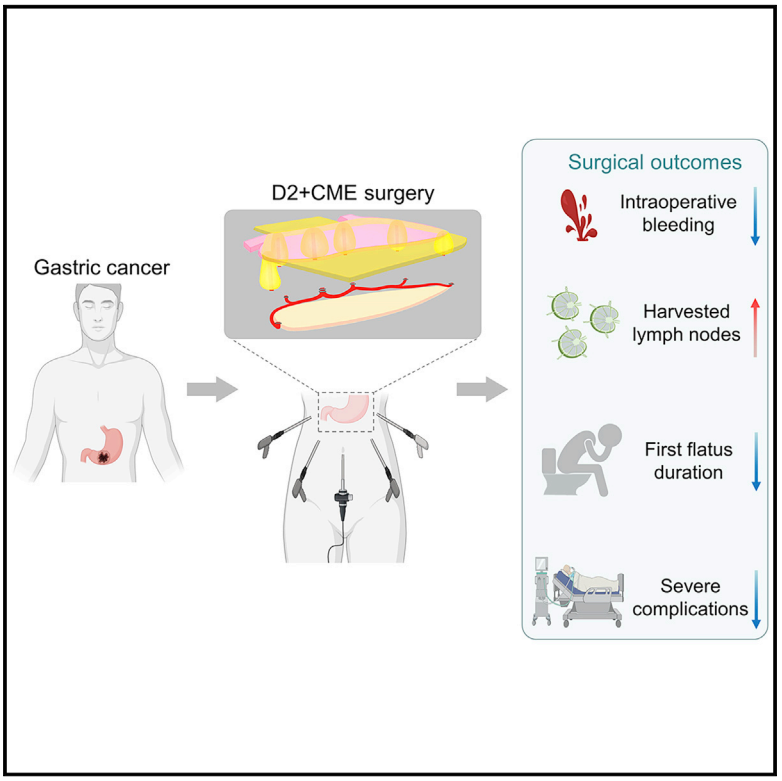
Cell Reports
Medicine

Article

Complete mesogastric excision for locally advanced gastric cancer: Short-term outcomes of a randomized clinical trial

Graphical Abstract



Authors

Daxing Xie, Jie Shen, Liang Liu, ..., Junbo Hu, Ping Yin, Jianping Gong

Correspondence

dxxie@tjh.tjmu.edu.cn

In brief

Xie et al. demonstrate the short-term outcomes of a surgical procedure named D2+CME in gastric cancer patients. They compare D2+CME with conventional D2 radical surgery and show that D2+CME has better outcomes and surgical safety. This provides an optimal surgical approach for patients with gastric cancer.

Highlights

- Gastric cancer patients receiving D2+CME exhibit less intraoperative blood loss
- The number of lymph nodes harvested with D2+CME is significantly improved
- D2+CME surgery could provide faster postoperative flatus
- D2+CME is less likely to cause severe complications than conventional surgery

Xie et al., 2021, Cell Reports Medicine 2, 100217
March 16, 2021
https://doi.org/10.1016/j.xcrm.2021.100217

CellPress

Cell Reports Medicine

CellPress
OPEN ACCESS

Article

Complete mesogastric excision for locally advanced gastric cancer: Short-term outcomes of a randomized clinical trial

Daxing Xie,[1] Jie Shen,[1] Liang Liu,[1] Beibei Cao,[1] Yatao Wang,[1] Jichao Qin,[1] Jianhong Wu,[1] Qun Yan,[1] Yuanlong Hu,[1] Chuanyong Yang,[1] Zhixin Cao,[1] Junbo Hu,[1] Ping Yin,[2] and Jianping Gong[1,3,*]

[1]Department of Gastrointestinal Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, China

[2]Department of Epidemiology and Biostatistics, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, China

[3]Lead contact

*Correspondence: dxxie@tjh.tjmu.edu.cn

https://doi.org/10.1016/j.xcrm.2021.100217

SUMMARY

Implementation of complete mesogastric excision in gastric cancer surgery, named D2 lymphadenectomy plus complete mesogastric excision (D2+CME), has recently been proposed as an optimal procedure. However, the safety and efficacy of D2+CME remain uncertain. In this randomized controlled trial, patients receiving D2+CME exhibit less intraoperative blood loss, more lymph node harvesting, and earlier postoperative flatus than patients receiving conventional D2 radical surgery. Univariate Cox regression analysis reveals that the risk ratio for postoperative flatus in D2+CME group is 1.247 ($p = 0.044$). Overall postoperative complications are comparable between the two groups, but complications are significantly less severe in the D2+CME group than the D2 group (Clavien-Dindo classification grade $\geq$ IIIa: 4 D2+CME patients [11.8%] versus 9 D2 patients [33.3%]; $p = 0.041$). In conclusion, our work shows that D2+CME is associated with better short-term outcomes and surgical safety than conventional D2 dissection for patients with advanced gastric cancer.

INTRODUCTION

Gastric cancer is the fourth most common malignancy and the second leading cause of cancer death worldwide.[1] Radical surgery remains the main treatment modality.[2] Currently, the standard operation for advanced gastric cancer (AGC) is gastrectomy with D2 lymphadenectomy.[3] However, 38% to 50% of patients develop recurrent disease after curative surgery.[4,5] In the past three decades, implementation of the complete mesocolic excision (CME)/total mesorectal excision (TME) technique in colorectal cancer surgery has successfully reduced local relapse and improved tumor survival.[6–11] A similar surgical technique of complete mesogastric excision has not been established in gastric cancer surgery. Conventional D2 lymphadenectomy, which dissects lymph nodes (LNs) along the celiac axis and its branches, as well as perigastric nodes, is still the recommended procedure to date.[3,12]

Previously, our studies have demonstrated the presence of cancer cells in the mesogastrium (metastasis V),[13,14] and we also presented the anatomical architecture of gastric mesentery with a distinct mesogastrium model (PSDM).[15] As a consequence, D2 lymphadenectomy plus complete mesogastric excision (D2+CME) was proposed as a mesentery-concept-based procedure in the surgical treatment of gastric cancer.[16,17] Our retrospective studies showed that D2+CME surgery under laparoscopy was safe and feasible, with less intraoperative bleeding and improved short-term surgical outcomes.[16,17] Further study demonstrated that D2+CME could reduce the number of free intraperitoneal cancer cells during surgery and was associated with a better disease-free survival than conventional D2 dissection.[18]

To obtain a high level of evidence for D2+CME surgery, we conducted a prospective, randomized clinical trial (RCT) to compare D2+CME with conventional D2 dissection for gastric cancer treatment (DCGC01, http://www.clinicaltrials.gov, NCT01978444). The protocol was published in *Trials*.[19] The primary end point, 3-year disease-free survival, is being assessed in the follow-up phase. The current study presents short-term outcomes, including surgical results, morbidity, and mortality within 30 days after surgery.

