13 AUGUST 2022

Journal Club #3

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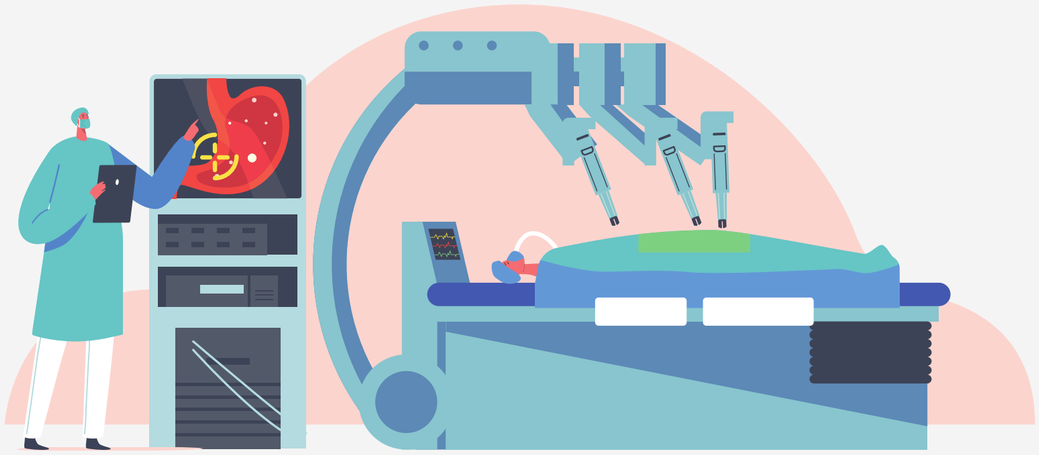
Surgical Interest Group
Monash University Malaysia



Topic for discussion

Short-term Outcomes of a Multicentre Randomized Controlled Trial comparing **Laparoscopic Distal Gastrectomy with D2 Lymphadenotomy** to **Open Distal Gastrectomy** for **Locally Advanced Gastric Cancer**

KLASS-02-RCT

Annals of Surgery

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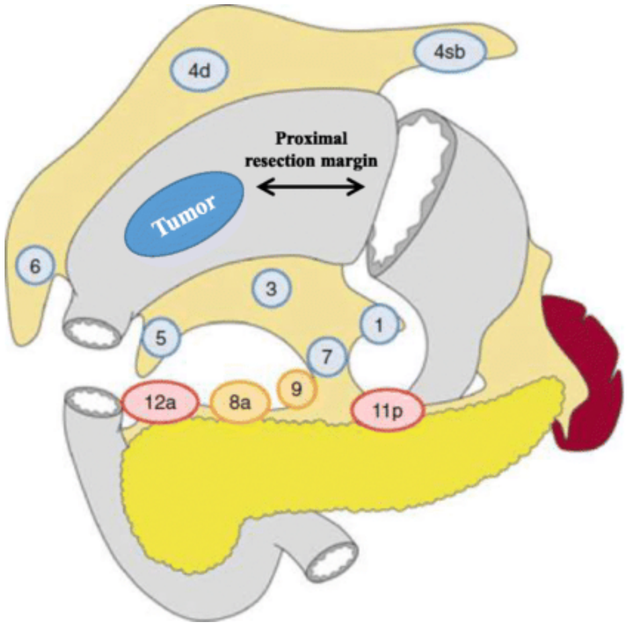
Distal Gastrectomy

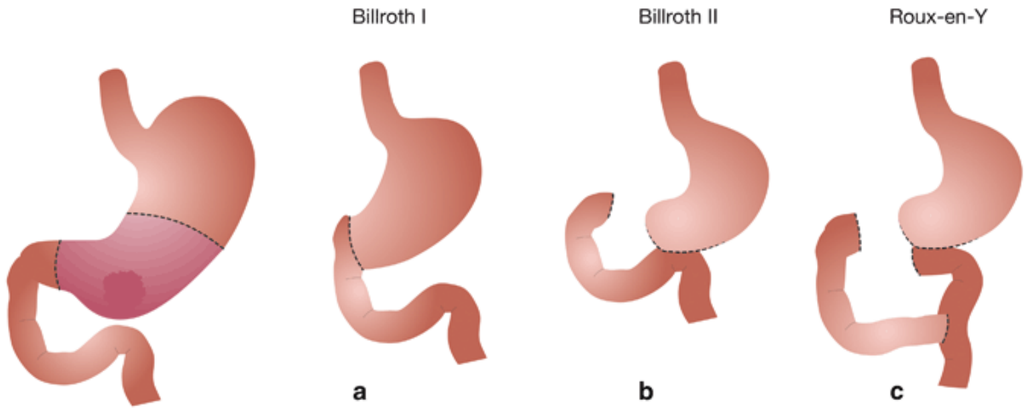
Removal of lower part of stomach until good clearance of tumor is achieved, usually done with lymphadenectomy.



