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

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Presentation plan

1. Clinical trial introduction,
2. population study analysis,
3. secondary outcomes results,
4. summary of the trial.

About the paper

- **Title**: „*Complete mesogastric excision for locally advanced gastric cancer: Short-term outcomes of a randomized clinical trial*"
- **Authors**: Daxing Xie, Jie Shen et al.
- **Date of study**: 2014-2018 (paper published in 2021)
- Study performed at the Tongji Hospital in **Wuhan, China**
- **Work goals**: To determine whether **D2+CME** is superior treatment compared to conventional **D2** dissection in patients with locally advanced gastric cancer.

Introduction

- **Gastric cancer** is the fourth most common malignancy and the second leading cause of cancer death worldwide.
- Standard treatment is **D2 lymphadenectomy,** a removal of lymph nodes around the stomach.
- Nevertheless, up to 50% of patients develop recurrent disease after curative surgery.
- Proposed improvement of the procedure is **D2+CME** - lymphadenectomy combined with **complete mesogastric excision**.

Graphical abstract

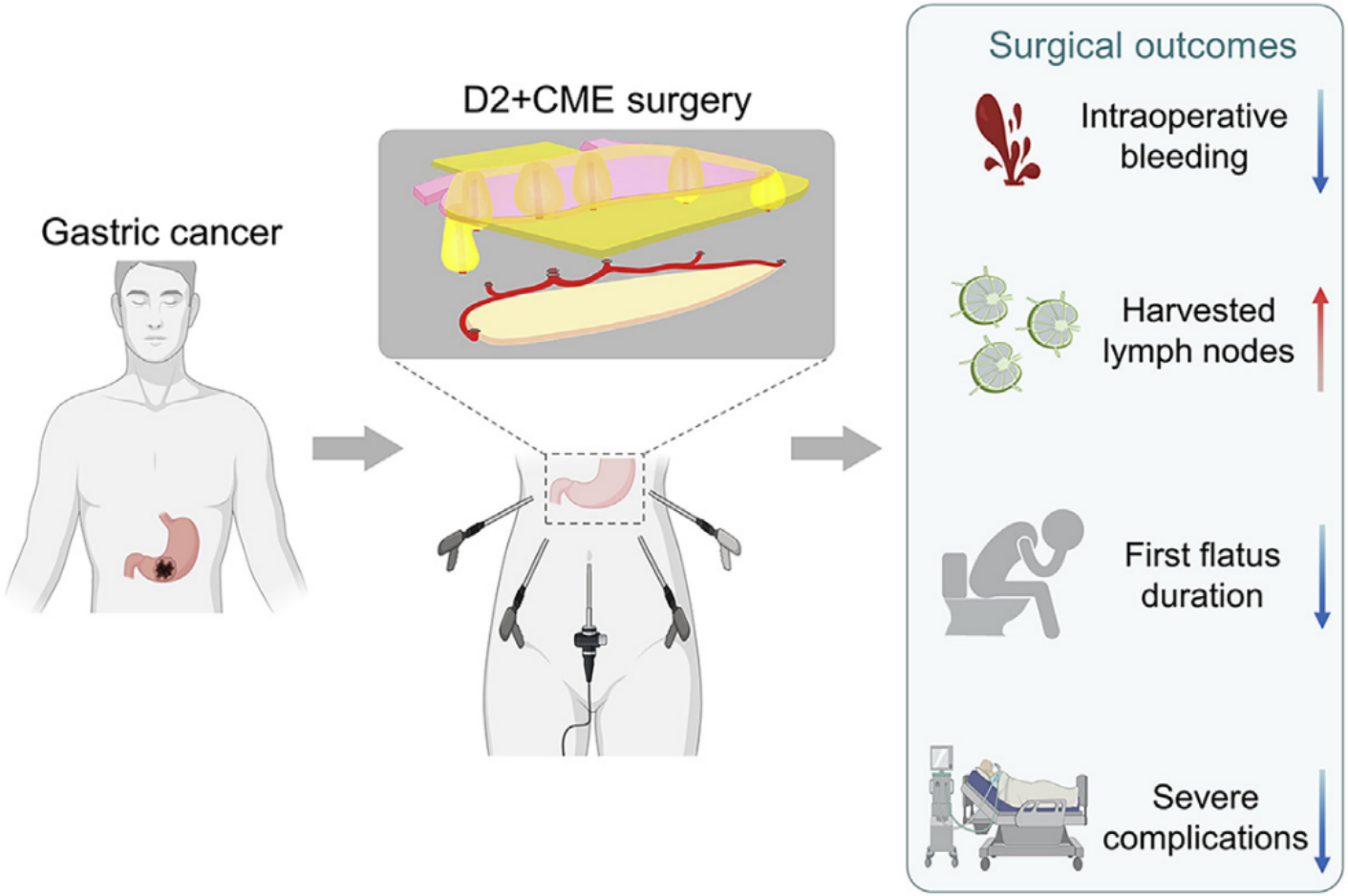


Figure 1: Graphical abstract summarizing the findings, provided by the authors of the article.

