follow-up was set up on 1st June 2019. At that time, for alive patients (N = 118) the median follow-up time was 16.76 years; at least 71% (84/118) of these patients had at least 15 years of follow-up.

This study is registered with the controlled trials registration number: ISRCTN11154654 (http://www.controlled-trials.com).

2.6 Role of the funding source

The study was funded by a small Piedmont Regional source, without any role in study design, in the collection, analysis and interpretation of data, in the writing of the report and in the decision to submit the paper for publication.

3 Results

Fig. 1 shows the Consolidated Standards of Reporting Trials (CONSORT) diagram. Between June 1998 and December 2006, 617 patients were registered from 5 participating centres. Of these, only 267 patients who fulfilled the eligibility criteria and gave informed consent were enrolled into the IGCSG trial and randomised to receive either a D1 (133 patients) or a D2 (134 patients) procedure. Details of demographics, surgery performed, pathology, early outcomes and 5-year survival have already been reported in our previous papers [13,17]. Briefly, the two arms were well balanced with respect to age, sex, tumour site and size, extent of resection (total vs. distal) and pathology. Despite a 18.0% contamination in D1 arm and a 33.6% non-compliance in D2 patients, there was a significant difference of the median number of LNs retrieved between the two arms (25 for D1 vs. 33 for D2; $p < 0.001$), documenting that the extension of LN dissection was effectively different in the two procedures. Morbidity (D1, 12.0% vs. D2, 17.9%, $p = 0.183$) and mortality (D1, 3.0% vs. D2, 2.2%, $p = 725$) rates were comparable in the two groups of patients both in overall study population and in a subsite of patients (n = 115) with advanced cancer (pT > 1) and LN positive (N+) ($p = 0.618$ for mortality and $p = 0.575$ for morbidity) (Table 1). Seven patients who died within 30 d of surgery were excluded from the survival analysis. Data were collected prospectively, and all patients were followed up. At the end of this follow-up (1st June 2019), 142 of 260 (54.6%) patients had died, 82 (31.5%) from recurrence/progression of GC and 44 (16.9%) without recurrence; for 16 patients (6.1%) the cause of death was unknown. One hundred patients (38.5) were alive without recurrence. Eighteen patients (6.9%) were lost to follow-up. The median follow-up for all alive patients was 16.77 years (range 0.99–21.10) and for patients who died was 3.53 years (range 0.18–19.07). In overall population, gastric cancer-related death (Fig. 2A) and death due to other causes were higher in the D1 group compared with the D2 group (32.6% vs. 30.5%, hazard ratio [HR] 1.02 for D1 vs. D2, 95% confidence interval [CI] 0.66–1.57, log-rank $p = 0.941$ and 17.6% vs. 16.3%, HR 0.83 for D1 vs. D2, 95% CI 0.46–1.49, log-rank $p = 0.524$, respectively) but the difference between the two procedures was not significant. Causes of death were analysed separately for the subgroup of patients with advanced disease and LN positive (pT > 1N+, n = 111). In these patients, death from gastric cancer was significantly lower after D2 procedure than after D1 ($p = 0.035$) (Fig. 2B) while death due to other causes was lower in the D1 group compared with the D2 group (10.5% vs. 12.1%, HR 0.98 for D1 vs. D2, 95% CI 0.33–2.91, log-rank $p = 0.965$) although the difference between the two procedures was not significant (see Table 2).

In overall population, 15-year OS rate was 51.3% (95% CI 43–61) for D1 and 46.8% (95%CI 39–56) for D2, without any significant difference (HR 1.18, 95% CI 0.85–1.65, log-rank $p = 0.314$; Fig. 1). Fifteen-year DSS was 65% (95% CI 57–74) for D1 and 67% (95% CI 59–76) for D2 patients. The difference between these two groups was not significant (HR 0.98, 95% CI 0.64–1.52, log-rank $p = 0.941$; Fig. 3) as well.

Survival analysis was done also for the subgroup of patients with pT > 1N+ tumour (n = 111). For this category, the 15-year OS rate was 22.0% for D1 (95% CI 13–36) and 33.4% for D2 (95% CI 23–48); the difference between the two subgroups was not significant (HR 0.74, 95% CI 0.48–1.14, log-rank $p = 0.166$; Fig. 2). The 15-year DSS rate for this subgroup of patients was

29.4% (19–46) for D1 and 51.4% (95% CI 39–67) for D2. The documented 22% difference of DSS was statistically significant (HR 0.58 95% CI 0.35–0.97, log-rank p = 0.035; Fig. 3).