Extent of D2 lymphadenectomy:

N1 station (perigastric)
1. Right cardiac nodes
3. Nodes along lesser curvature
4sb. Nodes along greater curvature (left gastroepiploic vessels)
4d. Nodes along greater curvature (right gastroepiploic vessels)
5. Supra-pyloric nodes
6. Infra-pyloric nodes

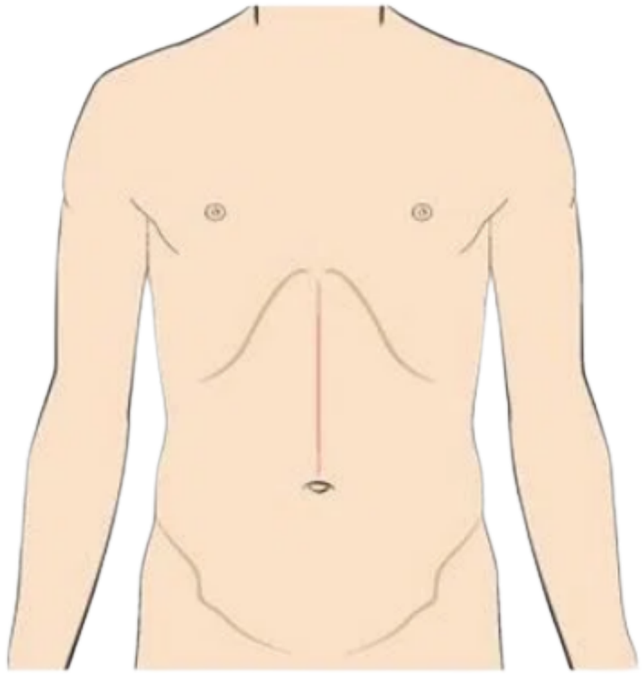
N2 station (branches coeliac axis)
7. Nodes along root left gastric artery
8a. Nodes along common hepatic artery
9. Nodes around coeliac axis
11p. Nodes along splenic artery (proximal)
12a. Nodes at hepatoduodenal ligament (hepatic artery)



D2 Lymphadenectomy

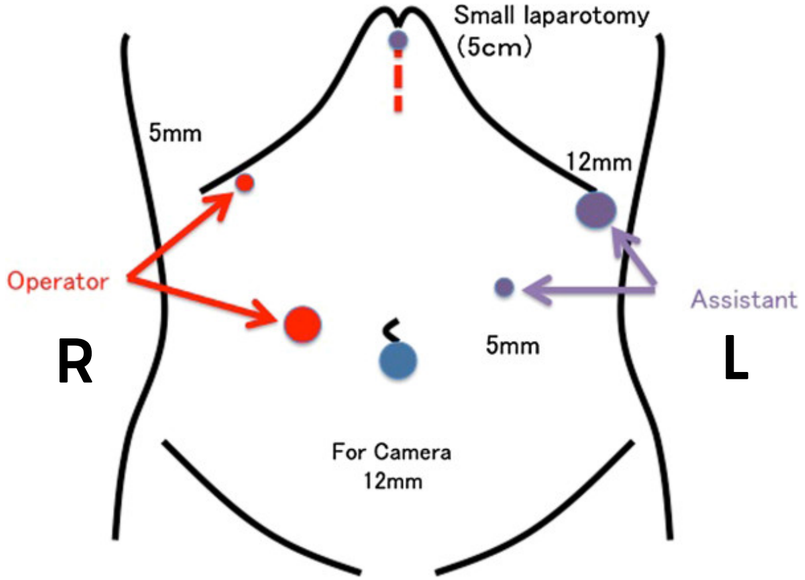
Reconstruction

Open Distal Gastrectomy (ODG)

