August 2022 Journal Club #3
Gastrointestinal

Surgical Interest Group
Monash University Malaysia

Critical Analysis

PRESENTED BY
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Background

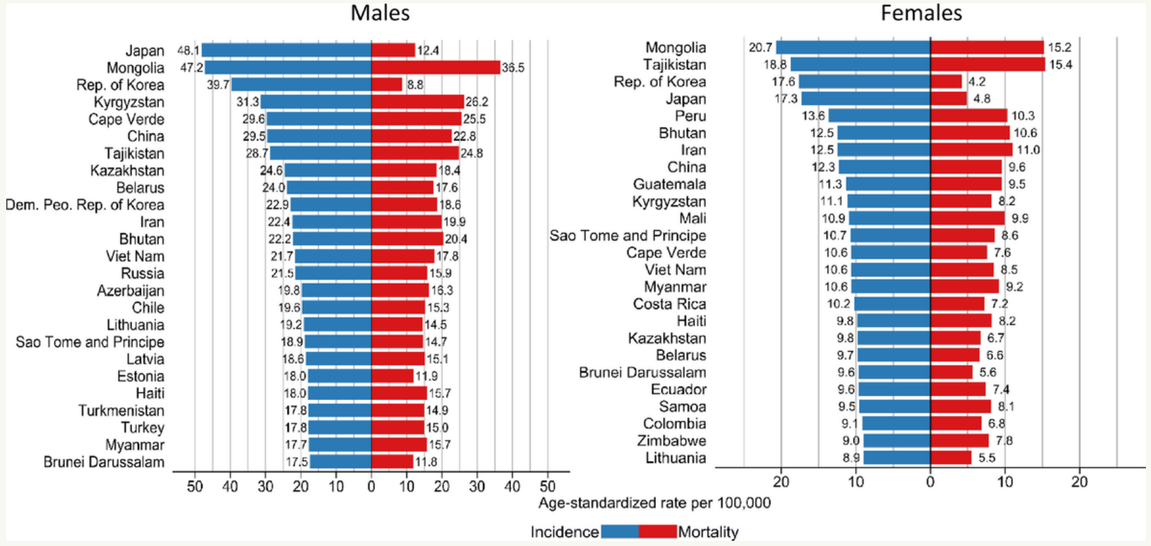
DEFINITION

EPIDEMIOLOGY

AIMS

PICO

	Primary tumor (T)
TX	primary tumor cannot be assessed
T0	no evidence of primary tumor
Tis	carcinoma in situ: intraepithelial tumor without invasion of the lamina propria
T1	tumor invades the lamina propria, the muscularis mucosa, or the submucosa
T1a	tumor invades the lamina propria or muscularis mucosa
T1b	tumor invades the submucosa
T2	tumor invades the muscularis propria layer
T3	tumor invades the subserosa layer without invasion of the serosa and adjacent structures
T4	tumor penetrates the serosa (visceral peritoneum) or adjacent structures
T4a	tumor penetrates the serosa (visceral peritoneum)
T4b	tumor invades adjacent structures
	Regional lymph nodes (N)
NX	regional lymph node(s) cannot be assessed
N0	no regional lymph node metastasis
N1	metastasis in 1 to 2 regional lymph nodes
N2	metastasis in 3 to 6 regional lymph nodes
N3	metastasis in more than 7 regional lymph nodes
N3a	metastasis in 7 to 15 regional lymph nodes
N3b	pmetastasis in more than 16 regional lymph nodes
	Distant metastasis (M)
M0	no distant metastasis
M1	distant metastasis



Definition

- Cancerous cells grow within the lining of the stomach
- cT2-T4aN0-1M0

Epidemiology

- 1.1 million new cases and 770,000 deaths of gastric cancer were estimated in 2020
- Incidence rates were 2-fold higher in males than females on average
- Higher incidence rates were observed in Eastern Asia, Japan, Mongolia and Korea in the world

WERE THE AIMS CLEARLY STATED?