Study

- Randomized Clinical Trial (RCT) comparing conventional D2 with D2+CME
- Two data collection points: short-term (30 days after surgery) and long-term (3 years after surgery)
- 3-year disease-free survival is still being assessed; article focuses on short-term outcomes

Inclusion criteria

1. **Age** between 18 and 70
2. **BMI** lower than 30
3. **Primary gastric adenocarcinoma** confirmed by endoscopic biopsy
4. **Curative resection** expected
5. **No pregnancy** or breastfeeding
6. **No previous neoadjuvant chemotherapy** or radiotherapy
7. **No previous** upper abdominal **surgery**
8. **No total gastrectomy**
9. **No** other **malignant diseases**
10. **ECOG** performance status 0 or 1
11. **ASA** class *I* – *III*
12. **Written informed consent**

Study population

To detect a supposed difference in 3-year disease-free survival with a two-sided α of 0.05 and statistical power of 80%, calculated sample size was at least 302 (336 considering expected dropout rate of 10%).

- Investigated 2588 patients between 22 September 2014 and 28 June 2018
- 2102 of them excluded, of which 1998 did not meet inclusion criteria (age, BMI, no neoadjuvant radiotherapy etc.) and 104 declined to participate
- Remaining patients (486) randomly (randomization by SAS software) assigned to either D2 (control) or D2+CME groups

Study population

- 48 out of 243 patients assigned to D2 group and 40 out of 243 patients assigned to D2+CME group could not receive allocated intervention
- Most of them (30 and 24, respectively) were excluded due to tumor metastasis or resection being impossible
- 16 patients in D2 group and 15 patients in D2+CME group received total gastrectomy instead
- In each group there was one patient with more tumors found

In the end, 195 patients in control group and 203 patients in D2+CME group received their allocated interventions.

Study population

	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.

	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.

Figure 2: Table of characteristics of patients in both study groups.

Study population

- Follow-up data received from all patients
- 26 patients from control group and 34 patients from D2+CME group excluded from analysis
- 21 and 25 of them, respectively, were diagnosed pT1N0M0 (breast carcinoma)

Details about outcomes

Primary outcome:

- to measure 3-year disease-free survival after the operation,
- Follow-up after operation: telephones and out-patient interviews, held at 3-month intervals for the first 2 years and at 6-month intervals afterward,
- patients would receive tumor assessment by every 6 months during the follow-up.

Secondary outcomes:

- recurrence pattern,
- surgical outcomes,
- morbidity and mortality,

Operation and post operation statistics

Evaluation details

A lot of markers has been measured during operations and after them.

Surgical intervention staff who delivered the operation were not responsible for taking outcome measurements.

Surgical outcomes such as 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.

Patients and the follow-up staff who studied specimens were not aware of randomization assignment.

Operation and post operation statistics

Measure	D2	D2+CME	p value
Intralaparoscopic bleeding(mL), median ± IQR	37.0 ± 33.5	15.0 ± 23.0	<0.0001
Laparoscopic dissection time(min), mean ± SD	106.8 ± 24.5	133.1 ± 23.6	<0.0001
Total operation time(min), mean ± SD, mean ± SD	259.9 ± 41.5	293.1 ± 42.4	<0.0001
Number of LNs harvested, median ± IQR	27 ± 13	34 ± 16	<0.0001
Number of positive LNs, median ± IQR	3 ± 7	2 ± 5	0.099
Total hospital stay (days), median ± IQR	16 ± 5	16 ± 5	0.033
Postoperative hospital stay (days), median ± IQR	10 ± 2	10 ± 2	0.053

Table 1: Qualitative surgical results of patients who underwent D2 and D2+CME. All comparisons was done using Mann-Whitney test.

Post operation statistics

Table 2: Method of gastrointestinal reconstruction after partial gastrectomy. p value for χ^2 test was less than 0.0001.

	D2	D2+CME
BII	167 (0.988)	94 (0.556)
Roux-en-Y	2 (0.012)	75 (0.444)

Table 3: Severity of complications (Clavien-Dindo classification). p value for χ^2 test was 0.499.

Grade	D2	D2+CME
I and II	18 (0.666)	30 (0.883)
$\geq$ IIIa	9 (0.334)	4 (0.118)

Table 4: Combined resection due to surgical injury. p value for Fisher's exact test was 0.499.

	D2	D2+CME
No	167 (0.988)	169 (1)
Yes	2 (0.012)	0 (0)

Differences between approaches

Short-term outcomes of RCT approach are presented in table below. The medians of each group are compared using nonparametric Mann-Whitney statistical test. Low pvalue (less then 0.05) means that there is a difference between two compared group.

	D2	**D2+CME**	**pvalue**
Estimated intralaparoscopic bleeding (mL), median ± IQR	37.0 ± 33.5	15.0 ± 23.0	<0.0001
Total operation time (min), mean ± SD	259.9 ± 41.5	293.1 ± 42.4	<0.0001
Number of LNs harvested, median ± IQR,	27 ± 13	34 ± 16	<0.0001
Laparoscopic dissection time (min), mean ± SD	106.8 ± 24.5	133.1 ± 23.6	<0.0001

Table 5: Surgical results of patients who underwent D2 and D2+CME

15 LNs are required by the guidelines to be harvest during examination. Thank to it we can maintain the quality of LN dissection.
The D2+CME surgery will be further verified by oncological survival results, which are being assessed in the follow-up phase of the trial.