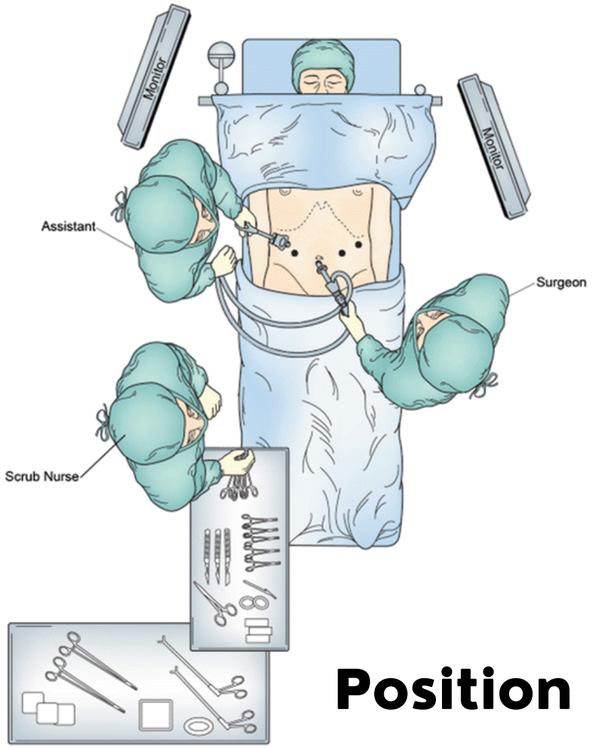


SINGLE incision made usually from xiphysternum to umbilicus

Laparoscopic Distal Gastrectomy (LDG)



Total of 6 trocars



Position

1. 12 mm trocar below umbilicus for laparoscope
2. Four 5-mm trocars inserted in the upper right, median left, left abdomen and middle right abdomen
3. One 12-mm trochar was inserted in the middle left abdomen

