Comparable hematologic and nutritional outcomes of proximal gastrectomy with double-tract reconstruction compared with total gastrectomy for early gastric cancer in the upper stomach

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Directed by Professor Woo Jin Hyung

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ABSTRACT

Comparable hematologic and nutritional outcomes of proximal gastrectomy with double-tract reconstruction compared with total gastrectomy for early gastric cancer in the upper stomach

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(Directed by Professor Woo Jin Hyung)

Potential benefits of proximal gastrectomy in terms of hematologic and nutritional outcomes over total gastrectomy have been theoretically suggested in several studies. However, no proven evidences for the hematological and nutritional outcomes have been demonstrated. Thus, we compared hematologic and nutritional outcomes after proximal gastrectomy with double-tract reconstruction with those after total gastrectomy.

From September 2014 to December 2015, there were 80 patients underwent minimally invasive surgery, proximal gastrectomy or total gastrectomy, for stage I gastric cancer. We divided patients into two groups: proximal gastrectomy group, 38 patients underwent proximal gastrectomy with double-tract reconstruction and total gastrectomy group, 42 patients underwent total gastrectomy. We retrospectively analyzed clinicopathologic, hematologic, and nutritional features.

We found no significant differences in hematologic outcomes. Change of hemoglobin level and cumulative incidence of iron deficiency anemia between the two groups were similar (p = 0.250 and 0.971, respectively) with a median follow up period of 24 months (range 18 – 30 months) after surgery. Cumulative incidence of vitamin B12 deficiency did not significantly differ between the proximal gastrectomy group and the total gastrectomy group (p = 0.087). There was no significant difference in the patients' BMI changes from

baseline between the proximal gastrectomy group and the total gastrectomy group (p = 0.591). In the nutritional features, there were no statistically significant differences.

This study showed that proximal gastrectomy with double-tract reconstruction and total gastrectomy have no statistically different outcomes in terms of hematologic and nutritional aspect, especially in emergence of iron deficiency and vitamin B12 deficiency anemia. In conclusion, for patients with gastric cancer located in upper third of the stomach, proximal gastrectomy with double-tract reconstruction can be considered as an alternative option with comparable outcomes of total gastrectomy, if oncological safety is assured.

Key words : proximal gastrectomy, double-tract reconstruction, total gastrectomy, hematologic, nutritional, iron deficiency anemia, vitamin B12 deficiency

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I. INTRODUCTION

In recent years adenocarcinoma in the proximal stomach is increasing, although the overall incidence of gastric cancer has decreased[1-3]. In Korea and Japan, the proportion of early gastric cancer has been increased due to mass screening program[3-5]. These tendencies lead increasing incidence of proximal early gastric cancer especially in East Asian countries.

Although the current standard treatment for proximal early gastric cancer is total gastrectomy, proximal gastrectomy has been applied as a function-preserving surgery to improve quality of life[6-9]. It saves gastric reservoir and parietal cells by preserving distal stomach[10]. This reduction of the extent of gastrectomy might improve oral intake after surgery through remnant gastric reservoir. Preservation of intrinsic factor secretion from the parietal cells in the distal remnant stomach maintains vitamin B12 absorption. Furthermore, proximal gastrectomy provides route of iron absorption by allowing food passage to the duodenum[11,12]. Therefore, proximal gastrectomy is expected to be theoretically beneficial for nutrients absorption and oral intake, in terms of hematologic, nutritional and metabolic aspects[9,13-16].

Despite above theoretical advantages, however, surgeons are reluctant to

perform proximal gastrectomy due to reflux esophagitis after esophagogastrostomy or gastric stasis after jejunal interposition[17,18]. To overcome these drawbacks, double-tract reconstruction after proximal gastrectomy was developed[19] and performed frequently[3,20-23]. As surgical feasibility of double-tract reconstruction after proximal gastrectomy with resolution of those drawbacks have been demonstrated[21,24], this new reconstruction method becomes major reconstruction method after proximal gastrectomy in Korea[3]. However, there are only few studies evaluating hematologic and nutritional outcomes of proximal gastrectomy with double-tract reconstruction compared with total gastrectomy[25]. Therefore we aimed to assess effects of proximal gastrectomy with double-tract reconstruction on hematologic and nutritional outcomes by comparing with those of total gastrectomy.