Table 3 shows the results of univariate analysis of OS and HR according to subgroups based on several prognostic factors in overall patient population (pT1-4, pN0 and pN+). OS was significantly higher after D1 than after D2 gastrectomy in patients older than 70 years (37.1%, 95% CI 25–55 and 12.3%, 95% CI 5–31 respectively, log-rank p = 0.003). It was higher after D1 procedure also in patients with a pT1 tumour (75.5% vs. 63.6%, p = 0.25), LNs negative (75.3% vs. 62.3%, p = 0.07), early TNM stages (IA and IB, 75.6% vs. 72.9%, p = 0.86 and 84.2% vs. 63.6%, p = 0.11) and distal gastrectomy (59% vs. 49%, p = 0.11) although not significantly. On the opposite, OS was higher after D2 gastrectomy in patients with LN positive (37.3% vs. 28.7%, p = 0.34), locally advanced TNM stage (IIIA, 32.4% vs. 15.8%, p = 0.43) and total gastrectomy (39.5% vs. 28.1%, p = 0.54); however, the difference between the two arms was not statistically significant. Gender did not influence patients' OS.

The univariate analysis of OS and HR related to several prognostic factors was done also for the subgroup of patients with advanced disease (pT > 1N+, n = 111). In this category, OS was always higher after D2 than after D1 procedure in each subgroup of prognostic factors (male, female, up to 70-year-old, T2, T3, TNM stages II, IIA and IIIB, total and distal gastrectomy) except from patients older than 70 years. Nevertheless, the differences reported among subgroups were not statistically significant (Table 4).

Table 5 documents the results of the univariate analysis of DSS and HR in overall patient population. DSS was 67.1% (95% CI 59–76) in the D1 arm and 65.2% (95% CI 57–74) in the D2 arm, with no significant difference (HR 0.98, 95% CI 0.64–1.52, log-rank p = 0.94). It was significantly higher after D1 procedure in patients with age >70 (70.8% vs. 32.4%, HR 2.8, 95% CI 1.3–6.06, p = 0.006) and with T1 cancer (EGC) (95.2% vs. 77.2%, HR 5.97, 95% CI 1.27–28.15, p = 0.01). On the contrary, D2 gastrectomy offered better DSS in subgroups of patients with T2/T3, LN positive, advanced stages (TNM > II) and total gastrectomy, but this was not statistically significant.

Univariate analysis of DSS was also performed in pT > 1N+ patients (n = 111). For these patients with locally advanced disease, D2 gastrectomy had a DSS significantly higher than D1 (51.4% vs. 29.4%, HR 0.58, 95% CI 0.35–0.97, log-rank p = 0.035). In all subgroups based on prognostic factors excluding patients >70 years, D2 was always better than D1 (Table 6).

Therefore, univariate Cox regression analysis of DSS for PT > 1N+ patients showed that D2 LN dissection represents a significant independent favourable prognostic factor. This result was confirmed with multivariable Cox regression model. The application of this model documented that D2 resection (HR 0.43, 95% CI 0.23–0.79, p = 0.007), pTNM stage 2, 3 and 4 versus 1 (HR 2.41, 95% CI 1.11–5.20, p = 0.025; HR 2.97, 95% CI 1.28–6.88, p = 0.011 and HR

7.12, 95% CI 3.01–16.80, p = 0.000 respectively), together with surgical complications (HR 0.58, 95% CI 0.35–0.94, p = 0.029) represented independent prognostic factors for DSS in advanced disease (Table 7). Age, type of resection (distal vs. total) and splenectomy were not recognised as significant prognostic variables for these patients.

4 Discussion

Findings from 15-year follow-up data of the IGCSG RCT document that, due to the high proportion of early cases and of significant contamination and non-compliance observed in D1 and D2 procedures respectively, in overall study population patients' survival was not influenced by the more extended dissection. Notwithstanding, in patients with advanced disease and positive nodes these findings show that D2 dissection is significantly associated with lower gastric cancer-related mortality.

Although D2 dissection has been performed routinely for decades in eastern countries with successful survival rates and low postoperative complications, in western patients its superiority with respect to standard D1 dissection has been demonstrated only in the Dutch RCT and only after 15-year follow-up [16].

The negative results of MRC trial and of the first reports of the Dutch trial were strongly influenced by higher morbidity and mortality rates as compared to D1, mostly related to splenectomy or pancreato-splenectomy routinely performed in case of D2 total gastrectomy [14,18]. These unfavourable reports were also referred to inadequate experience and low case volume of the hospitals and surgeons involved in these trials. Both these findings were claimed to have nullified any survival benefit of D2. Based on these findings, the IGCSG could document the feasibility and safety of D2 dissection in western patients with the adoption of pancreas-preserving splenectomy procedures in addition to a strict quality control and a high case volume [19]. Low postoperative morbidity and mortality after this modified D2 gastrectomy were documented both in a Phase 1/2 study and in the following RCT [13,19].

