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February 2021
Ph.D. Dissertation

**Comparative Analysis of Surgical
Outcomes and Quality of Life after
Cardia-Preserving Proximal
Gastrectomy and Conventional
Proximal Gastrectomy for Early
Gastric Cancer of Upper Third of the
Stomach**

Graduate School of Chosun University

Department of Medicine

Wei Jie He

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위의 상부에 위치한 조기 위암의 분문 보존 근위 절제술과
기존 근위 절제술 후 수술결과 및 삶의 질에 대한 비교 분
석

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Comparative Analysis of Surgical Outcomes and Quality of Life after Cardia-Preserving Proximal Gastrectomy and Conventional Proximal Gastrectomy for Early Gastric Cancer of Upper Third of the Stomach

Advisor: Prof. Moon Sung Pyo

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ABBREVIATIONS

CPPG	Cardia-preserving proximal gastrectomy
PPG	pylorus-preserving gastrectomy
EGC	Early gastric cancer
LACPPG	laparoscopy-assisted Cardia-preserving proximal gastrectomy
QOL	Quality of life
EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
LN	Lymph nodes
DGE	Delayed gastric emptying
CBVN	Celiac Branch of Vagal nerve
FPG	Function preserving gastrectomy
DG	Distal gastrectomy
PG	Proximal gastrectomy
SG	Segmental gastrectomy
LG	local gastrectomy
LES	low esophageal sphincter
SG	Segmental gastrectomy
TG	Total gastrectomy
SNNS	Sentinel node navigation surgery
E-G junction	Esophago-gastric junction
LES	lower esophageal sphincter
PEL	phrenoesophageal ligament

GSRS

Gastrointestinal Symptom Rating Scale

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ABSTRACT

Comparative Analysis of Surgical Outcomes and Quality of Life after Cardia-Preserving Proximal Gastrectomy and Conventional Proximal Gastrectomy for Early Gastric Cancer of Upper Third of the Stomach

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Background: Proximal gastrectomy (PG) has become an optional surgical procedure for early cancer in upper third of the stomach but gastroesophageal reflux (GER) is a main issue of this operation. We previously reported a kind of new function preserving gastrectomy for early gastric cancer (EGC) of upper stomach, cardia-preserving proximal gastrectomy (CPPG), in which the new technique could prevent reflux esophagitis and anastomotic stricture. This study aimed to compare the surgical outcomes and quality of life (QOL) of CPPG and conventional proximal gastrectomy (CPG).

Method: A retrospective comparative analysis of patients who underwent CPPG and CPG from October 2006 to July 2019 was performed. Surgical outcomes such as operative time, bleeding, complications and modified Postgastrectomy Syndrome Assessment Scale-45 (mPGSAS-45) questionnaires of two procedures were compared.

Results: Operative times of CPPG and CPG were 189 and 177 minutes respectively ($P < 0.05$). There were no differences in terms of blood loss, hospital stay, complication rate and 5-year survival rate. CPPG has similar QOL and lower incidence of GER compared to CPG.

Conclusions: CPPG is a feasible and safe surgical procedure for EGC of upper stomach. CPPG has favorable surgical outcomes and superior to CPG in terms of GER.

Keywords: Cardia preserving proximal gastrectomy; Early gastric cancer; Surgical outcomes; Quality of life.

국문초록

위의 상부에 위치한 조기 위암의 분문 보존 근위 절제술과 기존 근위 절제술 후 수술결과 및 삶의 질에 대한 비교 분석

하 위 걸

지도교수: 문성표

의학과

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배경 근위 절제술은 위의 상부 3 분의 1 에 위치한 조기 위암의 치료에 선택적인 수술이 되었지만 위식도 역류가 이 수술의 주요 문제점이다. 저자의 기관에서는 이전에 조기 위암에 대한 새로운 기능 보존 위절제술 중 하나인 "분문 보존 근위 절제술"에 대해 보고한 바 있으며 이 새로운 방법은 역류성 식도염과 문합부 협착을 예방할 수 있는 새로운 수술법이다. 본 연구의 목적은 "분문 보존 근위 절제술"과 "기존의 근위 절제술"을 받은 환자들의 임상적 결과와 삶의 질을 비교 분석하는 것이다.