RESULTS

Study population

Between 22 September 2014 and 28 June 2018, a total of 2,588 gastric cancer patients were investigated. Among them, 2,102 patients were excluded due to the exclusion criteria in the preoperative evaluation period, and the remaining 486 patients were randomly assigned to either the D2 group or the D2+CME group.

Of these 486 patients, 88 (48 in D2 and 40 in D2+CME) could not receive allocated intervention due to the following reasons: 54 patients (30 in D2 and 24 in D2+CME) were diagnosed with severe tumor infiltration or metastasis during laparoscopic exploration and could not receive the radical operation; 2 patients (1 in D2 and 1 in D2+CME) were found to have other abdominal tumors during the operation; 31 patients (16 in D2 and 15 in D2+CME) received total gastrectomy due to an insufficient proximal resection margin; and 1 patient in the D2 group could not tolerate the laparoscopic operation. After the operation, 46 patients (21 in D2 and 25 in D2+CME) were diagnosed with pT1N0M0, and 14 patients (5 in D2 and 9 in D2+CME) were found not to have adenocarcinoma through pathological biopsy (gastrointestinal stromal tumor, 2 patients; lymphoma, 2 patients; neuroendocrine tumor, 1 patient; and dysplasia, 9 patients); thus, these patients were excluded from the final analysis. Finally, 338 patients (169 per group) were categorized into the modified intention-to-treat (mITT) analysis in this study (Figure 1).

Baseline characteristics

In the current study, 338 patients were included in the mITT analysis, which comprised 169 patients (111 men and 58 women; mean [SD] age, 54.5 [9.3] years) in the D2 group and 169 patients (102 men and 67 women; mean [SD] age, 54.8 [9.5] years) in the D2+CME group. The BMI (mean [SD]) of patients in the D2 and D2+CME groups was 22.19 (3.18) kg/m^2 and 22.70 (3.03) kg/m^2, respectively, with no significant difference between groups ($p = 0.123$). No significant differences were observed between the two groups with respect to American Society of Anesthesiology (ASA) score ($p = 0.241$). The comorbidity rate of the D2 group and the D2+CME group was 41.4% and 52.1%, respectively, with no statistically significant difference between groups ($p = 0.050$) (Table 1).

With respect to tumor location, primary lesion size, and TNM (primary tumor, regional lymph nodes, and distant metastasis) pathological stage,[20] no significant differences were observed between the D2 and D2+CME groups. Compared with the D2 group, patients in the D2+CME group suffered from poorer differentiation ($p = 0.029$). However, there was no significant difference in Lauren classification ($p = 0.263$) (Table 2).

Surgical outcomes

Surgical characteristics are shown in Table 3. All patients in the mITT population who underwent either D2+CME or conventional D2 surgery had R0 tumor resection, achieved negative margins, and passed surgical quality control (results of the surgical video review are shown in Table S1). D2+CME was associated with a longer laparoscopic dissection time (mean [SD], 106.8 [24.5] min for D2 versus 133.1 [23.6] min for D2+CME, $p < 0.0001$) and a longer total operation time (mean [SD], 259.9 [41.5] min for D2 versus 293.1 [42.4] min for D2+CME, $p < 0.0001$). Additionally, owing to the preference of surgeons, patients in the D2+CME group received more Roux-en-Y reconstructions (1.2% in D2 versus 44.4% in D2+CME, $p < 0.0001$) compared with patients in the D2 group. Patients in the D2+CME group showed statistically significant less intralaparoscopic blood loss (median [interquartile range (IQR)], 37.0 [33.5] mL for D2 versus 15.0 [23.0] mL for D2+CME, $p < 0.0001$) and more LN harvesting (median [IQR], 27 [13] for D2 versus 34 [16] for D2+CME, $p < 0.0001$) than those in the D2 group. No statistically significant difference was found in the number of positive LNs between the two groups (median [IQR], 3 [7] for D2 versus 2 [5] for D2+CME, $p = 0.099$).

During the surgical procedures, two patients in the D2 group (1.2%) received combined organ resection due to injury of the supplying vessels, including one patient who received transverse colectomy and another who received splenectomy. In contrast, no patients in the D2+CME group received excessive organ resection.

Postoperative recovery and complications

The first flatus duration is an optimal parameter to evaluate the recovery of the gastrointestinal tract after abdominal surgery. In this study, the starting point of the first flatus duration was on the first day after the operation; meanwhile, no patient was lost during the evaluation period. Kaplan-Meier curve and log-rank test revealed that D2+CME exhibited a significant advantage in shortening the postoperative flatus time compared with D2 surgery (Figure 2; $p = 0.009$). Univariate Cox regression analysis also revealed that the risk ratio (RR) for postoperative flatus in the D2+CME group was 1.247 (95% confidence interval [CI], 1.006-1.545, $p = 0.044$; Table S2). Although a slight difference was observed in duration of total hospital stay (median [IQR], 16[5] days for D2 versus 16 [5] days for D2+CME, $p = 0.033$), the postoperative hospital stay duration was comparable between the two groups, with no statistically significant difference (median [IQR], 10 [2] days for D2 versus 10 [3] days for D2+CME, $p = 0.053$, Table 3).

Table 4 shows postoperative morbidities and mortality. The overall 30-day postoperative morbidity rate in the D2 and D2+CME groups was 16.0% (27/169) and 20.1% (34/169), respectively, with no statistically significant difference between groups ($p = 0.322$). When comparing complication grades (Clavien-Dindo classification[21]), the D2+CME group was less likely to have severe complications (grade IIIa or higher) than the D2 group (4 in D2+CME versus 9 in D2, $p = 0.041$). Grade IIIa complications occurred in seven patients (intraluminal bleeding in four patients, anastomosis leakage in one patient, anastomosis stenosis in one patient, and intra-abdominal bleeding in one patient) in the D2 group and four patients (intra-abdominal infection in one patient, dehiscence of incision in one patient, and pleural effusion with percutaneous drainage in two patients) in the D2+CME group. Grade IVa complications occurred in two patients (one had an unplanned re-operation due to anastomotic bleeding and leakage, and the other received intensive care unit [ICU] care for severe pneumonia and respiratory failure) in the D2 group. In contrast, no grade IVa complications occurred in the D2+CME group. No death within 30 days after the procedure occurred in either group (Table 4).