Nevertheless, despite these successful early outcomes, 5-year OS and DSS analysis of IGCSG could not find out a significant advantage of D2 procedure in overall study population [17]. The higher proportion of early tumours (with significantly better survival outcome) in the D1 arm and of more advanced tumours in the D2 arm could partially explain these findings. Moreover, contamination and non-compliance, identified in 17.3% and 33.6% of D1 and D2 resections respectively despite the strict quality control applied, could certainly have been responsible for an underestimation of the difference in survival between the two arms. Other arguments claimed to explain the overall failure of the Italian trial to detect an OS benefit of D2 gastrectomy were the absolute high proportion of pT1 tumours (for which the recent literature and worldwide guidelines have documented and recommended that D2 procedure is not necessary) and the excessive median number of LN harvested during a D1 procedure compared with that of previous report (25 vs. 15).

Notwithstanding, for locally advanced disease (pT > 1) with LN metastases (pN+), a tendency to improved DSS was already documented at 5-year follow-up in D2 arm (HR 0.63, 95% CI 0.36–1.06, p = 0.078) [17]. This finding is similar to the survival advantage of D2 dissection in

advanced tumours with N2 positive nodes observed in the Dutch trial after 11-year follow-up [18].

After a median follow-up time of 15 years, Dutch surgeons managed to detect lower locoregional relapse and gastric cancer-related mortality in the D2 arm [16]. After the same study period, the IGCSG RCT can now document that the difference of DSS between pT > 1N+ patients submitted to D2 and D1 resection has become statistically significant in favour of the extend procedure (p = 0.035). Despite any considerations concerning the role of neoadjuvant treatment in these patients, findings of this trial corroborate the evidence that locally advanced disease should undergo extensive dissection and that D2 dissection is better than standard limited dissection. These information seem beneficial as this subset of patients is likely to be identified during preoperative staging workup with the help of new generation imaging technologies (mostly CT, multidetector CT and EUS) [20] which should be available in referral centres and that can now provide clinical T and N stages with high accuracy, leading to adequate planning of different treatment pathways (endoscopic treatments or minimally invasive approach with limited dissection for early cancers and multimodal management with extensive dissection for advanced disease).

This long-term analysis could detect or confirm further findings. First, in overall study population, in patients older than 70 years D2 dissection does not carry any survival advantage. The negative effect of age on survival is also documented in the multivariate analysis of DSS in overall population. After all, the unfavourable effect of age on patients' survival was already reported in the Dutch trial in both treatment arms (p < 0.0001 for both D1 and D2), but was not studied comparing D1 versus D2 [16]. In the present study, the effect of age is mostly evident in overall population, while it is not significant in the subset of advanced stage. This finding could support the choice of submitting older patients with early stages to less extensive dissection. On the other hand, the same subset analysis confirms that extended dissection provides better outcomes to younger patients (<70 years) with more advanced disease (p = 0.007).

Second, the better survival of early cancers submitted to standard D1 resection already reported in our previous manuscript (p = 0.015) is confirmed by this long-term analysis where D2 resection is reported with a 6-fold increased risk of death in patients with EGC (D2 vs. D1 DSS, 77.2% vs. 95.2%, HR 5.97, p = 0.01) [17]. A supplementary analysis could document that the worse survival results of D2 gastrectomy in EGC patients was mostly due to a significantly higher rate of node positive patients in D2 arm (supplementary material), and that survival of early cancer is mostly related to nodal stage rather than to the extension of nodal dissection (tables 8 suppl and 9 suppl). Anyways, these data are in line with recent worldwide guidelines recommending surgery with less extensive LN dissection (D1, D1 plus) for patients with early cancers not suitable for endoscopic treatment [21–23].

Finally, after a median follow-up time of 15 years, the OS and DSS were high in both D1 and D2 groups of overall study population (51.3% and 65.0%, and 46.8% and 67.0% respectively) and in subgroup of advanced disease (Figs 4Suppl and 5Suppl). These proportions of survival are substantially higher than those reported by previous western studies and European RCTs, but in line with Japanese and Korean reports [3,24]. Irrespective of the type of dissection performed (D1 or D2), and despite contamination and non-compliance during LN dissection,

this trial has shown that removing a high absolute number of LNs can contribute to provide patients with successful outcomes [25].

The results of this trial are in line with recent worldwide guidelines. The evidence that D2 dissection is not useful in case of early cancers is consistent with recommendation to submit EGC patients not suitable for endoscopic treatment to surgical resection with more restricted LN dissection. This trial did not use preoperative or postoperative chemotherapy as it was conducted before medical treatment became standard practice [22,26–28]. Therefore, results of standard or extended surgery for advanced cancers are not influenced by external biases. Given these premises, this trial cannot give answer whether effective neo-adjuvant chemotherapy may compensate extended nodal dissection or not. To answer this question, further trials are needed.

This trial has several limitations. First, the rate of EGC is 39% in the D1 versus 29% in the D2 group; this difference can contribute to alter survival results in the whole population, as T1 tumours is excellent regardless of the type of lymphadenectomy performed. Second, although the extension of LN dissection was effectively different in the two procedures, the median number of LNs retrieved during a D1resection is exceptionally high (i.e. 25), also giving that this number was often considered as the threshold to identify a D2 dissection. The combination of these two factors can contribute to explain the unusually high survival rate observed in the D1 group. Third, DSS of EGC was documented to be significantly worse after D2 than after D1 dissection, but this CT could be mostly referred to the higher rate of N+ patients in the D2 group ($p < 0.001$) due to unbalanced pT1 subpopulations (D1 and D2 groups). Finally, mostly as the inevitable consequence of conducting the study among selected centres for the sake of quality control, this trial had a small sample size, which could have contributed to enhance the effect of even small differences of variable distributions between arms on final findings.