Evaluate the short-term outcomes of KLASS-02-RCT a multicenter randomized controlled trial comparing laparoscopic distal gastrectomy (LDG) with D2 lymphadenopathy with open distal gastrectomy (ODG).

PICO

P Adult with locally advanced gastric cancer

I Laparoscopic distal gastrectomy

C Open distal gastrectomy

O Short-term outcome

Study Design

LEVEL OF EVIDENCE

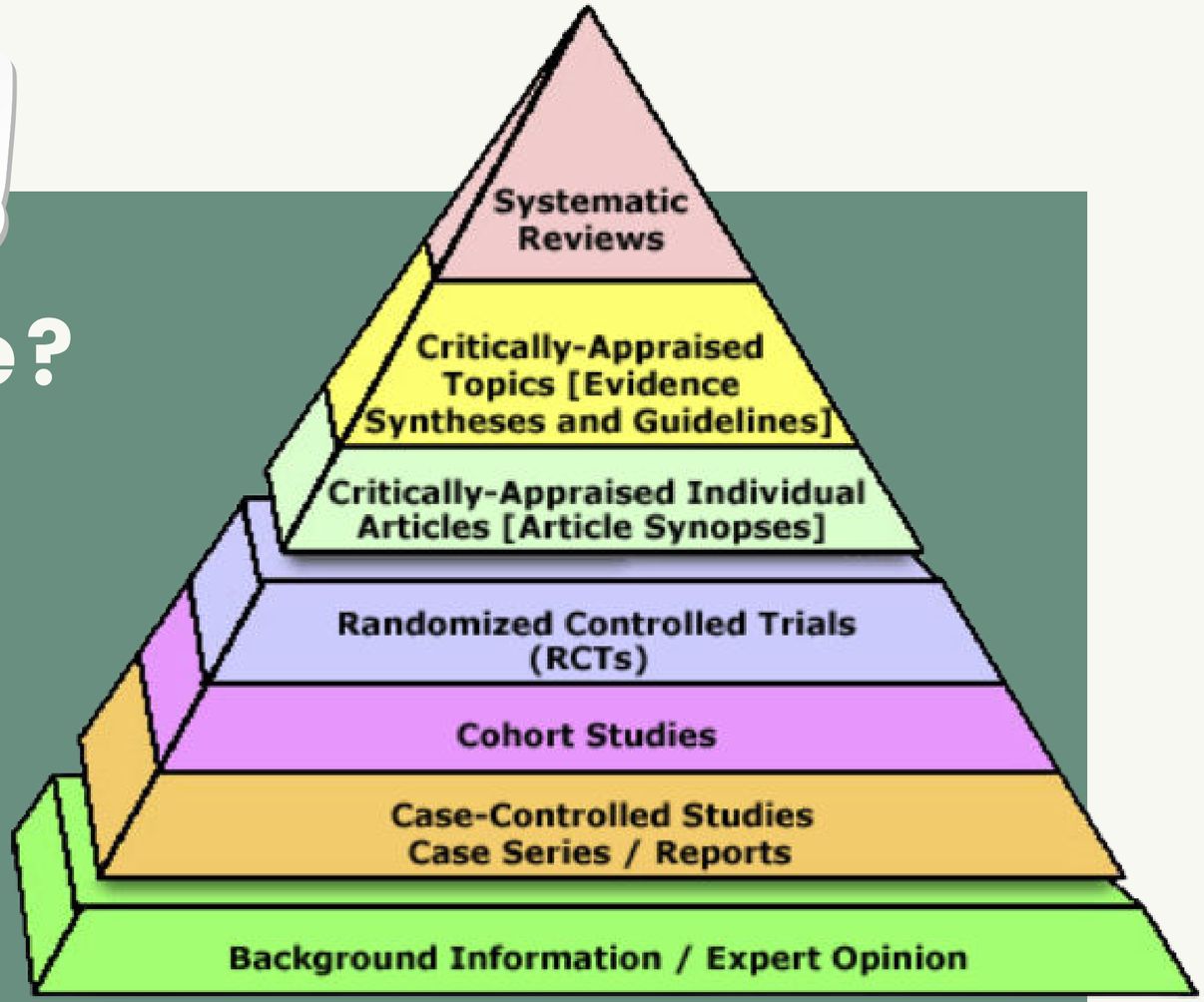
IS THE STUDY APPROPRIATE

What level of evidence has this paper presented? (using CEBM levels)

Level 1b Individual RCTs

Is the study appropriate?