Logistic regression analysis revealed that age (odd ratio [OR], 1.056; 95% CI, 1.021–1.091), comorbidity (OR, 1.830; 95% CI, 1.042–3.212), and total operation duration (OR, 1.008; 95% CI, 1.002–1.014) were the risk factors for postoperative complications ($p < 0.05$). When these three parameters were included in a multivariate analysis, patient age (OR, 1.056; 95% CI, 1.021–1.092) and operation duration (OR, 1.008; 95% CI,

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram

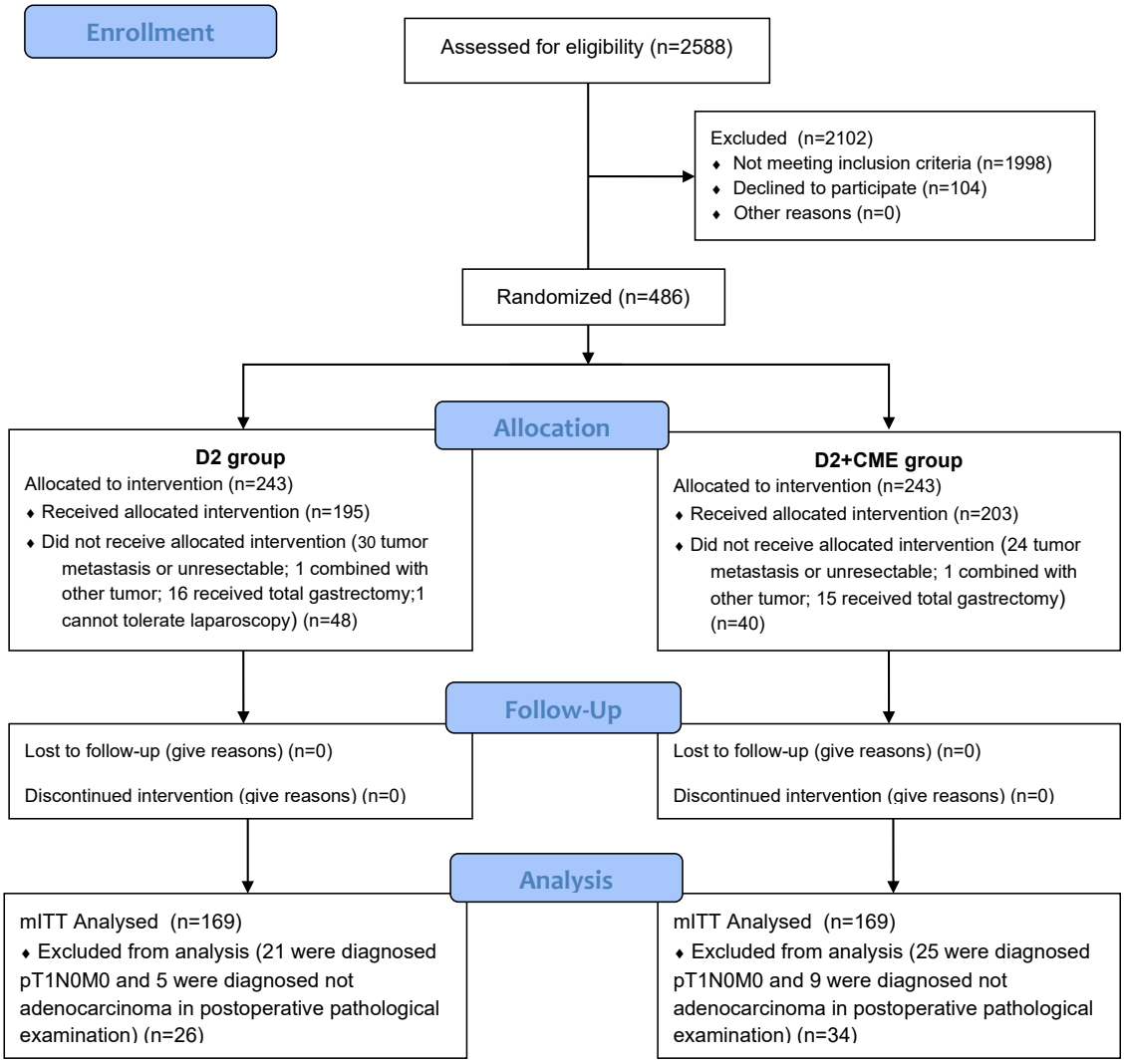


Figure 1. Study flow chart

1.002–1.0014) were considered as independent risk factors for postoperative morbidities ($p < 0.05$) (Table S3).

DISCUSSION

Considering the high rates of morbidities and recurrence after D2 gastrectomy, reducing surgical risks and improving long-term survival of gastric cancer patients remain a challenge for surgeons. The short-term outcomes of our RCT have shown that D2+CME surgery is associated with advantages in intraoperative blood loss, LN harvest, and postoperative flatus duration and could provide better surgical safety than conventional D2 for patients with AGC.

Recently, three multicenter RCTs from Japan (JLSSG0901[22]), China (CLASS-01[23,24]), and Korea (KLASS-02[25,26]) have evaluated

Table 1. Baseline characteristics of patients who underwent D2 and D2+CME

	D2 (n = 169)	D2+CME (n = 169)	p value
Gender, n (%)			
Male	111 (65.7)	102 (60.4)	0.311[a]
Female	58 (34.3)	67 (39.6)	
Age (years), mean ± SD	54.5 ± 9.3	54.8 ± 9.5	0.772[b]
BMI (kg/m^2), mean ± SD	22.19 ± 3.18	22.70 ± 3.03	0.123[b]
ASA score, n (%)			
1	32 (18.9)	31 (18.3)	0.241[a]
2	124 (73.4)	132 (78.1)	
3	13 (7.7)	6 (3.6)	
Comorbidities, n (%)			
No	99 (58.6)	81 (47.9)	0.050[a]
Yes	70 (41.4)	88 (52.1)	
Hypertension	23	29	
Diabetes mellitus	5	12	
Chronic gastritis	6	8	
Pulmonary	2	5	
Heart and cardiovascular	7	2	
Renal	5	5	
Liver and gallbladder	9	13	
Brain and cerebrovascular	6	2	
Others	15	26	

SD, standard deviation; BMI, body mass index.
[a]χ^2 test.
[b]Mann-Whitney *U* test.