5 Conclusion

After 15-year follow-up, findings of the IGCSG RCT on D1 versus D2 resection for gastric cancer show that, irrespective of the type of LN dissection performed, a high number of LN retrieved is associated with successful survival. Moreover, despite no relevant difference in overall study population, DSS and gastric cancer-related mortality of patients with advanced disease and LN metastases are improved by the more extended procedure without any increase in postoperative morbidity and mortality. Further data available from this trial suggest that D1 procedure should be preferably used in older patients and in early disease. As accurate detection of advanced diseases can be currently provided by adequate preoperative staging workup in referral centres, D2 procedure should be recommended in these cases.

Author contributions

MD, MM and MS made substantial contributions to the conception or design of the work; MD, MS, MM, RR, AP, and MT made contributions to the acquisition, analysis or interpretation of data for the work.

All Authors participated in drafting the work or revising it critically for important intellectual content.

All Authors gave final approval of the version to be published.

All Authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

MD, MT and RR have verified the underlying data.

All authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication.

Conflict of interest statement

All authors declare that they have no conflicts of interest.

Appendix

Data sharing statement

Research in context

Evidence before this study

This randomised trial was started in 1998, and the present manuscript describes the 15-year follow-up analysis of survival and gastric cancer-related mortality of patients submitted to either a standard limited D1 LN dissection or an extended D2 lymphadenectomy for gastric cancer. Despite a large and successful use of D2 lymphadenectomy in eastern countries (mostly Japan and Korea) since many decades, the survival benefit of proper D2 dissection had never been demonstrated in RCTs in those nations until a Taiwanese trial, reported in 2006 in the Lancet Oncology, documented a clear OS advantage. However, these results were referred to a node dissection named D3 or D2+ (or D2 plus), in which nodes along the superior mesenteric vein and behind the head of the pancreas were added to D2 nodes.

Western countries adopting the more limited dissection have always reported lower survivals and higher rates of recurrence. Since the late 1980s, several western surgeons went to Japan and then to Korea to learn the technique of D2. In quick succession, a British (MRC), a Dutch (Dutch D1D2) and an Italian (IGCSG) randomised trial were designed and carried on. The MRC and Dutch trial initially failed to demonstrate a survival benefit of D2 over D1, mostly due to the high rate of postoperative mortality related to the procedure, which nullified the favourable effect of the extended dissection. Only 15 years after the conclusion of the trial, Dutch authors documented that D2 was associated with lower cancer-related mortality and local recurrence rate. Nevertheless, these advantages were lowered by the significantly higher postoperative morbidity and mortality related to the more extended dissection. Indeed, to date this is the only favourable report supporting the adoption of the extended resection in western patients with resectable gastric cancer, despite its stage.

In the meantime, eastern and western gastric cancer treatment guidelines (European Society of Medical Oncology [ESMO], European Society of Surgical Oncology [ESSO], Italian Group for the Research on Gastric Cancer [GIRCG], National Comprehensive Cancer Network [NCCN],

Japanese Guidelines, Korean Guidelines) have recently documented that the treatment of gastric cancer should be tailored on its clinical stage and patients' characteristics and that D2 dissection is not recommended in every case. Actually, most of early cancers should preferably undergo endoscopic treatment. Moreover, recent molecular classifications have identified further types of cancer with special indication to new molecular treatments. Finally, there are consistent data supporting multimodality treatment of locally advanced gastric cancer, particularly related to the adoption of preoperative or perioperative chemotherapy.

The early (5 year) survival results of the Italian IGCSG trial, published in 2014 in British Journal of Surgery (BJS), documented that overall survival after D1 and D2 procedures was not different. Due to a high proportion of early cases in both arms and to a high LN yield also in D1 arm, the difference between the two arms in terms of absolute number of LN retrieved was too small. The consequence of this was a high survival in both arms, comparable to those reported by eastern authors. Nevertheless, in patients with advanced disease and LNs positive (pT > 1N+), 5 years after the resection a tendency to improve DSS was already evident in D2 arm.

Added value of this study

After a 15-year median follow-up, this trial has confirmed that, due to the high proportion of early cases and the high absolute number of LNs removed also in D1 arm and to the consequent high survival in both arms, in the overall population the survival benefit (both OS and DSS) of D2 dissection is not evident. However, this trial has documented that, for patients with advanced but resectable disease (pT > 1 and LN positive), D2 gastrectomy is associated with better cancer-related mortality. Further analyses showed that, consistent with actual recommendations, D2 dissection is not necessary for patients with early-stage disease and for patients older than 70 years.