- Gold standard for experimenting clinical trials by providing the highest level of evidence among the unfiltered information
- Minimize risk of confounding factors



Methodology

RECRUITMENT

RANDOMIZATION

PROCESS & FOLLOW UP

Recruitment

Are the groups defined precisely?

YES!

How were they recruited?

Inclusion Criteria

Methodology

1. Patient's age between 20 and 80 years
2. Histologically confirmed gastric adenocarcinoma
3. Tumour of cT2 to cT4a (tumor invaded proper muscle to exposed to serosa) and of cN0 to cN1 (metastasis in perigastric lymph nodes or lymph nodes along the left gastric artery) in preoperative gastroscopy, endoscopic ultrasound, and/or abdominal computed tomography
4. Tumor can be resected by distal gastrectomy in curative intention
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
6. American Society of Anesthesiology (ASA) score of class I to III
7. Patient agreed to participate this trial through informed consent

Exclusion Criteria

Methodology

1. Possible metastasis
2. Existence of other malignancies within last 5 years
3. History of previous gastric resection
4. Gastric cancer-related complication (complete obstruction or perforation)
5. History of gastric cancer treatment by endoscopic resection, chemotherapy and/or radiotherapy

- Hospital-based recruitment in Korea
- Patient's information were entered into a web-based electrical clinical report form (eCRF) after consent were obtained
- Patients will be randomly assigned at each surgery group if they meet the inclusion criteria

WERE THERE ANY DIFFERENCES IN BASELINE CHARACTERISTICS OF THE STUDY PARTICIPANTS?

Patient demographics and baseline characteristics including sex, age, body mass index, ECOG and ASA scores, comorbidity, a history of previous abdominal operation, and clinical T and N stages were well balanced between both treatment groups.

TABLE 1. Patients' Demographics

Variables	AT Analysis			mPP Analysis		
	Laparoscopy (n = 513)	Open (n = 498)	*P*	Laparoscopy (n = 460)	Open (n = 458)	*P*
Sex (M:F)	370:143 (male 72.1%)	346:152 (male 69.5%)	0.369	333:127 (male 72.4%)	321:137 (male 70.1%)	0.466
Age, yrs	59.8 ± 11.1	59.6 ± 11.5	0.803	59.9 ± 10.8	59.5 ± 11.6	0.593
BMI, kg/m^2	23.5 ± 2.9	23.7 ± 3.3	0.201	23.5 ± 2.9	23.7 ± 3.3	0.264
ASA score			0.821			0.967
I	246 (48.0%)	243 (48.8%)		222 (48.3%)	223 (48.7%)	
II	240 (46.8%)	233 (46.8%)		216 (47.0%)	215 (46.9%)	
III	27 (5.3%)	22 (4.4%)		22 (4.8%)	20 (4.4%)	
ECOG			0.717			0.444
1	444 (86.5%)	427 (85.7%)		401 (87.2%)	391 (85.4%)	
2	69 (13.5%)	71 (14.3%)		59 (12.8%)	67 (14.6%)	
Comorbidity	230 (44.8%)	224 (45.0%)	1.000	205 (44.6%)	207 (45.2%)	0.894
Previous abdominal operation	78 (15.2%)	67 (13.5%)	0.473	72 (15.7%)	61 (13.3%)	0.349
cT stage			0.737			0.928
cT2	214 (41.7%)	205 (41.2%)		198 (43.0%)	194 (42.4%)	
cT3	192 (37.4%)	197 (39.6%)		175 (38.0%)	180 (39.3%)	
cT4a	107 (20.9%)	96 (19.3%)		87 (18.9%)	84 (18.3%)	
cN stage			0.409			0.642
cN0	226 (44.1%)	206 (41.4%)		203 (44.1%)	195 (42.6%)	
cN+	287 (55.9%)	292 (58.6%)		257 (55.9%)	263 (57.4%)	