방법 2006 년 10 월부터 2019 년 7 월까지 "분문 보존 근위 절제술" 또는 "기존의 근위 절제술"을 받은 환자들을 대상으로 후향적 비교 분석을 수행하였다. 두 군 간의 수술시간, 수술 중 출혈, 수술 후 합병증 및 "변형 위 절제 후 증후군 평가 척도"(mPGSAS-45) 설문지 조사와 같은 임상적 결과를 비교하였다.

결과 "분문 보존 근위 절제술"과 "기존의 근위 절제술"의 수술시간은 각각 189 분과 177 분이였다($P < 0.05$). 수술 중 출혈, 입원기간, 수술 후 합병증 그리고 5 년 생존율은 차이가 없었다. "분문 보존 근위 절제술"은 "기존의 근위 절제술"과 비교하여 유사한 삶의 질과 낮은 위식도 역류 발생률을 보였다.

결론: “분문 보존 근위 절제술”은 위의 상부에 위치한 조기 위암의 치료를 위해 안전하게 할 수 있는 수술법이며 또한 수술 후 임상적 결과가 더 좋으며 위식도 역류의 측면에서 “기존의 근위 절제술”보다 우수한 수술법이다.

Comparative Analysis of Surgical Outcomes and Quality of Life after Cardia-Preserving Proximal Gastrectomy and Conventional Proximal Gastrectomy for Early Gastric Cancer of Upper Third of the Stomach

Background: Proximal gastrectomy (PG) has become an optional surgical procedure for early cancer in upper third of the stomach but gastroesophageal reflux (GER) is a main issue of this operation. We previously reported a kind of new function preserving gastrectomy for early gastric cancer (EGC) of upper stomach, cardia-preserving proximal gastrectomy (CPPG), in which the new technique could prevent reflux esophagitis and anastomotic stricture. This study aimed to compare the surgical outcomes and quality of life (QOL) of CPPG and conventional proximal gastrectomy (CPG).

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Conclusion: CPPG is a feasible and safe surgical procedure for EGC of upper stomach.

Wei Jie He Ph.D. Thesis

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CPPG has favorable surgical outcomes and superior to CPG in terms of GER.

**Keywords: Cardia preserving proximal gastrectomy; Early gastric cancer;
Surgical outcomes; Quality of life**

I. INTRODUCTION

With the increase in the incidence and mortality of gastric cancer worldwide, many countries have launched health checkup programs and the proportion of early gastric cancer (EGC) has been increasing. EGC accounts for more than 70% of all gastric cancers and has an increased five years survival rate higher than 90%. Therefore, the treatment of EGC, including eradicating the tumor, providing minimal invasiveness and improving patients' quality of life (QOL), has become a focus of study. Originally, total gastrectomy (TG) was performed for the EGC of upper third of stomach. Poor QOL of patients after TG make surgeons carry out function preserving gastrectomy such as conventional proximal gastrectomy (CPG) or jejunal interposition (JI). However, CPG is not commonly performed for severe gastroesophageal reflux (GER) and JI is complicated surgical procedure making several additional bowel anastomoses. Cardia-preserving proximal gastrectomy (CPPG) can complement the TG or JI. CPPG preserve cardia and reduce GER and avoid additional jejunal resection and anastomosis. It is performed not only with the goal of curing the tumor, but also with consideration of the patient's postoperative QOL. We reported a new method of CPPG in EGC of upper stomach in a series of 10 cases in 2012.¹ However, its clinical feasibility such as short-term surgical results, long-term oncologic results and QOL of patients are not investigated yet. This study aimed to compare the surgical outcomes and QOL of CPPG as a modified treatment for EGC in the upper third of the stomach with the CPG.