Worldwide, this is the second observation in a RCT that proper D2 dissection may have a curative value for GC western patients. Findings from the trial are mostly in line with actual indications of treating cancer patients according to tumour and hosts characteristics; indeed, the trial documented that patients with resectable locally advanced disease should preferably undergo D2 dissection. As a result of further analyses, the trial showed also that the extensive dissection is not useful for patients older than 70 years and in early stage. This observation was not reported until now in any RCTs, which generally stated that age is an independent risk factor for survival but did not study the effect of the extension of LN dissection in older patients.

Implications of all the available evidence

Long-term survival results of this trial can have some implications in specific indications:

1.

Patients with resectable locally advanced disease should preferably undergo D2 dissection.

2.

D2 dissection is not necessary in early gastric cancer.

3.

Older patients should be submitted to the standard D1 dissection as the extended D2 procedure is not superior and can be dangerous.

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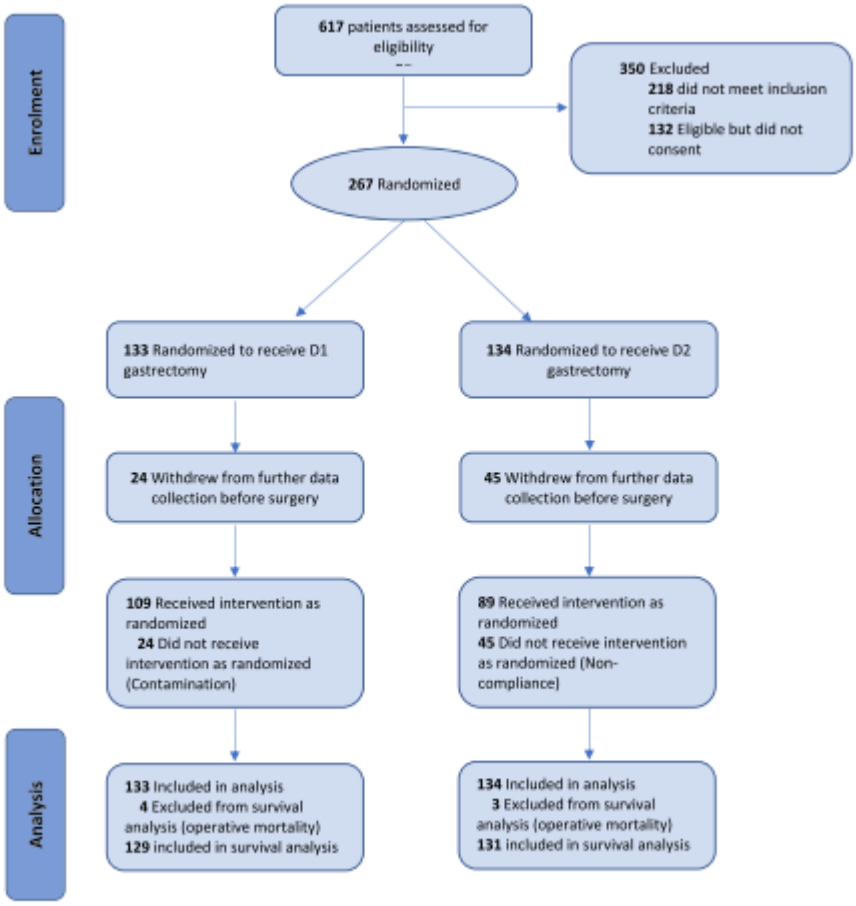

Fig. 1. CONSORT diagram for the IGCSG trial.

Table 1
Morbidity and mortality in overall patient population and in pT > 1N+.

	Overall patient population			pT > 1N+		
	D1 (133)	D2 (134)	*p*-value	D1 (60)	D2 (59)	*p*-value
Morbidity, *n* (%)	16 (12.0)	24 (17.9)	0.240[a]	7 (11.6)	10 (16.9)	0.575[a]
30-d mortality, *n* (%)	4 (3.0)	3 (2.2)	0.722[b]	3 (5)	1 (1.7)	0.618[b]

[a] Chi-squared test.
[b] Fisher test.

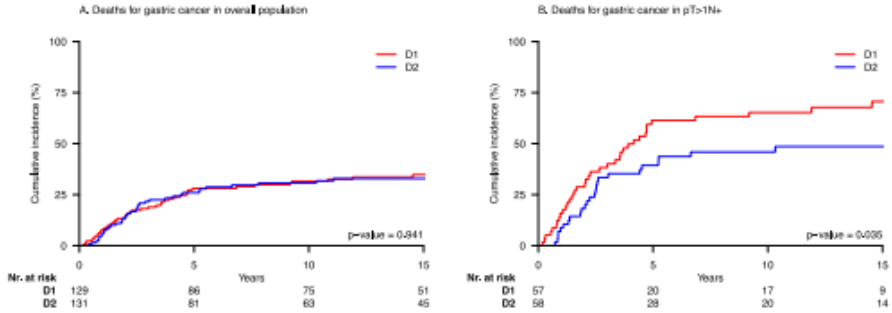

Fig. 2. **(A) Death for gastric cancer in the overall population (n = 260) and (B) death for gastric cancer in patients with locally advanced disease (pT > 1N+, n = 115).** D1 = standard limited lymph node dissection; D2 = extended lymph node dissection; pT > 1N+ = disease with pathological tumour status greater than 1 and positive pathological lymph node status according to the fifth edition of the International Union Against Cancer/American Joint Committee on Cancer tumour node metastasis (TNM) staging system.