ASA indicates American Society of Anesthesiology score; AT, actual treatment; BMI, body mass index; cN stage, clinical N stage; cT stage, clinical T stage; ECOG, Eastern Cooperative Oncology Group performance status; F, female; M, male; mPP, modified per protocol.

Was the sample size collected justified?

YES!

- With early morbidity as one of the secondary endpoints of KLASS-02-RCT, the reports of Sano et al and Deguili et al were adopted for sample size calculation
- With a type I error of 0.025 (one-sided) and 90% of power, 242 patients were required in each group

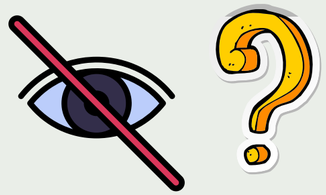
RECRUITMENT

Randomization

HAS RANDOMIZATION BEEN DONE?

- Blocked randomization
- Stratified by the participating investigators
- 1:1 allocation ratio using a confidential block size
- Reduce selection bias

HAS BLINDING BEEN USED?



- Not entirely!
- Surgeon and patient blinding is impossible owing to the nature of surgical RCT (performance bias)
- However, the protocol recommends that ward staff members evaluating patient outcomes be blinded, if possible (detection bias)

PROCESS & FOLLOW UP

WERE THERE ANY DIFFERENCES BETWEEN CONTROL & INTERVENTION GROUPS APART FROM THE EXPOSURE?

MINIMIZE PERFORMANCE BIAS

No clear difference in treatment of the patient in both groups.

Although it can be argued that the skills of surgeons can be different considering it is a multicenter trial, skills of surgeons were accessed and met certain qualifications before being accepted in the trial.

Both groups were given equal care according to the needs of the patients perioperatively.

WAS FOLLOW UP COMPLETE AND CONSISTENT IN EACH GROUP?

No clear statement on how long each group were followed up after surgeries. It seems that patients were followed up to 90 days post operation as one of its outcome monitored : "surgical mortality" is defined as death related to surgical complications within 90 days.

In terms of long term outcomes and primary outcome (3-years mortality rate), follow up is INSUFFICIENT.

Short term follow up for post-op complications prior to discharge of patient seems to be complete in both groups.

There was no statement on amount of patients lost to follow up at the end of the trial.

Results & Statistics

OUTCOMES

STATISTICAL ANALYSIS

Were all appropriate outcomes considered?

SURGICAL & PATHOLOGICAL OUTCOMES

- Operation time
- Blood loss
- Laparoscopic length
- Anastomotic type
- Mean lymph nodes number retrieved
- Incision length

SURGICAL MORBIDITY & MORTALITY

- Post op complications
- Readmission rates
- 90 days mortality rates & cause of mortality

POSTOPERATIVE RECOVERY & LABORATORY DATA

- Time to first flatus
- Time to start first liquid/solid diet
- Postoperative stay
- Postoperative pain
- Number of applications of analgesics in addition to PCA within first 3 postoperative days
- WBC, Hb, platelets, total bilirubin, amylase

STATISTICS

WERE THE RESULTS STATISTICALLY SIGNIFICANT?