Table 2. Tumor characteristics of patients who underwent D2 and D2+CME

	D2	D2+CME	p value
Tumor location, n (%)			
Middle	44 (26.0)	59 (34.9)	0.076[d]
Lower	125 (74.0)	110 (65.1)	
Differentiation, n (%)			
High	6 (3.6)	2 (1.2)	0.029[d]
Moderate	83 (49.0)	66 (39.1)	
Low	76 (45.0)	100 (59.2)	
Other[a]	4 (2.4)	1 (0.5)	
Lauren classification, n (%)			
Intestinal	45 (26.6)	37 (21.9)	0.263[d]
Diffuse	79 (46.7)	94 (55.6)	
Mix	45 (26.6)	38 (22.5)	
Tumor size (cm), median ± IQR	3.0 ± 1.5	3.0 ± 1.5	0.511[b]
pT stage,[c,e] n (%)			
T1	16 (9.5)	12 (7.1)	0.354[d]
T2	39 (23.1)	45 (26.6)	
T3	99 (58.6)	104 (61.5)	
T4a	15 (8.8)	8 (4.8)	
pN stage,[c,f] n (%)			
N0	54 (32.0)	68 (40.2)	0.070[d]
N1	28 (16.6)	37 (21.9)	
N2	40 (23.6)	25 (14.8)	
N3	47 (27.8)	39 (23.1)	
p stage,[g] n (%)			
Ib	31 (18.3)	35 (20.7)	0.267[d]
IIa	39 (23.1)	50 (29.6)	
IIb	23 (13.6)	26 (15.4)	
IIIa	34 (20.1)	24 (14.2)	
IIIb	35 (20.7)	32 (18.9)	
IIIc	7 (4.2)	2 (1.2)	

IQR, interquartile range.
[a]Others included mucinous adenocarcinoma, signet ring cell carcinoma, adenosquamous carcinoma, and adenocarcinoma with lymphoid stroma.
[b]Mann-Whitney *U* test.
[c]pT and pN stage were based on the AJCC Cancer Staging Manual, 7th Edition.
[d]χ^2 test.
[e]pT stage: pathological primary tumor (T) stage.
[f]pN stage: pathological regional lymph nodes (N) stage.
[g]p stage: pathological stage.

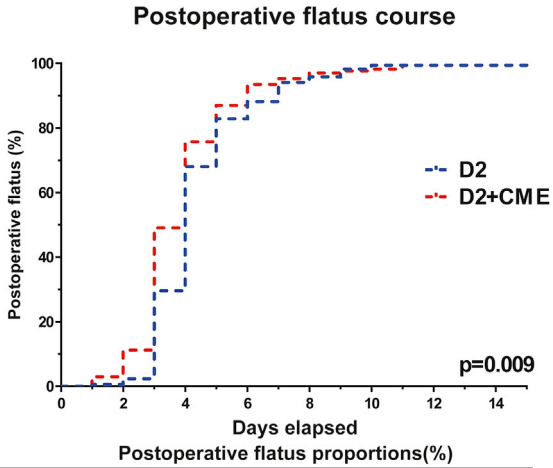
the short-term outcomes of conventional D2 for local AGC. In their studies, the intraoperative blood loss during D2 dissection under laparoscopy ranged from 30 to 150 mL.[23,26] In our study, blood loss during extracorporeal reconstruction was low and hardly estimated; thus, we mainly focused on intralaparoscopic bleeding during surgery. As shown in Table 3, blood loss was significantly lower in the D2+CME group than in the D2 group, and even the latter is equivalent to the JLSSG0901 study.[22] This amount of blood loss during D2+CME surgery is consistent with our retrospective studies.[16,17] Although the total operation duration was longer for D2+CME than for D2, no more surgery-related side events occurred during D2+CME (Table 4). During the postoperative recovery course, the mean first flatus time after D2 surgery was reported as 3.5 days.[23,26] In our study, both the Kaplan-Meier curve and Cox regression analysis indicated that D2+CME could shorten the postoperative gastrointestinal tract dysfunction duration (Figure 2; Table S2). These results showed that D2+CME had advantages in intraoperative blood loss and postoperative flatus, which revealed that D2+CME surgery could cause less surgical burden and provide faster recovery than conventional D2.

Our results indicate the superiority of D2+CME surgery in the number of LNs harvested. In both groups, the mean number of LNs harvested (34 in the D2+CME group and 27 in the D2 group) far exceeded the 15 LNs required by the guidelines; thus, the quality of LN dissection can be maintained. These numbers appear to be slightly lower than those reported in other trials (47 in JLSSG0901,[22] 36 in CLASS-01,[23] and 46 in KLASS-02[26]). Li et al. summarized several factors that affect the number of retrieved LNs, including the innate number of LNs, the extent of the surgery, the retrieval technique, the fat volume of the specimens, and nodal status.[27] In our study, the specimens and LNs were examined thoroughly by experienced pathologists who

Table 3. Surgical results of patients who underwent D2 and D2+CME

	D2	D2+CME	p value
Estimated intra-laparoscopic bleeding (mL), median ± IQR	37.0 ± 33.5	15.0 ± 23.0	<0.0001[a]
Laparoscopic dissection time (min), mean ± SD	106.8 ± 24.5	133.1 ± 23.6	<0.0001[a]
Total operation time (min), mean ± SD	259.9 ± 41.5	293.1 ± 42.4	<0.0001[a]
Number of LNs harvested, median ± IQR	27 ± 13	34 ± 16	<0.0001[a]
Number of positive LNs, median ± IQR	3 ± 7	2 ± 5	0.099[a]
Reconstruction, n (%)			
BII	167 (98.8)	94 (55.6)	<0.0001[b]
Roux-en-Y	2 (1.2)	75 (44.4)	
Combined resection due to surgical injury,[c] n (%)			
No	167 (98.8)	169 (100.0)	0.499[d]
Yes	2 (1.2)	0 (0.0)	
Total hospital stay (days), median ± IQR	16 ± 5	16 ± 5	0.033[a]
Postoperative hospital stay (days), median ± IQR	10 ± 2	10 ± 3	0.053[a]

[a]Mann-Whitney *U* test.
[b]χ^2 test.
[c]Two patients in the D2 group received combined organ resection (one received transverse colectomy, and the other received splenectomy) due to the surgical injury.
[d]Fisher's exact test.



Postoperative flatus proportions(%)

Days elapsed	0	2	4	6	8	10	12	14
D2 group	0.0	2.4	68.0	88.2	95.9	99.4	99.4	99.4
D2+CME group	0.0	11.2	75.7	93.5	97.0	98.2	99.4	100.0

Figure 2. Kaplan-Meier analysis of postoperative flatus duration
A log-rank test was used for statistical analysis.

were blinded to surgical interventions.[19] Consistent with our retrospective studies on LN dissection,[16,17] this advantage of D2+CME surgery is convincing and will be further verified by oncological survival results, which are being assessed in the follow-up phase of the trial.