II. Materials and methods

A retrospective comparative analysis of 21 patients who had undergone CPPG and 14 patients who had undergone CPG from October 2006 to July 2019 in Chosun University

Hospital was performed. All patients were clinically diagnosed as EGC (T1N0) by esophagogastroduodenoscopy (EGD), computed tomography (CT) and located 4-5 cm below esophagogastric junction (EGJ). They were informed about this new technique and gave their consents.

2.1. Surgical procedure of CPPG and CPG

In all patients, CPPG or CPG with D1+ dissection was performed according to the Japanese gastric cancer treatment guidelines.² The range of lymph node (LN) dissection in CPPG was similar to that used in CPG and the hepatic branch of the vagus nerve was preserved in all cases. Frozen biopses were performed on selectively dissected LN No. 1, 2, 5 and 6. Then, if positive, the conventional method of total gastrectomy and Roux-en-Y reconstruction were performed. During partial omentectomy, to preserve the right gastroepiploic artery, LN No. 6 was checked with fingers without en bloc dissection. The greater omentum was dissected toward the spleen to remove all LN No. 4 and the gastroepiploic vessels were dissected on 2/3 from the top to the bottom of the greater curvature and divided the short gastric vessels to separate the fundus from the spleen. The lesser curvature including LN No. 3 and 5 was dissected toward from the origin of the right gastric artery to the esophagus. The branches of perigastric vessels in the 2/3 of the lesser curvature were divided from the top and removed with the lesser omentum. The abdominal esophagus was not widely dissected to avoid damage of phrenoesophageal ligament on the diaphragm and the palpated LN No. 1 and 2 were excised. In case of CPPG, a negative metastasis to these LNs was confirmed on the frozen biopsy, an excision was performed about 1.5-2 cm below EGJ and securing the proximal free resection margin was confirmed through a frozen biopsy. The anastomosis

of remaining stomach with layers, mucosa-submucosa and sero-muscular suture, was performed by hand-sewn for laparotomy, and the gastro-gastrostomy was performed by linear stapler in case of the laparoscopic surgery. The pyloroplasty was not performed and the nasogastric tube was not inserted. The oral intake started from the 4th day after the surgery (Figure 1).

2.2. Postoperative assessment

Patients' demographic characteristics and short-term postoperative outcome data were surveyed. Reflux symptoms and oral intake were determined in an interview 1 year postoperatively because several studies had revealed that the patients with 1 year after gastrectomy were generally stable. Endoscopy was performed every-year postoperatively. The Postgastrectomy Syndrome Assessment Scale (PGSAS)-45 was used for QOL assessment in this study, multidimensional quality of life questionnaire based on the 8-Item Short-Form Health Survey (SF-8) and the Gastrointestinal Symptom Rating Scale (GSRS). The PGSAS-45 questionnaire consisted of a total of 45 questions, with 8 items from the SF-8, 15 items from the GSRS, and 22 clinically important items selected by the Japan Postgastrectomy Syndrome Working Party.³ Among 45 questions of PGSAS-45, 27 questions were selected and QOL survey was carried out at 1 year after surgery. Originally, PGSAS-45 was invented for the patients to select five to seven - point Likert scale according to the items. However, many patients could not select the point because there was not clear definition of the point in some items. The scale was modified in this study using more clear definition as followings; 0 = none, 1 = mild, not require medication, 2 = moderate, relieved by medication, 3 = severe, not relieved by medication. For the subdomain of satisfaction

and dissatisfaction, we used 5-point scale; 1 = strongly disagree, 2 = disagree, 3 = do not know, 4 = agree, 5 = strongly agree. This study was approved by the Institutional Review Board of Chosun University Hospital (No. 2020-11-005).