SURGICAL & PATHOLOGICAL OUTCOMES

	AT Analysis			mPP Analysis		
Variables	**Laparoscopy (n = 513)**	**Open (n = 498)**	***P***	**Laparoscopy (n = 460)**	**Open (n = 458)**	***P***
Op. time, min	227.1 ± 68.5	165.0 ± 46.3	<0.001	225.7 ± 67.9	162.3 ± 44.1	<0.001
Blood loss, mL	153.8 ± 258.1	230.1 ± 258.2	<0.001	138.3 ± 166.8	222.0 ± 212.4	<0.001
Extent of resection			1.000			NA*
Distal	496 (96.7%)	482 (96.8%)		460 (100%)	458 (100%)	
Total	17 (3.3%)	16 (3.2%)		0 (0.0%)	0 (0.0%)	
Combined operation	19 (3.7%)	20 (4.0%)	0.871	0	0	NA
LN dissection			0.445			NA
<D2	2 (0.4%)	4 (0.8%)		0 (0.0%)	0 (0.0%)	
D2	511 (99.6%)	494 (99.2%)		460 (100%)	458 (100%)	
Anastomosis			<0.001			<0.001
GD (Billroth I)	177 (34.5%)	282 (56.6%)		170 (37.0%)	270 (59.0%)	
GJ (Billroth II)	280 (54.6%)	161 (32.3%)		257 (55.9%)	149 (32.5%)	
GJ (Roux-en-Y)	56 (10.9%)	55 (11.0%)		33 (7.2%)	39 (8.5%)	
Omentectomy			0.038			0.062
Partial	8 (1.6%)	1 (0.2%)		5 (1.1%)	0 (0.0%)	
Total	505 (98.4%)	497 (99.8%)		455 (98.9%)	458 (100%)	
Incision length, cm	5.0 ± 2.9	17.7 ± 3.1	<0.001	4.6 ± 1.5	17.6 ± 2.9	<0.001
R-category			0.627			0.374
R0	503 (98.1%)	491 (98.6%)		456 (99.1%)	457 (99.8%)	
R1/2	10 (1.9%)	7 (1.4%)		4 (0.9%)	1 (0.2%)	

AT indicates actual treatment; GD, gastroduodenostomy; GJ, gastrojejunostomy; LN, lymph node; mPP, modified per protocol.
*Not applicable.

TABLE 3. Pathologic Outcomes

	AT Analysis			mPP Analysis		
Variables	**Laparoscopy (n = 513)**	**Open (n = 498)**	***P***	**Laparoscopy (n = 460)**	**Open (n = 458)**	***P***
Size, cm	4.7 ± 2.5	4.6 ± 2.4	0.649	4.5 ± 2.4	4.5 ± 2.2	0.846
Retrieved LNs	46.6 ± 17.9	47.4 ± 16.5	0.451	46.6 ± 17.7	46.9 ± 15.9	0.741
Retrieved LNs < 15	2 (0.4%)	2 (0.4%)	1.000	2 (0.4%)	1 (0.2%)	1.000
Proximal RM, cm	4.7 ± 3.1	5.0 ± 3.0	0.091	4.6 ± 3.0	5.0 ± 3.1	0.053
Distal RM, cm	4.8 ± 3.2	4.9 ± 3.2	0.660	4.8 ± 3.2	4.8 ± 3.1	0.870
Positive margin						
Proximal	1 (0.2%)	1 (0.2%)	1.000	0 (0.0%)	1 (0.2%)	0.499
Distal	3 (0.6%)	1 (0.2%)	0.624	1 (0.2%)	1 (0.2%)	1.000
pT stage			0.713			0.648
T1	140 (27.3%)	127 (25.5%)		135 (29.3%)	121 (26.4%)	
T2	104 (20.3%)	114 (22.9%)		100 (21.7%)	111 (24.2%)	
T3	137 (26.7%)	137 (27.5%)		121 (26.3%)	128 (27.9%)	
T4a	129 (25.1%)	115 (23.1%)		103 (22.4%)	98 (21.4%)	
T4b	3 (0.6%)	5 (1.0%)		1 (0.2%)	0 (0.0%)	
pN stage			0.347			0.274
N0	226 (44.1%)	222 (44.6%)		208 (45.2%)	207 (45.2%)	
N1	96 (18.7%)	103 (20.7%)		85 (18.5%)	97 (21.2%)	
N2	90 (17.5%)	73 (14.7%)		84 (18.3%)	66 (14.4%)	
N3a	64 (12.5%)	74 (14.9%)		56 (12.2%)	68 (14.8%)	
N3b	37 (7.2%)	26 (5.2%)		27 (5.9%)	20 (4.4%)	
M1 (distant metastasis)	9 (1.8%)	7 (1.4%)	0.802	4 (0.9%)	1 (0.2%)	0.374
TNM stage			0.437			0.233
I	181 (35.3%)	167 (33.5%)		173 (37.6%)	159 (34.7%)	
II	151 (29.4%)	170 (34.1%)		136 (29.6%)	159 (34.7%)	
III	172 (33.5%)	154 (30.9%)		147 (32.0%)	139 (30.3%)	
IV	9 (1.8%)	7 (1.4%)		4 (0.9%)	1 (0.2%)	