According to results of recent RCTs, postoperative complications and mortality rates of conventional D2 under laparoscopy are 15% and 0% in Japan,[22] 15.2% and 2% in China,[23] and 16.6% and 0.4% in Korea,[26] respectively. In addition, a retrospective study of AGC patients from 10 Korean institutions reported a morbidity rate of 15.9% and a mortality rate of 0.8% after laparoscopic D2 dissection.[28] In our study, the overall morbidity and mortality rates in the D2 group are equivalent to those reported in above studies, which suggests that the surgeons who participated are well qualified, with experience performing the D2 technique. In subgroup analysis of different complication grades, the rate of severe complications (grade IIIa or higher) after D2 was 3.5% in the CLASS-01 trial[23], 8.9% in the KLASS-02 trial,[26] and 5.3% in our study (Table 4), respectively. However, compared to conventional D2, D2+CME is less likely to cause severe complications, such as intra-abdominal bleeding, anastomosis leakage, and re-operation. Considering that two patients in the D2 group underwent excessive organ resection during the operation (compared with no patients in the D2+CME group; Table 3), D2+CME appears to provide better surgical safety during both the intra- and postoperative period. Further studies with a large-scale population are needed.

The advantages of the short-term outcomes and surgical safety after D2+CME surgery are likely due to the recognition of mesogastrium and its bed (i.e., membrane anatomy) during the operation.[15] Conventional D2, which dissects LNs along the blood vessels, has the risk of vascular injury and might break the gastric mesentery, resulting in bleeding or remnants of tissues containing LNs and disseminated cancer cells. In contrast, D2+CME, aiming to *en bloc* resect the mesogastrium with an intact envelope that contains blood vessels, LNs, and adipose tissues, helps surgeons better define the anatomical boundaries of mesogastrium and dissect it in the embryological plane. We previously presented the anatomical architecture of gastric mesentery with a model of proximal segment of dorsal mesogastrium (PSDM).[15] Different from bursa sac or greater omentum, PSDM envelopes the feeding structure (blood and lymphatic vessels) of the stomach and adjacent adipose tissues. Under such conditions, D2+CME surgery could lead to less surgical trauma, fewer severe complications, and more LNs harvested, since the vessels, LNs, and adipose tissues are all enveloped in the PSDM.[19]

In conclusion, D2+CME exhibits advantages in terms of intraoperative blood loss, LNs harvested, and postoperative flatus duration. Although the overall postoperative complications were comparable, complications in the D2+CME group were significantly less severe than those in the D2 group. Therefore, D2+CME is associated with better short-term outcomes and surgical safety than conventional D2 dissection for patients with advanced gastric cancer.

Limitations of study

There are some limitations of the study. First, as a developed surgical procedure, D2+CME is based on the CME concept of

Table 4. Postoperative complication of patients who underwent D2 and D2+CME

	D2	D2+CME	p value
Overall complications	27 (16.0)	34 (20.1)	0.322[a]
Clavien-Dindo classification of complications			
Grade I	4 (2.4)	8 (4.7)	0.240[a]
Delay recovery of bowel movement	1	2	
Small amount of pleural effusion	2	2	
Transient hypoproteinemia	1	0	
Fever	0	1	
Small amount of ascites	0	1	
Transient neurological symptoms	0	1	
Postoperative sinus bradycardia	0	1	
Grade II	14 (8.3)	22 (13.0)	0.158[a]
Pulmonary infection	8	10	
Urinary tract infection	1	1	
Postoperative ileus	1	3	
Leakage of lymphatics	0	1	
Gastroparesis	1	1	
Anemia with blood transfusion	2	2	
Intraluminal bleeding	0	2	
Fluid collection	0	1	
Coagulation abnormality	1	0	
Wound problem	0	1	
Grade IIIa	7 (4.1)	4 (2.4)	0.358[a]
Intraluminal bleeding	4	0	
Anastomotic leakage	1	0	
Anastomotic stenosis	1	0	
Intra-abdominal infection	0	1	
Intra-abdominal bleeding	1	0	
Pleural effusion with percutaneous drainage	0	2	
Dehiscence of incision	0	1	
Grade IIIb	0 (0.0)	0 (0.0)	NA
Grade IVa	2 (1.2)	0 (0.0)	0.499[b]
Anastomosis leakage	1	0	
Lung failure	1	0	
Grade IVb	0 (0.0)	0 (0.0)	NA
Grade V	0	0	NA
Severity of complications			0.041[a]
Grade I and II	18 (66.6)	30 (88.3)	
Grade $\geq$ IIIa	9 (33.3)	4 (11.8)	

Data are presented as n (%) of patients. NA, not applicable.
[a]χ^2 test.
[b]Fisher's exact test.

"membrane anatomy" in gastric cancer surgery. Our RCT is a phase 2 study to evaluate its safety and efficacy. To maintain the uniformity and quality of each treatment, D2+CME was performed only by its advocator, and D2 was performed by seven other surgeons who are skillful and well experienced in the conventional D2 procedure. This allocation might have resulted in potential bias due to personal experience. Large-scale phase 3 trials will be initiated to further validate the efficiency of D2+CME. Second, this study did not evaluate patient-centered outcomes (e.g., quality of life, satisfaction, or return to normal life functioning). Although our results showed that participants in the D2+CME group had less surgery-related trauma and shorter flatus duration, it is still unclear whether these benefits significantly improve the quality of life of AGC patients. Third, only distal gastrectomy was examined in this study. Thus, our results may be less pertinent to the western countries in which proximal gastric cancer is more prevalent and proximal/total gastrectomy is required.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

- KEY RESOURCES TABLE
- RESOURCE AVAILABILITY
  - Lead contact
  - Materials availability
  - Data and code availability
- EXPERIMENTAL MODEL AND SUBJECT DETAILS
- METHOD DETAILS
  - Study design
  - Patients
  - Randomization, allocation and masking
  - The selection of gastrectomy
  - Surgical intervention
  - Surgical quality control
  - Postoperative management and adjuvant chemotherapy
  - Outcomes measurements
  - Sample size and modified intention-to-treat (mITT) analysis
- QUANTIFICATION AND STATISTICAL ANALYSIS
- ADDITIONAL RESOURCES

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.xcrm.2021.100217.

ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (grants 81372324 and 81874185).

We thank the staff of the Department of GI Surgery of Tongji Hospital for providing support for this trial. We thank C. Jin, L. Zhu, J. Shi, J. Wu, M. Pan, J. Yuan, and F. Sheng for assistance with sample collection and follow-up. We are especially thankful to the Department of Epidemiology and Biostatistics of Tongji Medical College and the Department of Pathology of Tongji Hospital for providing support for our statistical analysis and pathological analysis. We sincerely appreciate Y. Li for her excellent work in our figures. We apologize to the colleagues whose work was not cited due to space constraints.