II. MATERIALS AND METHODS

1. Patients

We performed proximal gastrectomy with double-tract reconstruction from September 2014 for proximal early gastric cancer. We retrospectively reviewed the prospectively collected database of patients with gastric cancer who underwent curative gastrectomy from September 2014 to December 2015, at the department of Surgery, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea. This study was approved by the institutional review board of Severance Hospital, Yonsei University Health System (4-2016-0427).

There were a total of 108 consecutive patients who underwent minimally invasive (laparoscopic or robotic) proximal or total gastrectomy for stage I gastric cancer. Among these patients, we excluded 28 patients due to preoperative vitamin B12 deficiency (n = 1), insufficient evaluation of vitamin

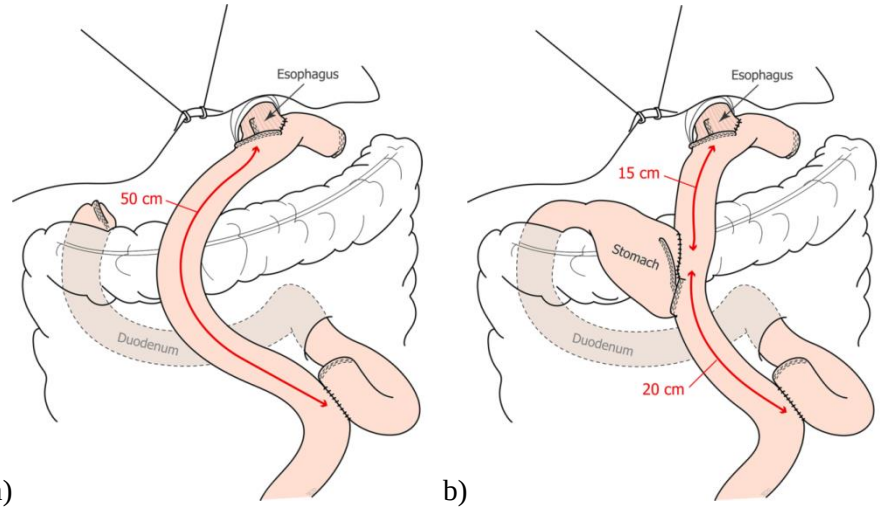
B12 or iron profile (n = 25), and follow-up loss (n = 2). Finally 80 patients were included in this study: 38 patients of proximal gastrectomy group who underwent minimally invasive proximal gastrectomy with double-tract reconstruction and 42 patients of total gastrectomy group who underwent minimally invasive total gastrectomy with Roux-en-Y esophagojejunostomy. The indication for proximal gastrectomy was patients who were diagnosed as clinical early gastric cancer without evidence of lymph node metastasis and located in the upper-third of the stomach. If there was any deformities or ulcer scar on distal stomach or duodenum, the proximal gastrectomy was not indicated.

2. Surgical procedure

A. Robotic/Laparoscopic total gastrectomy: The detailed procedures of minimally invasive total gastrectomies in our institution were described previously.[26,27] For reconstruction, the abdominal esophagus was fully mobilized and rotated 90-degree in counter-clockwise direction. After transection of esophagus using an articulating 45 mm linear stapler with blue cartridge, proximal jejunum was brought up to the esophageal stump then posterior wall of esophagus and anti-mesenteric side of jejunum was anastomosed intracorporeally using overlap method with linear stapler. The common entry hole was closed using stapler but hand-sewn closure also used occasionally when anastomosis level is high. Then jejunal loop 2–3 cm proximal to the anastomosis was divided without mesenteric division, and it was anastomosed to the Roux-limb at 50 cm below the esophagojejunostomy. All of the anastomoses were performed intracorporeally using a 45 mm linear stapler with white cartridge (Figure 1a).

B. Robotic/Laparoscopic proximal gastrectomy with double-tract reconstruction: Detailed procedure of laparoscopic proximal gastrectomy with double-tract reconstruction was also described in detail, previously[23]. Robotic procedures were not different from laparoscopic procedures except for devices used in

peritoneal cavity. The stomach was transected above the gastric angle using a 45 mm linear stapler with blue cartridges. Anastomoses including the esophagojejunostomy, jejunogastrostomy, and jejunojejunostomy were performed for double-tract reconstruction: the esophagojejunostomy was performed in same manner as in minimally invasive total gastrectomy, the jejunogastrostomy was made with blue cartridges at 15 cm below the esophagojejunostomy, and jejunojejunostomy was also made with white cartridges at 20 cm below the jejunogastrostomy (Figure 1b).



a) b)

Figure 1. Schema of reconstruction. a) Total gastrectomy with Roux-en-Y esophago-jejunostomy. b) Proximal gastrectomy with double-tract reconstruction.