AT indicates actual treatment; LN, lymph node; mPP, modified per protocol; RM, resection margin.

TABLE 4. Operative Morbidity and Mortality

Variables	AT Analysis			mPP Analysis		
	Laparoscopy (n = 513)	Open (n = 498)	*P*	Laparoscopy (n = 460)	Open (n = 458)	*P*
Overall morbidity	85 (16.6%)	120 (24.1%)	0.003	75 (16.3%)	105 (22.9%)	0.013
Local complication	63 (12.3%)	86 (17.3%)	0.027	55 (12.0%)	74 (16.2%)	0.072
Wound	23 (4.5%)	29 (5.8%)	0.393	23 (5.0%)	26 (5.7%)	0.663
Fluid collection	13 (2.5%)	25 (5.0%)	0.046	10 (2.2%)	22 (4.8%)	0.032
Intra-abdominal bleeding	2 (0.4%)	9 (1.8%)	0.035	2 (0.4%)	8 (1.7%)	0.064
Intra-luminal bleeding	2 (0.4%)	2 (0.4%)	1.000	1 (0.2%)	2 (0.4%)	0.624
Ileus	11 (2.1%)	16 (3.2%)	0.333	9 (2.0%)	12 (2.6%)	0.518
Anastomotic stricture	0 (0.0%)	3 (0.6%)	0.119	0 (0.0%)	3 (0.7%)	0.124
Anastomotic leakage	9 (1.8%)	7 (1.4%)	0.802	9 (2.0%)	5 (1.1%)	0.420
Pancreatitis/Pancreatic leakage	10 (1.9%)	3 (0.6%)	0.091	8 (1.7%)	3 (0.7%)	0.224
Systemic complication	19 (3.7%)	24 (4.8%)	0.437	19 (4.1%)	22 (4.8%)	0.636
Pulmonary	14 (2.7%)	17 (3.4%)	0.587	14 (3.0%)	16 (3.5%)	0.715
Urinary	4 (0.8%)	3 (0.6%)	1.000	4 (0.9%)	2 (0.4%)	0.686
Renal	2 (0.4%)	0 (0.0%)	0.500	2 (0.4%)	0 (0.0%)	0.499
Hepatic	1 (0.2%)	5 (1.0%)	0.119	1 (0.2%)	5 (1.1%)	0.123
Cardiac	0 (0.0%)	1 (0.2%)	0.493	0 (0.0%)	1 (0.2%)	0.499
Other complication	18 (3.5%)	18 (3.6%)	1.000	15 (3.3%)	16 (3.5%)	0.857
C-D grade						
I	20 (3.9%)	26 (5.2%)	0.345	17 (3.7%)	23 (5.0%)	0.407
II	47 (9.2%)	57 (11.4%)	0.051	41 (8.9%)	51 (11.1%)	0.036
IIIa	29 (5.7%)	34 (6.8%)	0.673	27 (5.9%)	29 (6.3%)	0.882
IIIb	7 (1.4%)	16 (3.2%)	0.037	7 (1.5%)	14 (3.1%)	0.093
IVa	5 (1.0%)	4 (0.8%)	0.682	5 (1.1%)	3 (0.7%)	1.000
IVb	2 (0.4%)	0 (0.0%)	—	2 (0.4%)	0 (0.0%)	—
V	2 (0.4%)	2 (0.4%)	1.000	2 (0.4%)	2 (0.4%)	1.000
Re-admission	20 (3.9%)	22 (4.4%)	0.754	16 (3.5%)	19 (4.2%)	0.731
90-d mortality	2 (0.4%)	3 (0.6%)	0.682	2 (0.4%)	3 (0.7%)	0.686