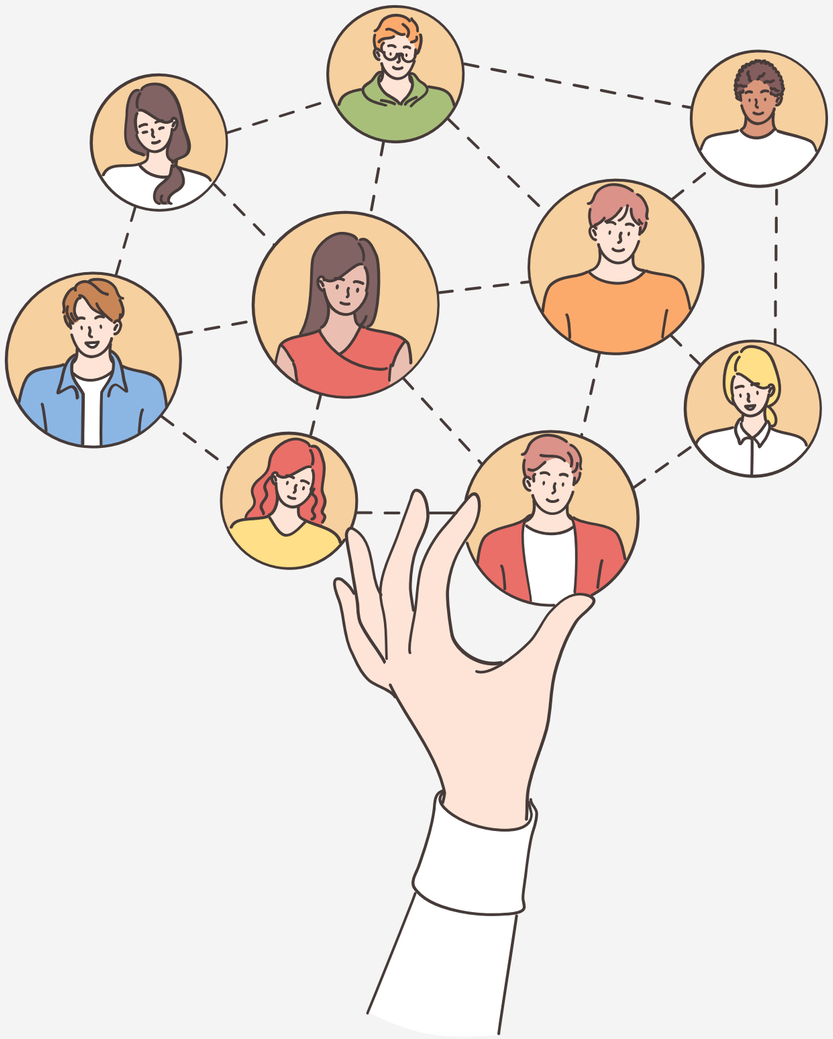
Aim of Study

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).**

Journal Club #3 | Gastrointestinal

Methodology

Recruitment



I

Randomization was performed before operation

II

Blocked randomization

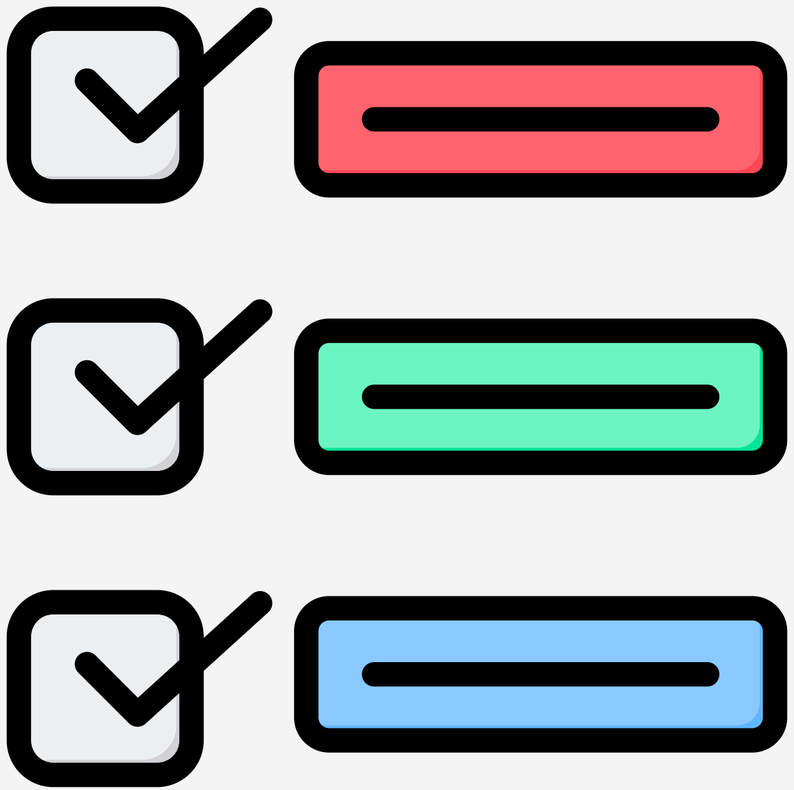
III

1:1 allocation ratio using a confidential block size

IV

After randomization, surgeons immediately informed the patient which type of operation they would undergo to meet a patient's "right to know", as recommended by the instituitional review board (IRB)

Inclusion Criteria



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

Eastern Cooperative Oncology Group (ECOG)

Performance status of patients with active cancer under treatment

0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature—for example, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

American Society of Anesthesiology (ASA) Score

ASA PS Classification	Definition	Examples, including, but not limited to:
ASA I	A normal healthy patient	Healthy, non-smoking, no or minimal alcohol use
ASA II	A patient with mild systemic disease	Mild diseases only without substantive functional limitations. Examples include (but not limited to): current smoker, social alcohol drinker, pregnancy, obesity (30<BMI<40), well-controlled DM/HTN, mild lung disease
ASA III	A patient with severe systemic disease	Substantive functional limitations. One or more moderate to severe diseases. Examples include (but not limited to): poorly controlled DM or HTN, COPD, morbid obesity (BMI≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, premature infant PCA < 60 weeks, history (>3 months) of MI, CVA, TIA, or CAD/stents.
ASA IV	A patient with severe systemic disease that is a constant threat to life	Examples include (but not limited to): recent (<3 months) MI, CVA, TIA, or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis
ASA V	A moribund patient who is not expected to survive without the operation	Examples include (but not limited to): ruptured abdominal/ thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes	

Table 1 ASA physical status (PS) classification and definition (Taken from https://www.asahq.org/resources/clinical-information/asa-physical-status-classification-system)

WHAT IS ASA SCORE?

It is used to classify patients heath status prior to surgery.
A subjective assessment of a patient's overall health that is based on 5 classes.