3. Data collection

Patients' demographics including age and gender, pathologic characteristics, operative data, clinical and surgical outcomes were collected. Patients' physical status with comorbidities was assessed by the American Society of Anesthesiologists Physical Status classification system[28]. Postoperative complications were graded by Clavien-Dindo classification of surgical complications[29]. We defined complications We classified the fever above 38.3℃, antipyretics or diuretics use, and correction of electrolyte imbalance as a grade I complication and chyle leakage, antibiotics use, hepatotonic agent use, medication for pancreatitis, correction of hypoalbuminemia, correction of

iron deficiency, and transfusion as a grade II complication. Grade III or higher complications were classified as major complications. Every patient's progress was reviewed weekly by surgeons and all complications were double-checked and recorded. Pathologic data was collected based on the 7th edition of the American Joint Committee on Cancer staging system[30] and histologic data was based on the Lauren classification[31].

4. Hematologic and nutritional outcome measures

The hematological parameters including hemoglobin, hematocrit, and iron profile (serum iron, ferritin, transferrin, transferrin saturation, and total iron-binding capacity (TIBC)) were measured. The serum ferritin levels were measured by a competitive immunoassay using direct chemiluminescence (ADVIA Centaur; Bayer Diagnostics, Tarrytown, NY) and serum transferrin levels were measured using a nephelometer (Dade Behring, Siemens Helathcare Diagnostics, Liederbach, Germany). Transferrin saturation was calculated as the ratio of the serum iron level to TIBC multiplied by 100. Anemia was defined by hemoglobin <13 g/dL in men or <12 g/dL in women according to the World Health Organization criteria[32] and iron deficiency was defined by serum ferritin level <30 ng/mL[33,34]. The serum vitamin B12 level was measured using an electrochemiluminescence immunoassay kit (Roche DiagnosticsGmbH, Mannheim, Germany) and vitamin B12 deficiency was defined as the serum level lower than 200 pg/mL[10]. For evaluation of nutritional features, neutrophil count, total lymphocyte count, serum protein and albumin, cholesterol levels were also measured.

5. Follow-up

We followed up all patients every 3 months for one year after the surgery, then every 6 months. We checked patients' weight at every visit and evaluated blood test for hematologic and nutritional features. We examined abdomino-pelvic CT scan every 6 months for initial two years then yearly after. We performed upper endoscopy every year. We followed up all patients with the

median duration of 24 months (range 18 – 30 months) in both groups.

6. Statistical analysis

The statistical analysis was performed with the IBM SPSS statistics for Windows, Version 23.0 program (Armonk, NY: IBM Corp.). Independent variables were compared by using the Chi-square test for categorical variables and the Mann-Whitney U test or the Kruskal-Wallis test for continuous variables. Cumulative occurrence of anemia and deficiency of vitamin B12 or iron was analyzed using the Kaplan-Meier method with the log-rank test. For the analysis of changes of continuous variables between two groups, mixed model analysis with post-hoc test was performed. A p value <0.05 was considered to be statistically significant.

III. RESULTS

1. Patients' characteristics and Surgical outcomes

There was no statistically significant difference in demographics (Table 1). Operation time, estimated blood loss, and length of hospital stay were also comparable between two groups (Table 2).

Table 1. Patients' characteristics

	Proximal gastrectomy (n = 38)	Total gastrectomy (n = 42)	*p* value
Gender			0.256
Male	32 (84.2%)	31 (73.8%)	
Female	6 (15.8%)	11 (26.2%)	
Age (years)	55.8 ± 11.6	59.3 ± 11.8	0.184
ASA-PS classification[1]			0.422
1	5 (13.2%)	9 (21.4%)	
2	27 (71.1%)	24 (57.1%)	
3	6 (15.8%)	9 (21.4%)	
Weight (kg)	69.1 ± 12.2	66.1 ± 12.6	0.289
BMI (kg/m^2)[2]	24.2 ± 3.1	23.5 ± 3.0	0.316
No. comorbidities			0.647
0	18 (47.4%)	21 (50.0%)	
1	18 (47.4%)	16 (38.1%)	
2	1 (2.6%)	4 (9.5%)	
3	1 (2.6%)	1 (2.4%)	
Comorbidity[2]			
Hypertension	12 (31.6%)	11 (26.2%)	0.595
Cardiac	0 (0.0%)	1 (2.4%)	>0.999
Diabetes	4 (10.5%)	5 (11.9%)	>0.999
Hepatic	1 (2.6%)	0 (0.0%)	0.475
Cerebrovascular	2 (5.3%)	1 (2.4%)	0.602
Old tuberculosis	3 (7.9%)	6 (14.3%)	0.487
Asthma	0 (0.0%)	1 (2.4%)	>0.999