Table 2
Causes of death in overall patient population and in pT > 1N+ after 15-year follow-up.

	Overall patient population			pT > 1N+		
	D1 group (n = 129)	D2 group (n = 131)	Log-rank p-value	D1 group (n = 57)	D2 group (n = 58)	Log-rank p-value
Alive, n (%)	62 (48%)	56 (43%)		12 (21%)	19 (33%)	
Deaths from gastric cancer, n (%)	42 (33%)	40 (31%)	0.31	37 (65%)	25 (43%)	0.035
Deaths from other causes, n (%)	21 (16%)	23 (18%)		6 (11%)	7 (12%)	
Deaths from unknown causes, n (%)	4 (3%)	12 (9%)		2 (4%)	7 (12%)	

n = number.
Seven patients who died within 30 d from operation were censored.

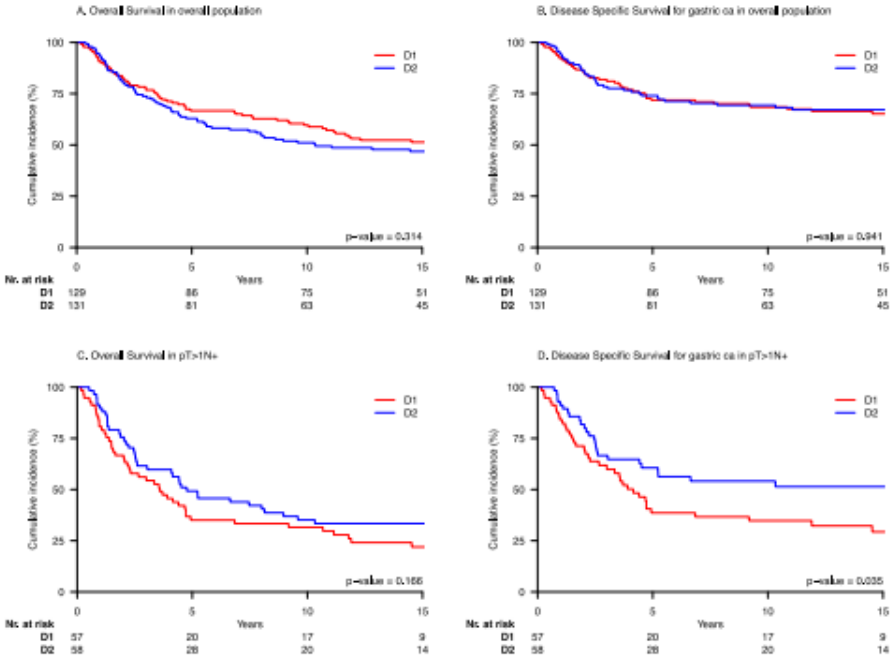

Fig. 3. **(A) Overall survival in the overall population (n = 260). (B) Disease-specific survival for gastric cancer in the overall population (n = 260). (C) Overall survival in patients with locally advanced disease (pT > 1N+, n = 115). (D) Disease-specific survival for gastric cancer in patients with locally advanced disease (pT > 1 N+, n = 115).** D1 = standard limited lymph node dissection; D2 = extended lymph node dissection; pT > 1N+ = disease with pathological tumour status greater than 1 and positive pathological lymph node status according to the fifth edition of the International Union Against Cancer/American Joint Committee on Cancer tumour node metastasis (TNM) staging system; gastric ca = gastric cancer.

Table 3
Univariate analysis of overall survival in overall study population after 15-year follow-up.