2.3. Statistical analysis

SPSS 25.0 (SPSS Inc., Chicago, IL, USA) statistical software was used for statistical analysis. Categorical data were evaluated by the chi-square test, and continuous data were evaluated by the Student's t-test. Statistical significance was defined as $p < 0.05$.

III. RESULTS OF THE RESEARCH

3.1. General characteristics of the patients

Table 1 showed the demographic characteristics of the patients in this study. A total of 35 patients were enrolled. CPPG was carried out for 21 patients and CPG for 14 patients. They were all treated for the first time. EGD and pathological confirm was performed before the surgery. The sex ratios were 1:1.3 and 1:2.5 in the CPPG and CPG groups, and the mean ages were 64.3 and 65.7 years without any significant differences. The mean body mass index and pathologic stage were not significantly different. There was not a significant difference between two groups.

3.2. Surgical outcomes

For short-term surgical outcomes, operative time in CPPG group was longer than in CPG group, 136.4 ± 17.0 and 127.5 ± 20.0 minutes respectively ($P < 0.05$). Total amount of blood loss during surgery in CPPG group was more than in CPG group, 115.0 ± 20.0 and 100.0 ± 18.0 ml respectively ($P < 0.05$). However, Total length of hospitalization in CPPG

group was shorter than in CPG group, 7.1 ± 2.5 and 7.9 ± 1.8 days ($P<0.05$). The incidence of GER in CPPG group was lower than in CPG group, 28.5% and 35.7% respectively ($P<0.01$). There were two cases of postoperative bleeding, one case of intra-abdominal abscess and one case of gastric stasis in CPPG group, and one case of postoperative bleeding, one case of anastomotic leakage, one case of gastric stasis and one case of intestinal obstruction in CPG group, but all cases were managed conservatively. There was no mortality between two groups and five-years survival rate was not different (Table 2).

3.3. Assessments of QOL

Calculated QOL measurements of patients in CPPG and CPG groups were compared according to the modified items (Table 3). Among the major outcome measures, CPPG group showed significantly lower score of acid reflux, bloating symptom and bile reflux than CPG group. There were no other significant differences in QOL between CPPG and CPG groups. Also, there was no significant difference in QOL measurements between the two groups of patients for other symptoms, meals, work, dissatisfaction, or satisfaction for daily life (Table 4).

IV. DISCUSSION

Classically, TG was performed for EGC of upper third stomach. However, TG lost all the function of stomach and resulted in poor QOL and nutritional status. CPG was developed to preserve the gastric function and overcome the disadvantage of TG. In spite of the issue of limited lymph node dissection, CPG with regional lymph node dissection had positive effects on maintaining body weight and preventing post-gastrectomy anemia.⁴ In spite of original intention of preserving function, CPG showed high incidence of GER and poor QOL.⁵ Several surgical techniques, such as double flap technique or jejunal interposition, were developed to reduce reflux.^{6,7} However, these techniques need additional surgery and bowel anastomosis. CPPG is relatively new surgical modification of CPG which preserve cardia and phrenoesophageal ligament which are most important anatomic structures to prevent GER. This technique does not make additional bowel resection contrary to previous surgical techniques.

CPPG showed longer operative time compared to CPG. This is because we separated LN No. 1, 2, 5 and 6 lymph nodes and performed frozen biopsy before excision of stomach. Function preserving should not place above the surgical radicality. Frozen biopsy of regional LN is troublesome and time-consuming but by now there is no reliable indicator of LN metastasis but frozen biopsy. Two-dimensional values measured using preoperative multidetector computed tomography or peak-standardized uptake value by preoperative positron emission tomography-computed tomography (PET-CT) can help to reduce the operative time for detecting LN metastasis.^{8,9} Recently, sentinel node navigation surgery is intensively investigated and show promising result

to decrease the time for LN dissection.¹⁰

Hospital stay is influenced by many factors but anastomotic leak is most important.¹¹ There was one case of anastomotic leak in CPG and this patient stayed hospital more than 90 days. Excluding this patient, there was no difference of hospital stay between CPPG and CPG groups. The rate of anastomotic leak of CPPG seems to be similar with CPG. CPPG has no advantage in terms of hospital stay. CPPG showed more blood loss during surgery than CPG. It was guessed that this was due to selective lymph node dissection for frozen section. Compared to en-bloc resection, separate lymph node dissection was delicate procedure and bled more. In many cases, electrocautery was used for lymph node dissection. Sometimes, ultrasonically activated shears had merits of decreasing bleeding and help to reduce blood loss during CPPG.¹²