AT indicates actual treatment; C-D grade, Clavien-Dindo complication grade; mPP, modified per protocol.

TABLE 5. Postoperative Course and Laboratory Findings

Variables	AT Analysis			mPP Analysis		
	Laparoscopy (n = 513)	Open (n = 498)	*P*	Laparoscopy (n = 460)	Open (n = 458)	*P*
First flatus, d	3.5 ± 1.1	3.7 ± 1.5	0.025	3.5 ± 1.1	3.7 ± 1.5	0.051
First diet, d	3.7 ± 1.6	3.9 ± 2.3	0.217	3.7 ± 1.7	3.8 ± 2.0	0.496
Postoperative stay, d	8.1 ± 6.5	9.3 ± 6.7	0.005	8.1 ± 6.7	9.1 ± 6.7	0.017
WBC, $\times 10^3/\mu L$						
Preop	6.7 ± 2.1	6.7 ± 2.0	0.990	6.6 ± 2.0	6.7 ± 1.9	0.562
POD1	11.1 ± 3.1	11.8 ± 3.2	<0.001	10.9 ± 3.0	11.8 ± 3.2	<0.001
POD5	7.1 ± 2.5	7.2 ± 2.7	0.710	7.1 ± 2.5	7.2 ± 2.7	0.573
Hb, g/dL						
Preop	13.4 ± 2.0	13.3 ± 2.0	0.447	13.5 ± 1.9	13.4 ± 2.0	0.240
POD1	12.1 ± 1.6	11.9 ± 1.8	0.024	12.2 ± 1.6	11.9 ± 1.8	0.005
POD5	11.6 ± 1.5	11.2 ± 1.6	<0.001	11.7 ± 1.5	11.2 ± 1.6	<0.001
Platelet, $\times 10^3/\mu L$						
Preop	257.3 ± 76.5	259.2 ± 73.9	0.701	253.1 ± 73.7	257.6 ± 73.6	0.365
POD1	208.2 ± 58.9	217.1 ± 63.8	0.022	205.5 ± 57.4	215.4 ± 63.1	0.013
POD5	240.8 ± 66.6	252.0 ± 70.8	0.010	237.8 ± 65.7	250.4 ± 70.4	0.006
Total bilirubin, mg/dL						
Preop	0.7 ± 0.3	0.7 ± 0.4	0.437	0.7 ± 0.3	0.7 ± 0.4	0.324
POD1	0.9 ± 0.5	0.9 ± 0.6	0.713	0.9 ± 0.5	0.9 ± 0.6	0.610
POD5	0.8 ± 0.5	0.8 ± 0.7	0.531	0.9 ± 0.5	0.8 ± 0.7	0.433
Amylase, U/dL						
Preop	74.2 ± 48.6	71.2 ± 34.1	0.295	74.6 ± 49.5	71.4 ± 34.7	0.303
POD1	141.2 ± 193.4	128.5 ± 178.7	0.285	137.2 ± 187.6	127.0 ± 182.2	0.405
POD5	93.3 ± 76.5	91.3 ± 80.8	0.701	92.9 ± 76.7	91.8 ± 82.0	0.839

AT indicates actual treatment; d, days; Hb, hemoglobin; mPP, modified per protocol; WBC, white blood cell.