	D1 group		D2 group		HR (95% CI)	Log-rank *p*-value
	N	15-year OS (%) (95% CI)	N	15-year OS (%) (95% CI)		
Total	129	51.3 (43–61)	131	46.8 (39–56)	1.18 (0.85–1.65)	0.31
Sex						
Male	65	49.2 (38–63)	64	47.4 (36–62)	1.16 (0.74–1.84)	0.51
Female	64	53.6 (42–68)	67	46.2 (36–60)	1.21 (0.75–1.95)	0.43
Age (years)						
Up to 70	87	58.2 (49–70)	96	58.7 (50–70)	1.06 (0.69–1.63)	0.79
>70	42	37.1 (25–55)	35	12.3 (5–31)	2.19 (1.29–3.71)	**0.003**
pT[a]						
T1	49	75.5 (64–89)	38	63.6 (49–82)	1.55 (0.74–3.24)	0.25
T2	41	50.3 (37–69)	55	51.8 (40–67)	1.01 (0.58–1.77)	0.97
T3	37	19.7 (10–39)	35	25.4 (14–45)	0.84 (0.51–1.40)	0.51
pN[a]						
N0	62	75.3 (65–87)	55	62.3 (50–77)	1.73 (0.95–3.15)	0.07
N+	65	28.7 (19–42)	73	37.3 (28–50)	0.82 (0.55–1.23)	0.34
N1	31	35.5 (22–57)	43	52.2 (39–70)	0.72 (0.39–1.33)	0.30
N2/N3	34	23.2 (12–43)	30	16.7 (7–37)	1.03 (0.60–1.77)	0.91
TNM stage[a]						
IA	41	75.6 (64–90)	24	72.9 (56–94)	1.09 (0.43–2.76)	0.86
IB	19	84.2 (69–100)	31	63.6 (48–83)	2.27 (0.80–6.40)	0.11
II	24	43.6 (27–70)	32	48.4 (34–70)	1.11 (0.54–2.26)	0.78
IIIA	19	15.8 (6–45)	18	32.4 (16–64)	0.75 (0.36–1.54)	0.43
IIIB/IV	23	17.4 (7–42)	23	13.0 (5–37)	0.87 (0.47–1.61)	0.65
Type of gastrectomy						
Distal	97	59.0 (50–70)	101	49.0 (40–60)	1.37 (0.92–2.04)	0.11
Total	32	28.1 (16–49)	30	39.5 (25–62)	0.83 (0.45–1.51)	0.54

Bold values signifies when Log-ran p-value is statistically significant. N = number; HR = hazard ratio; CI = confidence interval; pT, pN and TNM = pathologic staging according to the 5th edition of the Union for International Cancer Control/American Joint Commission on Cancer (UICC/AJCC) staging system.
[a] 5 patients with missing data.

Table 4
Univariate analysis of overall survival in pT > 1N+ after 15-year follow-up.

	D1 group		D2 group		HR (95% CI)	Log-rank *p*-value
	N	15-year OS (%) (95% CI)	*N*	15-year OS (%) (95% CI)		
Total	57	22 (13–36)	58	33.4 (23–48)	0.74 (0.48–1.114)	0.17
Sex						
Male	27	18.5 (8–41)	24	25 (13–50)	0.78 (0.43–1.44)	0.43
Female	30	25.1 (13–48)	34	39.5 (26–60)	0.74 (0.40–1.35)	0.32
Age (years)						
Up to 70	42	25.1 (15–43)	43	41.9 (29–60)	0.64 (0.38–1.07)	0.09
>70	15	13.3 (4–48)	15	7.3 (1–48)	1.19 (0.54–2.61)	0.66
pT						
T2	27	28.6 (15–53)	33	43.8 (30–65)	0.71 (0.37–1.35)	0.29
T3	30	16.0 (7–37)	25	20.0 (9–44)	0.84 (0.47–1.50)	0.56
pN						
N1	25	28% (15–52)	33	47% (33–68)	0.67 (0.34–1.3)	0.23
N2/N3	32	18.2% (9–38)	25	16% (7–39)	0.91 (0.52–1.6)	0.74
TNM stage						
IB	–		–			
II	15	40.0 (22–74)	22	57.1 (39–83)	0.64 (0.25–1.61)	0.34
IIIA	19	15.8 (6–45)	15	26.7 (16–62)	0.91 (0.43–1.93)	0.80
IIIB/IV	23	17.4 (7–42)	21	14.3 (5–41)	0.82 (0.43–1.55)	0.54
Type of gastrectomy						
Distal	35	26.9 (15–47)	45	36.4 (25–54)	0.80 (0.47–1.36)	0.41
Total	22	13.6 (5–39)	13	23.1 (9–62)	0.79 (0.37–1.71)	0.55

N = number; HR = hazard ratio; CI = confidence Interval; pT, pN and TNM = pathologic staging according to the 5th edition of the Union for International Cancer Control/American Joint Commission on Cancer (UICC/AJCC) staging system.

Table 5
Univariate analysis of disease-specific survival in overall study population after 15-year follow-up.