Exclusion Criteria

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

Primary Outcome

3-year disease-free survival

Secondary Outcome

1. **Surgical morbidity and mortality**
    a. overall morbidity, local complications (wound, fluid collection, intra-abdominal bleeding, intra-luminal bleeding, ileus, anastomotic stricture, anastomotic leakage, pancreatitis/pancreatic leakage), systemic complication (pulmonary, urinary, renal, hepatic, cardiac), other complication, C-D grade, readmission, 90-d mortality
2. **Postoperative pain and recovery**
    a. first flatus, first diet, postoperative stay, WBC, Hb, platelet, total bilirubin, amylase

Results

- Outcomes
- Analysis
- Results

Analysis

Two different populations were defined for analysis

First Population: actual treatment (AT) group

- Include all patients except patients who did not receive surgery or gastrectomy
- Patient who switched to the other surgical approach (laparoscopic vs open) after randomization (ie, swapping) at their own will were analyzed by the actual treatment, not by allocated treatment

Second Population: modified per protocol (mPP) group

- exclude 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

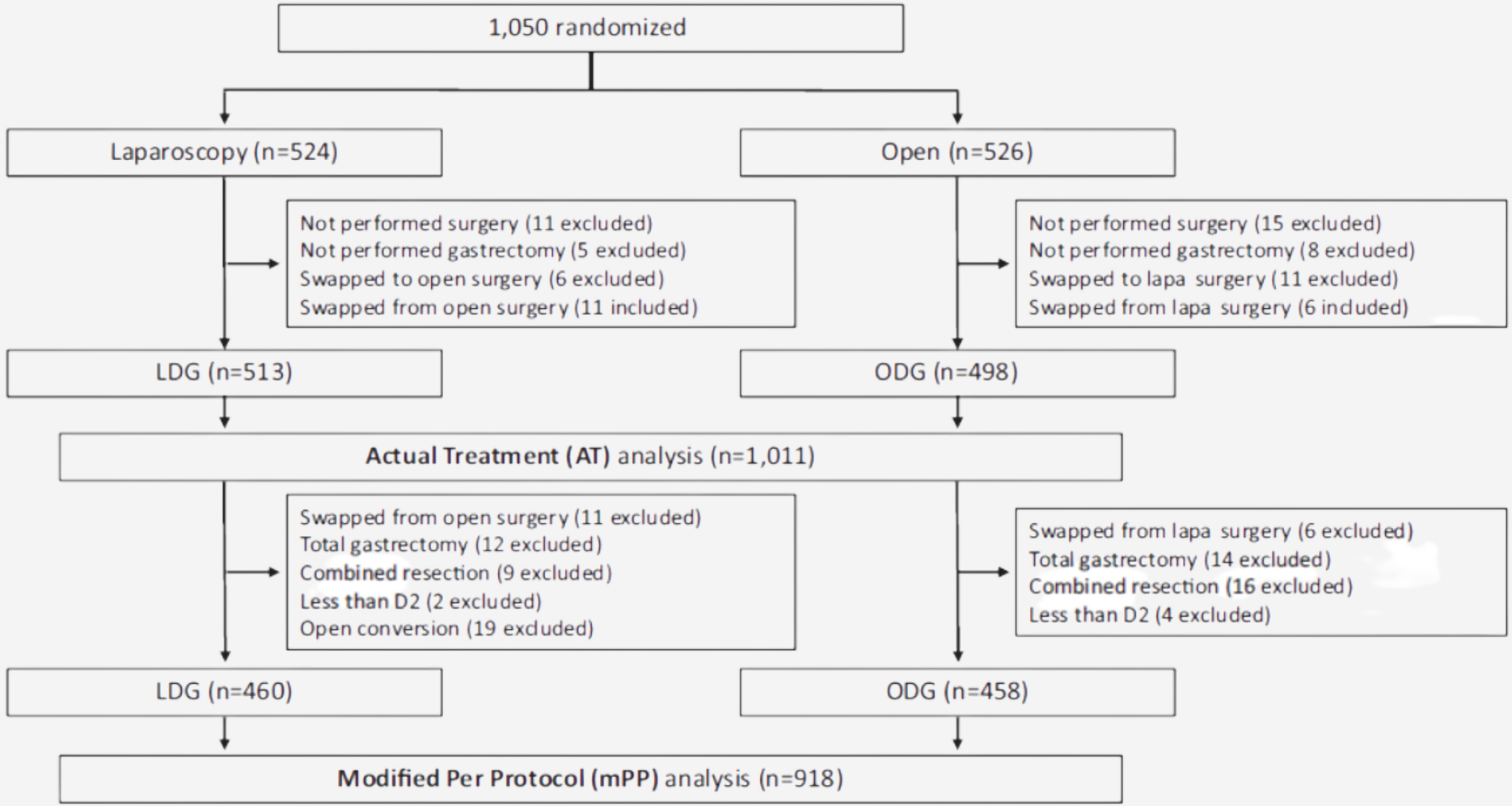


FIGURE 1. CONSORT chart.