VAS SCORE (LDG VS ODG)

first (4.2 ± 2.3 vs 4.5 ± 2.4, P = 0.039) and fifth (2.5 ± 1.6 vs 2.8 ± 1.7, P = 0.003) postoperative days were significantly lower in laparoscopic group than in open group.

NUMBER OF APPLICATIONS OF ANALGESICS IN ADDITION TO PCA WITHIN THE FIRST 3 POSTOPERATIVE DAYS

significantly lower in laparoscopic group (0.4 ± 0.9 vs 0.6 ± 1.1, P = 0.017)

Intention to treat (ITT) or per protocol analysis?

ANALYZATION DONE IN 2 ARMS

Actual treatment 'AT' group

All patients included except those who did not accept surgery or gastrectomy. Patients who switched to other surgical approach after randomization at their own will are **analyzed by actual treatment** not allocated treatment.

Modified per protocol (mPP)

ATTRITION BIAS & CONFOUNDING FACTORS

Exclusion of patients who swapped the group, underwent open conversion, total gastrectomy, combined resection except for cholecystectomy (for gallbladder diseases), or lymphadenectomy less than D2 from AT group

NO analyses done on the basis of ITT

Main analysis done using AT rather than ITT group as "actual received surgery" is more valuable than allocated surgery in analysis of morbidity & mortality

Statistical Method

Fishers exact test → investigate different proportions of patients between 2 groups

Student t test → continuous variables

Binary logistic regression (for multivariate and univariate analysis) → factors affecting morbidity

*Statistical analysis was conducted with help of SPSS 23.0 software

Discussion

CONFLICT WITH OTHER TRIALS

STRENGTHS/WEAKNESSES/ POTENTIAL BIASES

BARRIERS TO IMPLEMENTATION

Conflicts of evidence with other trials

Chinese Laparoscopic Gastrointestinal Surgery Study (CLASS) group

Morbidity rate in LDG (15.2%) slightly higher than ODG (12.9%). ***not statistically significant**

CLASS-01 : Lower number of retrieved lymph nodes in LDG (36.1) than ODG (36.9)

KLASS-02-RCT: LDG (46.6) vs ODG (47.4)

Hence researchers in our study think that superior short-term outcome in our study might be due to their qualification system

What are the strengths and weaknesses of this study?

STRENGTHS

Verified benefits of LDG that was not looked into by other studies

Faster recovery & less pain after surgery

Faster recovery may positively affect post-operative adjuvant chemotherapy

WEAKNESSES

Generalizability of study

Surgeons in this study underwent strict qualification

Long term benefits not accessed

Unable to fully conclude that it is a good treatment for locally advanced gastric cancer

Barriers to Implementation

LACK OF EVIDENCE OF LONG TERM BENEFITS

Unclear if there is any long term complications & its long term survival rates

Considering its costs and skills needed, if there is no long term benefits is it less encouraging for its implementation

LACK OF RESOURCES

Resource poor countries might lack skills and surgical instruments, maintenance costs for instruments may also be costly

Patients might also have financial barrier in receiving treatment

GENERALIZABILITY OF RESULTS

Due to the strict qualification system in choosing qualified surgeons, results might be affected by skills of surgeons.

Future Prospect

LOCAL POPULATION

Benefits

Feasibility

IMPROVEMENTS

Is the treament beneficial and feasible in your local YES! population?

- Benefits - lower local complication, faster recovery, less pain
- Laparoscopic gastrectomy has been widely accepted as a standard alternative to open gastrectomy

IMPROVEMENTS

How could you improve the trial?

INTENTION TO TREAT (ITT) ANALYSIS

Reduce attrition bias

LONG-TERM SURVIVAL DATA OF KLASS-02-RCT

Confirm the final impact of LDG

OTHER OUTCOMES

QoL after surgery, time to first walking

Conclusion

Laparoscopic distal gastrectomy with D2 lymph node dissection for locally advanced gastric cancer is safe and shows benefits such as lower complication rate, faster recovery, and less pain, when being compared to open surgery.

Thank you

FOR LISTENING

See you again!