AUTHOR CONTRIBUTIONS

Conceptualization, J.G. and D.X.; methodology, J.G., D.X., P.Y., and J.S.; resources, J.Q., J.W., Q.Y., Y.H., C.Y., Z.C., J.H., and J.G.; investigation, J.S., D.X., L.L., J.Q., J.W., Q.Y., Y.H., C.Y., Z.C., J.H., B.C., and Y.W.; formal analysis, J.S. and P.Y.; data curation, D.X., P.Y., and J.S.; writing – original draft,

J.S. and D.X.; writing – review & editing, D.X., J.S., and J.G.; visualization, J.S.; supervision, D.X. and J.G.; project administration, D.X. and J.G.; funding acquisition, J.G.

DECLARATION OF INTERESTS

The authors declare no competing interests.

Received: May 20, 2020
Revised: December 6, 2020
Accepted: February 16, 2021
Published: March 16, 2021

REFERENCES

1. Torre, L.A., Bray, F., Siegel, R.L., Ferlay, J., Lortet-Tieulent, J., and Jemal, A. (2015). Global cancer statistics, 2012. CA Cancer J. Clin. *65*, 87–108.
2. Sasako, M., Saka, M., Fukagawa, T., Katai, H., and Sano, T. (2007). Surgical treatment of advanced gastric cancer: Japanese perspective. Dig. Surg. *24*, 101–107.
3. Japanese Gastric Cancer Association (2011). Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer *14*, 113–123.
4. Sasako, M., Sano, T., Yamamoto, S., Kurokawa, Y., Nashimoto, A., Kurita, A., Hiratsuka, M., Tsujinaka, T., Kinoshita, T., Arai, K., et al.; Japan Clinical Oncology Group (2008). D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. N. Engl. J. Med. *359*, 453–462.
5. Yang, S.H., Zhang, Y.C., Yang, K.H., Li, Y.P., He, X.D., Tian, J.H., Lv, T.H., Hui, Y.H., and Sharma, N. (2009). An evidence-based medicine review of lymphadenectomy extent for gastric cancer. Am. J. Surg. *197*, 246–251.
6. Heald, R.J., Husband, E.M., and Ryall, R.D. (1982). The mesorectum in rectal cancer surgery–the clue to pelvic recurrence? Br. J. Surg. *69*, 613–616.
7. Heald, R.J., and Ryall, R.D. (1986). Recurrence and survival after total mesorectal excision for rectal cancer. Lancet *1*, 1479–1482.
8. Hohenberger, W., Weber, K., Matzel, K., Papadopoulos, T., and Merkel, S. (2009). Standardized surgery for colonic cancer: complete mesocolic excision and central ligation–technical notes and outcome. Colorectal Dis. *11*, 354–364, discussion 364–365.
9. Kim, N.K., Kim, Y.W., Han, Y.D., Cho, M.S., Hur, H., Min, B.S., and Lee, K.Y. (2016). Complete mesocolic excision and central vascular ligation for colon cancer: Principle, anatomy, surgical technique, and outcomes. Surg. Oncol. *25*, 252–262.
10. Siani, L.M., and Garulli, G. (2017). The importance of the mesofascial interface in complete mesocolic excision. Surgeon *15*, 240–249.
11. West, N.P., Hohenberger, W., Weber, K., Perrakis, A., Finan, P.J., and Quirke, P. (2010). Complete mesocolic excision with central vascular ligation produces an oncologically superior specimen compared with standard surgery for carcinoma of the colon. J. Clin. Oncol. *28*, 272–278.
12. Giacopuzzi, S., Bencivenga, M., Cipollari, C., Weindelmayer, J., and de Manzoni, G. (2017). Lymphadenectomy: how to do it? Transl. Gastroenterol. Hepatol. *2*, 28.
13. Xie, D., Osaiweran, H., Liu, L., Wang, X., Yu, C., Tong, Y., Hu, J., and Gong, J. (2013). Mesogastrium: a fifth route of metastasis in gastric cancer? Med. Hypotheses *80*, 498–500.
14. Xie, D., Liu, L., Osaiweran, H., Yu, C., Sheng, F., Gao, C., Hu, J., and Gong, J. (2015). Detection and Characterization of Metastatic Cancer Cells in the Mesogastrium of Gastric Cancer Patients. PLoS ONE *10*, e0142970.
15. Xie, D., Gao, C., Lu, A., Liu, L., Yu, C., Hu, J., and Gong, J. (2015). Proximal segmentation of the dorsal mesogastrium reveals new anatomical implications for laparoscopic surgery. Sci. Rep. *5*, 16287.
16. Xie, D., Yu, C., Liu, L., Osaiweran, H., Gao, C., Hu, J., and Gong, J. (2016). Short-term outcomes of laparoscopic D2 lymphadenectomy with complete mesogastrium excision for advanced gastric cancer. Surg. Endosc. *30*, 5138–5139.
17. Cao, B., Xiao, A., Shen, J., Xie, D., and Gong, J. (2020). An Optimal Surgical Approach for Suprapancreatic Area Dissection in Laparoscopic D2 Gastrectomy with Complete Mesogastric Excision. J. Gastrointest. Surg. *24*, 916–917.
18. Xie, D., Wang, Y., Shen, J., Hu, J., Yin, P., and Gong, J. (2018). Detection of carcinoembryonic antigen in peritoneal fluid of patients undergoing laparoscopic distal gastrectomy with complete mesogastric excision. Br. J. Surg. *105*, 1471–1479.
19. Shen, J., Cao, B., Wang, Y., Xiao, A., Qin, J., Wu, J., Yan, Q., Hu, Y., Yang, C., Cao, Z., et al. (2018). Prospective randomized controlled trial to compare laparoscopic distal gastrectomy (D2 lymphadenectomy plus complete mesogastrium excision, D2 + CME) with conventional D2 lymphadenectomy for locally advanced gastric adenocarcinoma: study protocol for a randomized controlled trial. Trials *19*, 432.
20. American Joint Committee on Cancer (2010). AJCC Cancer Staging Manual, 7th Edition (Springer-Verlag).
21. Clavien, P.A., Sanabria, J.R., and Strasberg, S.M. (1992). Proposed classification of complications of surgery with examples of utility in cholecystectomy. Surgery *111*, 518–526.
22. Inaki, N., Etoh, T., Ohyama, T., Uchiyama, K., Katada, N., Koeda, K., Yoshida, K., Takagane, A., Kojima, K., Sakuramoto, S., et al. (2015). A Multi-institutional, Prospective, Phase II Feasibility Study of Laparoscopy-Assisted Distal Gastrectomy with D2 Lymph Node Dissection for Locally Advanced Gastric Cancer (JLSSG0901). World J. Surg. *39*, 2734–2741.
23. Hu, Y., Huang, C., Sun, Y., Su, X., Cao, H., Hu, J., Xue, Y., Suo, J., Tao, K., He, X., et al. (2016). Morbidity and Mortality of Laparoscopic Versus Open D2 Distal Gastrectomy for Advanced Gastric Cancer: A Randomized Controlled Trial. J. Clin. Oncol. *34*, 1350–1357.
24. Yu, J., Huang, C., Sun, Y., Su, X., Cao, H., Hu, J., Wang, K., Suo, J., Tao, K., He, X., et al.; Chinese Laparoscopic Gastrointestinal Surgery Study (CLASS) Group (2019). Effect of Laparoscopic vs Open Distal Gastrectomy on 3-Year Disease-Free Survival in Patients With Locally Advanced Gastric Cancer: The CLASS-01 Randomized Clinical Trial. JAMA *321*, 1983–1992.
25. Hur, H., Lee, H.Y., Lee, H.J., Kim, M.C., Hyung, W.J., Park, Y.K., Kim, W., and Han, S.U. (2015). Efficacy of laparoscopic subtotal gastrectomy with D2 lymphadenectomy for locally advanced gastric cancer: the protocol of the KLASS-02 multicenter randomized controlled clinical trial. BMC Cancer *15*, 355.
26. Lee, H.J., Hyung, W.J., Yang, H.K., Han, S.U., Park, Y.K., An, J.Y., Kim, W., Kim, H.I., Kim, H.H., Ryu, S.W., et al.; Korean Laparo-endoscopic Gastrointestinal Surgery Study (KLASS) Group (2019). Short-term Outcomes of a Multicenter Randomized Controlled Trial Comparing Laparoscopic Distal Gastrectomy With D2 Lymphadenectomy to Open Distal Gastrectomy for Locally Advanced Gastric Cancer (KLASS-02-RCT). Ann. Surg. *270*, 983–991.
27. Li, M., Wang, X.A., Wang, L., Wu, X., Wu, W., Song, X., Zhao, S., Zhang, F., Ma, Q., Liang, H., et al. (2018). A three-step method for modular lymphadenectomy in gastric cancer surgery: The ability to retrieve sufficient lymph nodes and improve survival. Am. J. Surg. *215*, 91–96.
28. Park, D.J., Han, S.U., Hyung, W.J., Kim, M.C., Kim, W., Ryu, S.Y., Ryu, S.W., Song, K.Y., Lee, H.J., Cho, G.S., and Kim, H.H.; Korean Laparoscopic Gastrointestinal Surgery Study (KLASS) Group (2012). Long-term outcomes after laparoscopy-assisted gastrectomy for advanced gastric cancer: a large-scale multicenter retrospective study. Surg. Endosc. *26*, 1548–1553.
29. Bang, Y.J., Kim, Y.W., Yang, H.K., Chung, H.C., Park, Y.K., Lee, K.H., Lee, K.W., Kim, Y.H., Noh, S.I., Cho, J.Y., et al.; CLASSIC trial investigators (2012). Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet *379*, 315–321.
30. U.S. Department of Health and Human Services (2010). Common Terminology Criteria for Adverse Events (National Institutes of Health).

STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
Individual patient-level data	This clinical trial	https://doi.org/10.17632/23ghwhmhpm.1
Software and algorithms		
Prism version 8.0.2	GraphPad Software	https://www.graphpad.com/scientific-software/prism/
SAS version 9.4 for Windows	SAS Institute	https://www.sas.com/en_us/home.geo.html/

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the Lead Contact, Jianping Gong (dxxie@tjh.tjmu.edu.cn).

Materials availability

This study did not generate new unique reagents.

Data and code availability

Individual patient-level data (IPD) for this trial could be obtained from Mendeley Data (https://doi.org/10.17632/23ghwhmhpm.1). To protect patient privacy, names, birth date, address information, contact information, etc. were removed. There was no new code developed as part of this study.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

This investigation was approved by the Tongji Hospital Ethics Committee (ID: TJ-C20130811). Demographic information including age and gender are provided in Table 1.

METHOD DETAILS

Study design

This single-center, prospective, paralleled, randomized controlled trial (allocation ratio: 1:1), between September 2014 and June 2018, was conducted at the Department of Gastrointestinal Surgery, Tongji Hospital, Huazhong University of Science and Technology (HUST), Wuhan, China, where approximately 350 cases of laparoscopic radical gastrectomy were performed annually. The study was approved by the Tongji Hospital Ethics Committee (TJ-C20130811). All patients signed an informed consent document to participate in this study. The protocol of study was published in Trials[19] (Methods S1).

Patients

Patient inclusion criteria were as follows: 1) aged older than 18 and younger than 75 years; 2) body mass index less than 30 kg/m^2; 3) primary gastric adenocarcinoma pathologically confirmed by endoscopic biopsy; 4) cT2-4N0-3M0 at preoperative evaluation according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual 7^{th} Edition[20]; 5) expected curative resection via laparoscopic distal subtotal gastrectomy; 6) Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1 and American Society of Anesthesiology (ASA) class I, II, or III; 7) written informed consent. The patient exclusion criteria were the following: 1) pregnant or breast-feeding women, 2) severe mental disorder, 3) previous neoadjuvant chemotherapy or radiotherapy, 4) previous upper abdominal surgery, 5) other malignant diseases or other gastric malignant tumor (including lymphoma and gastric stromal tumor), or 6) total gastrectomy.

Randomization, allocation and masking

Randomization list was generated by SAS software (version 9.4, SAS Institute Inc., USA) with a 1:1 allocation using random block size of six. After preoperative evaluation and signed informed consent, eligible patient was submitted to an independent data center

(managed by Prof. P.Y, Department of Epidemiology and Biostatistics, Tongji Medical College, HUST, Wuhan, China) and allocated to each group in sequence according to the randomization list. Information on treatment allocation was subsequently sent to the surgical intervention staff, and the appropriate operation was performed. In this trial, patients and the follow-up staff were kept blind to the treatment allocation. Surgical intervention staff who delivered the operation did not take outcome measurement.

The selection of gastrectomy

According to the Japanese gastric cancer treatment guidelines 2010 (version 3)[3], distal gastrectomy was selected when a satisfactory proximal resection margin (at least 3 cm for T2 or deeper tumors with an expansive growth pattern and 5 cm for those with infiltrative growth pattern) could be obtained. The extent of gastrectomy was evaluated by abdominal CT and/or laparoscopic exploration. In current research, patients who were not suitable for distal gastrectomy would be excluded.