Reason to use AT rather than intention to treat (IIT)

investigator tried to minimize the swapping case number (17 swapping cases after randomization); “actually received surgery” more valuable than allocated surgery in the analysis of morbidity and mortality

Surgical & Pathological Outcome

OUTCOME	AT ANALYSIS	MPP ANALYSIS
Operation Time	LDG (longer) - 227.1 min, P<0.001	LDG (longer) - 225.7 min, P<0.001
Blood Loss	LDG (lesser) - 153.8 mL, P<0.001	LDG (lesser) - 162.3 mL, P<0.001

TABLE 2. Surgical 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.

Complications

3 cases of positive resection margins in AT group: 2 (in ODG) has distant metastases; 1 (in LDG) converted to ODG and from distal to total gastrectomy due to tumor aggressiveness.

Surgical Morbidity & Mortality

OUTCOME	AT ANALYSIS	MPP ANALYSIS
Overall Morbidity	LDG (lower) - 16.6%, P=0.003	LDG (lower) - 16.3%, P=0.013
Fluid Collection	LDG (lesser) - 2.5%, P=0.046	LDG (lesser) - 2.2%, P=0.032
Intra-abdominal bleeding	LDG (lesser) - 0.4%, P=0.035	LDG (lesser) - 0.4%, P=0.064
Clavien-Dindo Classification (Grade)		
II	*LDG (lower) - 9.2%, P=0.051*	LDG (lower) - 8.9%, P=0.036
IIIb	LDG (lower) - 1.4%, P=0.037	*LDG (lower) - 1.5%, P=0.093*

TABLE 4. Operative Morbidity and Mortality

	AT Analysis			mPP Analysis		
Variables	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.

Other local complications and all systemic complications were not different between groups

Clavien-Dindo Classification

Degree	Definition
I	Every deviation from normal postoperative course without the necessity for drug treatment or a surgical, endoscopic or radiological intervention. Permissible therapeutic measures: drugs from the substance classes antiemetics, antipyretics, analgesics, diuretics; electrolyte substitution and physiotherapy. Surgical treatment of wound infections at the bedside.
II	Drug treatment in excess of the pharmacological measures listed under degree I. Blood transfusions and parenteral nutrition.
III	Necessity for surgical, endoscopic or radiological intervention.
III a	Intervention without general anaesthesia.
III b	Intervention with general anaesthesia.
IV	Life-threatening complications leading to transfer to an intermediate care or intensive care unit.
IV a	Dysfunction of an organ system (including the necessity for temporary dialysis).
IV b	Multiorgan dysfunction.
V	Death of the patient.
Suffix d	The complication degree is given the suffix “d” if the complication needs further treatment after release of the patient from hospital.

Classification of complication based on therapy needed for complications

AT analysis

Fewer Grade IIIb complications seen in LDG group

mPP analysis

Lower rate of Grade II complications after LDG

Surgical Morbidity & Mortality

OUTCOME	AT ANALYSIS	MPP ANALYSIS
Readmission Rates	*LDG (lower) - 3.9%, P=0.754*	*LDG (lower) - 3.5%, P=0.731*
Ninety Days' Mortality Rate	*LDG (lower) - 0.4%, P=0.682*	*LDG (lower) - 0.4%, P=0.686*

Causes:

- 3 duodenal stump leakages (1 laparoscopy and 2 open)
- 1 intra-abdominal bleeding (laparoscopy)
- 1 aspiration pneumonia caused by ileus (open)

TABLE 4. Operative Morbidity and Mortality

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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.

Other local complications and all systemic complications were not different between groups

Postoperative Recovery

OUTCOME	AT ANALYSIS	MPP ANALYSIS
First Flatus	LDG (shorter) - 3.5d, P=0.025	*LDG (lower) - 3.5d, P=0.051*
First Diet	No difference	
Postopera-tive Stay	LDG (shorter) - 8.1d, P=0.035	LDG (shorter) - 8.1d, P=0.017
WBC	Significantly lower in LDG	
Hb	Higher in LGD	
Total Bilirubin & Serum Amylase	No difference	