CPPG helped to reduce acid or bile reflux. However, this advantage failed to promote patients' overall QOL. QOL is decided by multiple factors. It is suggested that mild to moderate GER symptoms can be controlled by medication and does not impact on overall QOL. Robertson et al showed similar results. They assessed the GER symptoms and QOL following laparoscopic sleeve gastrectomy. In their study, small portion of patients had troublesome GER but overall satisfaction was high.¹³ Nutritional status, strength of skeletal muscle, weight gaining or symptoms after chemotherapy that were not well controlled by medication seemed to be stronger impact on QOL than reflux.^{14,15}

CPG has an issue of surgical radicality. Contrary to TG, CPG has a limitation to carry out standard D2 lymph node dissection. However, if we select patients cautiously, surgical radicality does not matter. Nai et al investigated the survival rate of CPG and

TG for EGJ adenocarcinoma (Siewert II types) and reported the overall 3-year survival rate in CPG and TG group was 65.6% and 62.6% respectively, and the overall 5-year survival rate was 53.8% and 44.5% respectively. No significant difference was found between the two groups.¹⁶ PU et al made meta-analysis comparing CPG and TG about long-term survival and complications. They showed that 5-year survival rate was similar but CPG had higher recurrence rate and anastomotic stenosis rate.¹⁷ By now, CPG is not inferior to TG for 5-year survival rate. Because CPPG needs to retain the nerve and blood supply of the cardia, the dissection of corresponding regional lymph nodes is greatly affected. This is main debate about the radicality of CPPG. In this study, the 5-year survival rate of CPPG was not different from CPG. CPPG has similar surgical radicality but superior in some aspect compared to CPG. So, it is suggested that CPPG as a modified surgical procedure for upper third EGC rather than TG.

Because this study was retrospective in design and the degree of gastrectomy was not controlled and there was a significant difference in the size of the residual stomach. To evaluate the GER or other postoperative complication, this study needed to measure residual volume of stomach after CPPG. Namikawa reported that a larger proximal residual stomach resulted in less weight loss and dissatisfaction with meals and daily life. To evaluate the true impact of CPPG on QOL, it need to measure the metric of remnant stomach.¹⁸ CPG is being tried for advanced gastric cancer of upper stomach. It need to evaluate the clinical feasibility of CPPG for advanced gastric cancer.^{19,20}

V. CONCLUSION

Classically proximal gastrectomy was carried out for the EGC of upper third of stomach. Compared to CPG, CPPG has similar short-term and long-term surgical outcomes and

better QOL reducing GER and hospital stay. CPPG seems to be used to substitute CPG in EGC of upper third gastric cancer. Surgeon need to consider CPPG as the useful option for the treatment of early upper third gastric cancer.