	D1 group		D2 group		HR (95% CI)	Log-rank *p*-value
	N	15-year OS (%) (95% CI)	*N*	15-year OS (%) (95% CI)		
Total	129	65 (57–74)	131	67 (59–76)	0.98 (0.64–1.52)	0.94
Sex						
Male	65	61 (50–75)	64	70 (59–83)	0.8 (0.44–1.46)	0.46
Female	64	70 (59–83)	67	64 (53–78)	1.25 (0.66–2.34)	0.49
Age (years)						
Up to 70	87	63 (53–74)	96	76 (68–85)	0.64 (0.37–1.1)	0.1
>70	42	71 (57–87)	35	32 (17–63)	2.8 (1.3–6.06)	**0.006**
pT[a]						
T1	49	95 (89–100)	38	77 (64–93)	5.97 (1.27–28.15)	**0.01**
T2	41	60 (46–78)	55	70 (59–84)	0.73 (0.36–1.47)	0.38
T3	37	28 (15–51)	35	50 (34–72)	0.62 (0.33–1.18)	0.14
pN[a]						
N0	62	92.7 (86–100)	55	85.3 (76–96)	2.58 (0.78–8.60)	0.11
N+	65	38.7 (28–54)	73	53.6 (43–67)	0.69 (0.43–1.12)	0.28
N1	31	52 (36–74)	43	67 (53–83)	0.66 (0.31–1.41)	0.28
N2/N3	34	27 (15–48)	30	35 (21–59)	0.81 (0.44–1.51)	0.52
TNM stage[a]						
IA	41	94 (87–100)	24	89 (76–100)	1.98 (0.28–14.09)	0.49
IB	19	100 (100–100)	31	83 (71–98)	–	0.07
II	24	66 (49–88)	32	66 (50–87)	0.91 (0.35–2.36)	0.84
IIIA	19	17 (6–47)	18	56 (36–88)	0.47 (0.2–1.11)	0.08
IIIB/IV	23	22 (10–51)	23	29 (15–57)	0.82 (0.4–1.66)	0.57
Type of gastrectomy						
Distal	97	75 (66–84)	101	69 (60–80)	1.33 (0.77–2.3)	0.31
Total	32	36 (22–59)	30	60 (44–82)	0.57 (0.27–1.2)	0.13

Bold values signifies when Log-ran p-value is statistically significant. N = number; HR = hazard ratio; CI = confidence interval; pT, pN and pTNM = pathologic staging according to The 5th edition of the Union for International Cancer Control/American Joint Commission on Cancer (UICC/AJCC) staging system.
[a] 5 patients with missing data.

Table 6
Univariate analysis of disease-specific survival in pT > 1N+ after 15-year follow-up.

	D1 group		D2 group		HR (95% CI)	Log-rank *p*-value
	N	15-year OS (%) (95% CI)	*N*	15-year OS (%) (95% CI)		
Total	57	29 (19–46)	58	51 (39–67)	0.58 (0.35–0.97)	**0.035**
Sex						
Male	27	23 (11–47)	24	51 (34–77)	0.53 (0.25–1.1)	0.08
Female	30	36 (21–62)	34	52 (36–74)	0.67 (0.33–1.37)	0.63
Age (years)						
Up to 70	42	29 (17–48)	43	62 (49–80)	0.43 (0.23–0.8)	**0.007**
>70	15	33 (15–73)	15	12 (2–72)	1.25 (0.5–3.09)	0.63
pT						
T2	27	38 (23–64)	33	60 (45–81)	0.56 (0.27–1.19)	0.12
T3	30	20 (9–45)	25	38 (22–69)	0.66 (0.33–1.32)	0.24
pN						
N1	25	40 (24–67)	33	62 (46–83)	0.56 (0.25–1.24)	0.15
N2/N3	32	21 (10–44)	25	40 (24–66)	0.68 (0.35–1.32)	0.25
TNM stage						
II	15	60 (40–91)	22	73 (56–96)	0.53 (0.16–1.75)	0.29
IIIA	19	17 (6–47)	15	45 (24–86)	0.57 (0.23–1.41)	0.29
IIIB/IV	23	22 (10–51)	21	32 (17–62)	0.75 (0.36–1.55)	0.43
Type of gastrectomy						
Distal	35	39 (25–62)	45	52 (39–71)	0.72 (0.38–1.35)	0.30
Total	22	14 (5–41)	13	51 (30–89)	0.52 (0.21–1.31)	0.16

Bold values signifies when Log-ran p-value is statistically significant. N = number; HR = hazard ratio; CI = confidence Interval; pT, pN and pTNM = pathologic staging according to the 5th edition of the Union for International Cancer Control/American Joint Commission on Cancer (UICC/AJCC) staging system.

Table 7
Cox proportional hazards regression model for multivariable analysis of disease-specific survival in pT > 1N+ after 15-year follow-up.

	HR	95% CI	*p*-value
D2 (vs. D1)	0.45	0.24–0.84	**0.012**
Age	1.02	0.99–1.05	0.129
Female (vs. men)	0.99	0.92–1.07	0.864
TNM stage			
IIIA	2.39	1.11–5.16	**0.026**
IIIB	2.51	1.05–5.97	**0.038**
IV	7.35	3.10–17.42	<**0.001**
Total (vs. distal) gastrectomy	1.66	0.95–2.92	0.077
Splenectomy	0.95	0.85–1.06	0.384
Surgical complications	4.34	1.53–12.29	**0.006**

Bold values signifies when Log-ran p-value is statistically significant.
HR = hazard ratio; CI = confidence interval.