Surgical intervention

Patients in the D2 group received conventional D2 resection under laparoscopy which was performed by 7 experienced surgeons (J.-C. Q, J.-H. W, Q. Y, Y.-L. H, C.-Y. Y, Z.-X. C, J.-B. H). All of the surgeons have performed at least 50 cases annually and had no experience of D2+CME technique. Patients in the D2+CME group received D2+CME surgery under laparoscopy which was performed as described previously.[16–19] As an optimal technique, D2+CME surgery was performed by the advocator Prof. J.-P.G who have performed nearly 100 cases annually in order to achieve a steady quality control. In both groups, dissection of No. 14v was optional, and omentectomy was necessary. Reconstruction was performed by the standard extracorporeal Billroth I/II or Roux-en-Y fashion, and the type of reconstruction was determined by the surgeon's experience.

Surgical quality control

Surgical quality control was evaluated by using intraoperative video recordings and photographs of the specimens.[19] In D2 group, the extent of D2 lymph node dissection are based on Japanese gastric cancer treatment guidelines 2010 (version 3)[3]. The intraoperative videos should clearly show the dissection of lymph node stations 1, 3, 4sb, 4d, 5, 6, 7, 8a, 9, 11p, and 12a. The dissected specimen should be examined by experienced surgeon and pathologist to ensure that the proximal resection margin and the removal of lymph nodes are satisfactory. In D2+CME group, the quality of D2+CME surgery is controlled based on intraoperative video recordings and a mesenteric scoring system[19]. Briefly, the CME technique should meet the following criteria: clear exposure of five mesenteries of stomach; complete mobilization of the mesentery covered by an intact visceral fascial layer; dissection in the embryological plane to remove an intact envelope of mesogastrium; ligation of supplying blood vessels at the root of D2 level. The detailed quality control measurements were described in our published protocol (Methods S1).

Postoperative management and adjuvant chemotherapy

Gastrointestinal function was evaluated twice per day in postoperative recovery course. After first flatus, the gastric tube was pulled out, and the patients were suggested to intake a liquid diet and gradually transited into soft diet.

All patients with locally AGC were recommended to receive postoperative chemotherapy. The first-line regimen was XELOX (oxaliplatin 130 mg/m^2 on day 1 and capecitabine 1,000 mg/m^2 twice daily on days 1-14 of a 3-week cycle for eight cycles over half a year).[29] After each cycle, patients received a toxicity assessment; toxicities were graded according to the Nation Cancer Institute's Common Terminology Criteria (NCI-CTC) for Adverse Events (version 4)[30]. If severe adverse effects occurred, chemotherapy could be reduced, delayed or terminated according to the actual situation.

Outcomes measurements

The primary outcome of this trial is 3-year disease-free survival. Patients participating in this trial were asked to complete at least 3 years of follow-up. Follow-up mainly consists of telephone and out-patient interviews, and it will be held at 3-month intervals for the first 2 years and at 6-month intervals afterward. During the follow-up period, patients would receive tumor assessment by every 6 months, including chest radiograph, abdominal CT and upper gastrointestinal endoscopy.

The secondary outcomes included recurrence pattern, surgical outcomes, morbidity and mortality. Recurrence pattern was identified by medical history, physical examination and imaging evaluation. Surgical outcomes including intra-operative bleeding, surgical duration, lymph node harvesting and surgical injury, were evaluated via video recording and postoperative specimen examination. Morbidity and mortality were evaluated within 30 days after surgery. Postoperative complications were diagnosed on the basis of symptom, physical examination, laboratory test and imaging evidence according to our published protocol (Methods S1). The severity of postoperative complications was assessed according to the Clavien-Dindo classification[23].

Sample size and modified intention-to-treat (mITT) analysis

This study was designed to evaluate the superiority of the D2+CME surgery in terms of 3-year disease-free survival. The sample size is calculated through two independent proportions power analysis. The calculated sample size was 304 (152 per group), with a two-sided α of 5% and 80% statistical power (z-test) to detect a supposing 3-year DFS difference of 15%. Given an expected drop-out rate of 10%, each group needed to enrol at least 168 patients, for a total of 336 patients. Sample size was calculated using PASS software, version 15.0 (NCSS, LLC). Detailed sample size calculation was described in our published protocol (Methods S1).

The modified intention-to-treat (mITT) population excluded patients who were randomized but met the post-randomized exclusion criteria, which including: 1) diagnosed with severe tumor infiltration or metastasis during laparoscopic exploration; 2) found combination with other abdominal tumors during operation; 3) received total gastrectomy due to insufficient proximal margin; 4) could not tolerate the laparoscopic operation; 5) diagnosed with AJCC TNM staging[20]: pT1N0M0 or found not to be adenocarcinoma through postoperative pathological biopsy. All the remaining patients (patients underwent laparoscopic radical distal gastrectomy and were pathologically diagnosed with gastric adenocarcinoma with TNM stage[20] pT1N1-3M0 and pT2-4N0-3M0) were kept in the same group in which they were originally randomized and analyzed.

QUANTIFICATION AND STATISTICAL ANALYSIS

The surgical outcomes, postoperative recovery data, morbidity and mortality were compared between the groups in a mITT analysis. Continuous variables were assessed for normality of distribution using the one-sample Kolmogorov–Smirnov test. Continuous variables with a normal distribution were reported as mean (standard deviations, SD). Continuous variables that were not normally distributed were expressed as median (inter quartile range, IQR). Mann-Whitney U test was used for the statistical analysis of continuous variables across the board. Categorical variables were expressed as absolute numbers and percentages and compared using Pearson's $\chi 2$ test or Fisher's exact test as appropriate. Multivariable binary logistic regression analysis was performed to identify independent risk factors for complications and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. The comparison of postoperative first flatus duration was analyzed via Log-Rank test and Cox regression analysis. All p values were based on two-sided statistical tests, and a two-sided P value < 0.05 was considered to be statistically significant. Statistical analysis was performed using the software package, SAS (version 9.4 for Windows; SAS Institute Inc., USA) and GraphPad Prism (version 8.0.2; GraphPad Software Inc., USA). Graphic abstract was created using Biorender (https://biorender.com/).

ADDITIONAL RESOURCES

The study has been registered on "ClinicalTrials.gov," the registration ID is NCT01978444. The access website is as follows: https://clinicaltrials.gov/ct2/show/NCT01978444?cond=NCT01978444&rank=1