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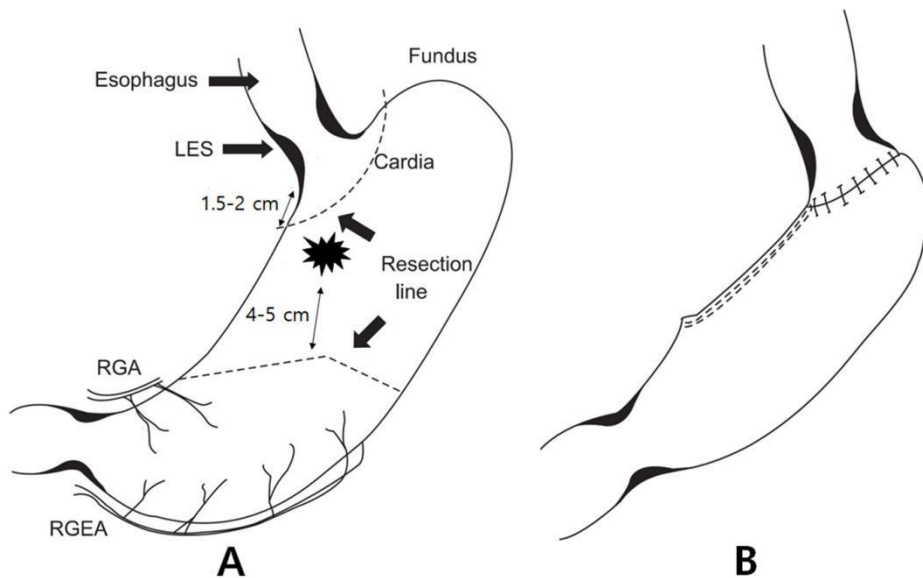


Figure 1. Illustration of CPPG. (A) The tumor located in the proximal stomach between 4 cm below EGJ and upper body. Resection was carried out 1.5 to 2 cm below the EGJ and 4 to 5 cm below the lower margin of tumor. (B) The anastomosis was performed by conventional methods or linear stapler. (CPPG; cardia-preserving proximal gastrectomy, EGJ; esophago-gastric junction, RGA; right gastric artery, RGEA; right gastroepiploic artery, LES: lower esophageal sphincter)

Table 1. General characteristics of patients

characteristics	CPPG (n=21)	CPG (n=14)	p value
Age (years)	64.3	65.7	NS
Sex ratio (male:female)	9:12	4:10	NS
Body mass index (kg/m ²)	24.6	24.3	
pT category (%)			
1a	16 (76.2)	8 (57.1)	NS
1b	5 (23.8)	6 (42.9)	NS
pN category (%)			
N0	21 (100)	14 (100)	
Surgical Approach			
Open	14 (66.7)	11 (78.6)	NS
Laparoscopic	7 (33.3)	3 (21.4)	NS

CPPG = cardia-preserving proximal gastrectomy.

CPG = conventional proximal gastrectomy.

NS = not significant (p>0.05).

Table 2. Surgical outcomes

Surgical results	CPPG (n=21)	CPG (n=14)	p value*
Operative time (minutes)	136.4 ± 17.0	127.5 ± 20.0	<0.05
Blood loss during surgery (ml)	115.0 ± 20.0	100.0 ± 18.0	<0.05
Length of hospitalization (day)	7.1 ± 2.5	7.9 ± 1.8	<0.05
Complications (Number of case)			
Postoperative bleeding	2	1	
Anastomotic leakage	0	1	
Intra-abdominal abscess	1	0	
GER (%)	6(28.5)	5(35.7)	<0.01
Gastric stasis (%)	1(4.7)	1 (7.1)	
Intestinal obstruction	0	1	
Recurrence (%)	0	0	
5 Year survival rate	21 (100)	14 (100)	

CPPG = cardia-preserving proximal gastrectomy.

CPG = conventional proximal gastrectomy.

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GER=gastroesophageal reflux.

* Only P values of statistical significance are shown.