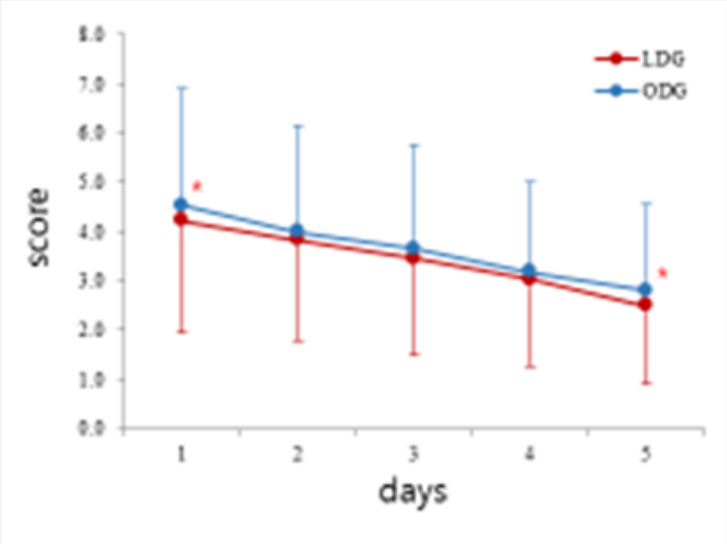
TABLE 5. Postoperative Course and Laboratory Findings

	AT Analysis			mPP Analysis		
Variables	**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

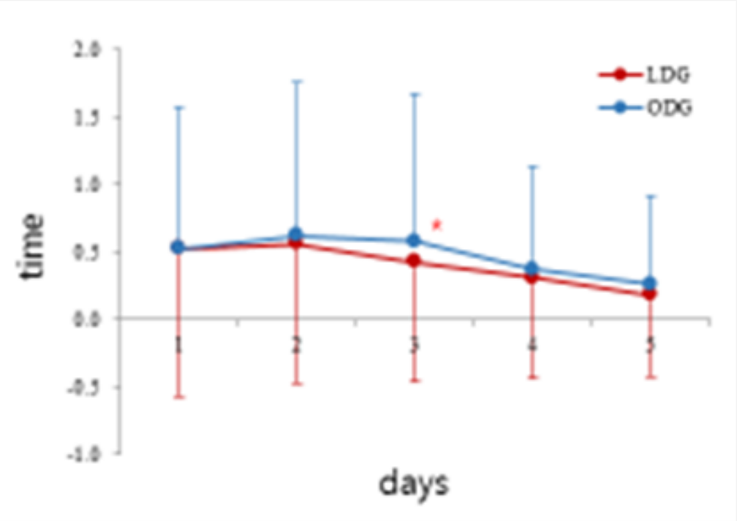
AT indicates actual treatment; d, days; Hb, hemoglobin; mPP, modified per protocol; WBC, white blood cell.

Postoperative Recovery

OUTCOME	AT ANALYSIS	MPP ANALYSIS
VAS Score		
1st Postoperative Day	LDG (lower) - 4.2, P=0.039	similar results to AT analysis
5th Postoperative Day	LDG (lower) - 2.5, P=0.003	similar results to AT analysis
Number of Applications of Analgesics in addition to PCA		
	LDG (lower) - 0.4, P=0.017	similar results to AT analysis