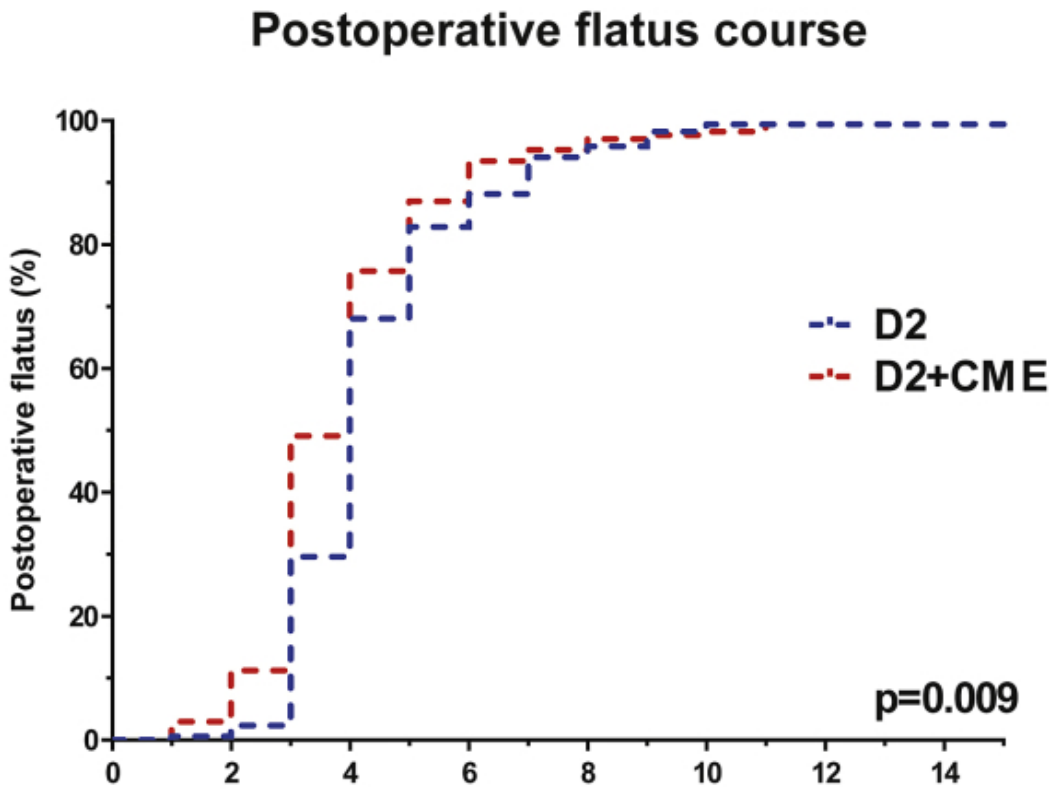
Surgery-related side events

	D2	D2+CME	pvalue
Total hospital stay (days), median $\pm$ IQR	16 $\pm$ 5	16 $\pm$ 5	0.033
Postoperative hospital stay (days), median $\pm$ IQR	10 $\pm$ 2	10 $\pm$ 3	0.053
Combined resection due to surgical injury	167	169	0.499

Table 6: Surgical results of patients who underwent D2 and D2+CME

The last p-value is obtained using exact Fisher test.
Two patients in the D2 group underwent excessive organ resection during the operation

Recovery of the gastrointestinal marker



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 3: Kaplan-Meier analysis of postoperative flatus duration; p-value of log-rank test on this data was 0.009.

The Kaplan-Meier curve and log-rank test showed that the D2+CME group had a significantly shorter time to postoperative flatus compared to the D2 group, p-value equals to 0.009.

Univariate Cox regression analysis showed that patients in the D2+CME group had a 24.7% higher chance of earlier postoperative flatus compared to the D2 group. This result was statistically significant, with a risk ratio (RR) of 1.247, a 95% confidence interval of 1.006 to 1.545, and a p-value equals to 0.044.

Results

D2+CME appears to provide better surgical safety during both the intra- and postoperative period.

Further studies with a large-scale population are needed.

We need to bear in mind that 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.

Limitations of the study

D2 procedure was performed by seven surgeons who are skillful and well experienced in the conventional D2 procedure whereas D2+CME was performed only by its advocator. It is because of the eager to maintain the uniformity and quality of each treatment.

This allocation might have resulted in potential bias due to personal experience.

In this study examined only distal gastrectomy. However in western countries proximal gastric cancer is more prevalent and proximal/total gastrectomy is required.

This study did not evaluate patient-centered outcomes like returning to normal life functioning. It is still unclear whether benefits (like shorter flatus duration) significantly improve the quality of life of patients.

Future plans

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 which 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.

Bibliography

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Thank You!