Table 3. QOL of cardia-preserving proximal gastrectomy and conventional proximal gastrectomy

Subdomains	Items	CPPG (n=21)	CPG (n=14)	p value**
SF-8	Physical functioning impairment*	1.36	1.63	
	Bodily pain*	1.33	1.67	
	General health impairment*	2.17	2.43	
	Vitality impairment*	2.45	2.22	
	Social functioning restriction*	2.22	2.46	
	Mental health impairment*	1.34	1.27	
GSRS	Abdominal pain	0.57	0.65	
	Stomach heat	1.23	1.20	
	Acid reflux	0.57	1.23	<0.05
	Nausea and vomiting	0.76	0.81	
	Constipation	0.12	0.23	
	Bloating	1.61	2.69	<0.05

	Loose stools	0.67	0.38	
	Abnormal bowel movements	0.23	0.41	
	Increased stool frequency	1.45	1.72	
PGSAS	Bile reflux	1.14	1.98	<0.05
	Early Satiety	1.08	0.78	
	Lower abdominal pain	0.43	0.32	
	Early dumping syndrome	1.76	1.53	
	Late dumping syndrome	0.45	0.38	
Meals	Decreased food intake per meal	2.71	2.54	
	Decreased food intake per day	2.65	2.53	
	Decreased complementary food	2.56	2.34	
	Decreased Appetite	1.34	1.46	
	Decreased Hunger	0.45	0.65	
	Abnormal satiety feeling	1.11	1.45	
Social activity	Impairment of ability to work	2.45	2.65	

In items with *, higher scores indicate better conditions.

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In items without *, higher scores indicate worse conditions.

QOL = Quality of life; SF-8 = Short-Form Health Survey.

GSRS = Gastrointestinal Symptom Rating Scale.

PGSAS = Postgastrectomy Syndrome Assessment Scale.

CPPG = cardia-preserving proximal gastrectomy.

CPG = conventional proximal gastrectomy.

**Only P values of statistical significance are shown.

Table 4. Main outcomes of overall quality of life following cardia-preserving proximal gastrectomy and conventional proximal gastrectomy

Subdomains	Main outcomes measures	CPPG (n=21)	CPG (n=14)	p value
Dissatisfaction	Dissatisfaction with symptoms	3.45	3.67	NS
	Dissatisfaction at the meals	3.34	3.65	NS
	Dissatisfaction at working	3.12	3.21	NS
Satisfaction	Satisfaction with the body	2.34	2.10	NS
	Psychological satisfaction	3.21	3.54	NS

CPPG = cardia-preserving proximal gastrectomy.

CPG = conventional proximal gastrectomy.

NS=not significant ($p>0.05$).

Appendix A

Acknowledgement

Now, at one o'clock in the morning, it is no longer known how many silent nights can't sleep at night. Looking up, there are still several windows in the Medical Sacred Hall showing lights, and I think it must be hardworking and serious professors! Looking back on my education, the strongest feeling is gratitude: my mentor gave me knowledge, my parents gave me life, my lover gave me happiness, my brothers and sisters gave me care, and my classmates and friends gave me support. There is an inextricable relationship between each other. If I don't know how to be grateful, I won't be able to stand up and be honest!

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Finally, I want to thank my wife in particular. I have been married for 10 years, and I have studied for 5 years. Without her supporting my sky, I don't think I can stay in the pure campus in the year of my standing, away from the complicated world outside, and devote myself to my wife. Study life. Thanks to my wife for allowing me to be an "old student" again in my thirties, without having to bear the burden of earning money to support my family; thanks to my lover for keeping my eyes bright and focused in my thirties, I was not bothered by the trivial family life; I thank my wife for frequenting my work, educating children, and caring for my parents during my years of schooling, and relieved me of all my worries. This love is worth cherishing in my life. I want to thank my parents for their upbringing and education over the years, for their meticulous care and support for my life, and for my daughter's understanding, so that I can complete the study and research of the doctor today.

In short, during these years of doctoral studies, I have not only improved my academic research capabilities, but also enriched my life experience. From admission to graduation, I sincerely thank all the professors, teachers, classmates, friends and family members, who have been with me all these years!

I thank everyone who directly and indirectly helped me to successfully complete my PhD study.

Appendix B

List of publications

1. 김수현, 박원철, 김민성, 김성수, **He WeiJie**, 민영돈. Prognostic Significance of P53,Ki-67and COX-2 in gastric cancer, KMBASE, 2017-08
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