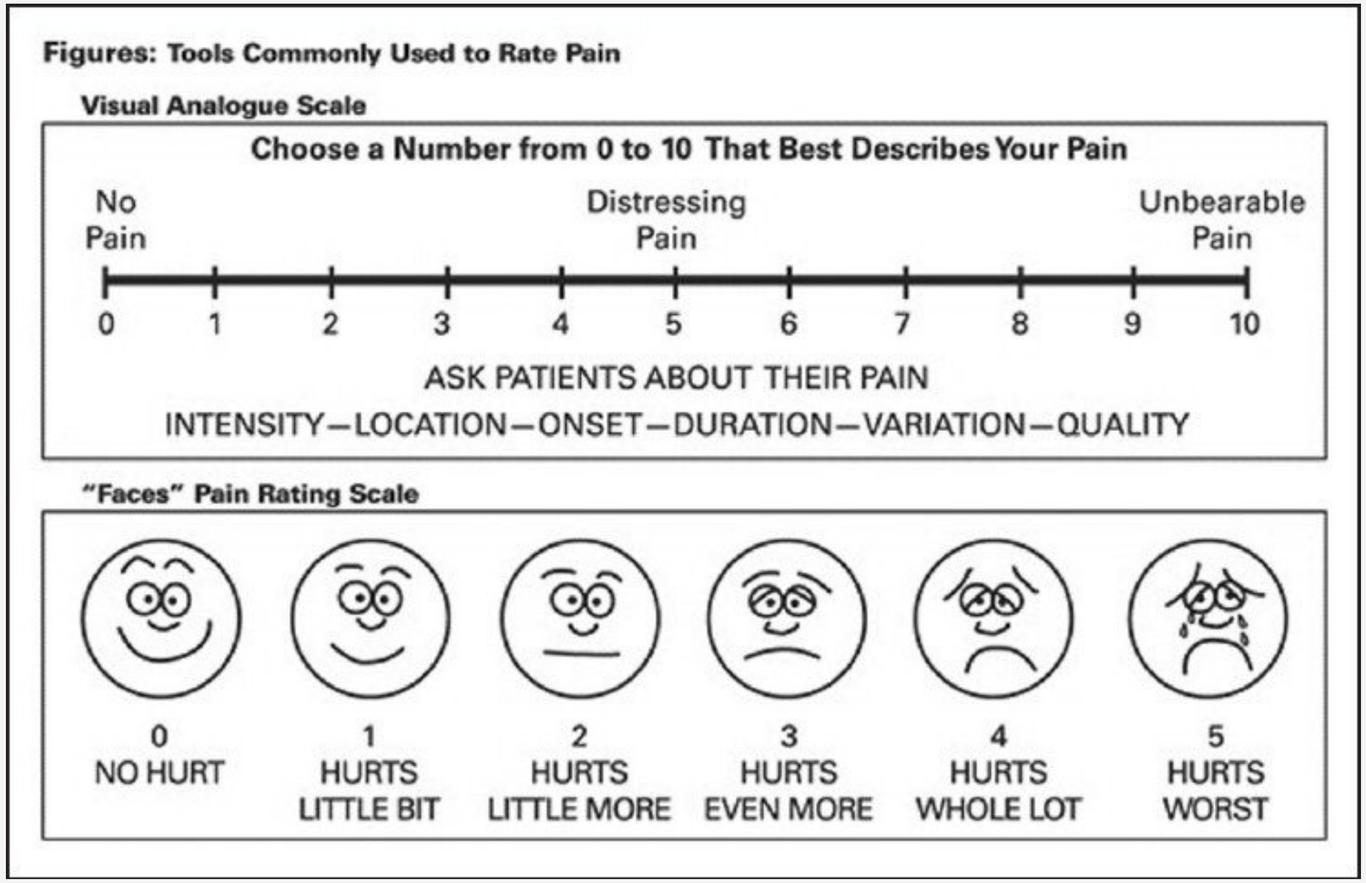


Visual Analogue Scale (VAS);
(Asterisk means statistically significant)



Time of analgesics use except PCA (patient-controlled analgesia);
(Asterisk means statistically significant)

VAS Score
Visual Analogue Score



RESULTS

AT analysis

VAS score on 1st post operative day: (4.2 ± 2.3 vs 4.5 ± 2.4, P = 0.039)

5th post operative day : (2.5 ± 1.6 vs 2.8 ± 1.7, P = 0.003)

mPP analysis

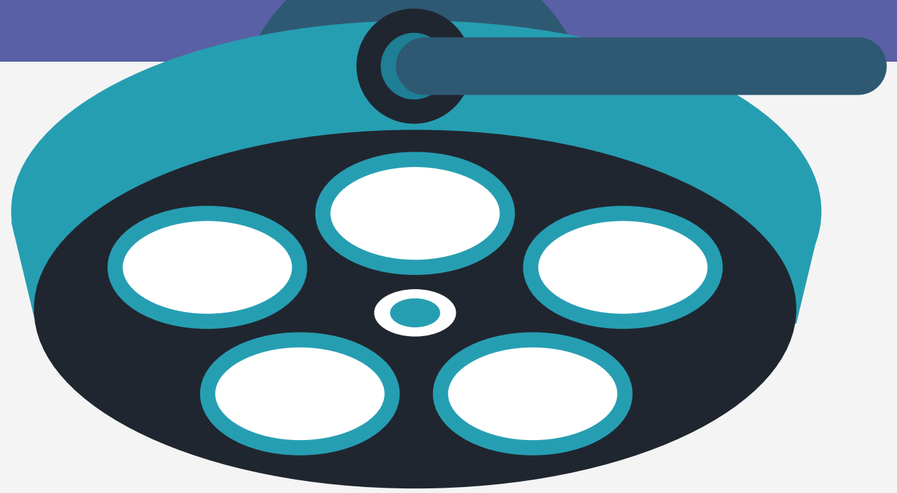
similar results as AT

Discussion

Long-term outcome of KLASS-02-RCT to confirm the final impact of LDG for locally advanced gastric cancer

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!