[1] American Society of Anesthesiologists Physical Status (ASA-PS) classification system
[2] Body mass index
[3] Includes all comorbidities in patients with multiple diseases

Table 2. Surgical outcomes

	Proximal gastrectomy (n = 38)	Total gastrectomy (n = 42)	*p* value
Method			0.133
Laparoscopic	27 (71.1%)	23 (54.8%)	
Robotic	11 (28.9%)	19 (45.2%)	
Lymph node dissection			0.001
D1+	38 (100%)	31 (73.8%)	
D2	0 (0.0%)	11 (26.2%)	
Combined resection			
Gall bladder	1 (2.6%)	2 (4.8%)	>0.999
Adrenal	1 (2.6%)	0 (0.0%)	0.475
Operation time (min)	217.7 ± 53.0	226.9 ± 66.2	0.498
Estimated Blood Loss (mL)	100.2 ± 92.0	118.8 ± 157.2	0.528
Intraoperative transfusion			0.495
No	38 (100%)	40 (95.2%)	
Yes	0 (0.0%)	2 (4.8%)	
Length of hospital Stay (day)	8.18 ± 5.72	8.44 ± 9.55	0.882

In terms of postoperative morbidity (Table 3), 17 complications occurred in 16 patients underwent proximal gastrectomy and 28 complications occurred in 26 patients underwent total gastrectomy. Although overall complication rate was lower in proximal gastrectomy group (42.1%) than in total gastrectomy group (61.9%), there was no statistical significance ($p = 0.077$). In the patients with complication, rate of major complications above grade III was also lower in proximal gastrectomy group (12.5%) than in total gastrectomy group (38.5%, $p = 0.102$, Table 4), however it was not statistically different.

Proximal gastrectomy group had lower incidence of anastomosis-related complications compared with total gastrectomy group, although it was not statistically significant (2.6% vs. 14.3%, $p = 0.112$). One patient in proximal gastrectomy group (2.6%) and four paitents in total gastrectomy group (9.5%) suffered from anastomotic leakage of esophagojejunostomy ($p = 0.362$). Among them, two patients in total gastrectomy group underwent re-operation

Table 3. Postoperative morbidity (within 30 postoperative days)

	Proximal gastrectomy (n = 38)	Total gastrectomy (n = 42)	*p* value
Complication			0.077
No	22 (57.9%)	16 (38.1%)	
Yes	16 (42.1%)	26 (61.9%)	
Intra-abdominal complication			
Fluid collection/abscess	3 (7.9%)	0 (0.0%)	0.103
Anastomotic leakage	1 (2.6%)	4 (9.5%)	0.362
Anastomotic stenosis	0 (0.0%)	2 (4.8%)	0.495
Duodenal stump leakage	0 (0.0%)	1 (2.4%)	>0.999
Cholecystitis	1 (2.6%)	0 (0.0%)	0.475
Pancreatitis	2 (5.2%)	1 (2.4%)	0.602
Chylous ascites	2 (5.2%)	0 (0.0%)	0.222
Profuse drainage	1 (2.6%)	0 (0.0%)	0.475
Wound complication	1 (2.6%)	4 (9.5%)	0.362
Medical complications			
Respiratory	1 (2.6%)	2 (4.8%)	>0.999
Cardiovascular	0 (0.0%)	1 (2.4%)	>0.999
Urinary	1 (2.6%)	3 (7.1%)	0.617

Table 4. Severity of complications according to Clavien-Dindo classification

	Proximal gastrectomy (n = 16)	Total gastrectomy (n = 26)	*p* value
Clavien-Dindo Grade			0.102
Grade I	4 (25.0%)	9 (34.6%)	
Grade II	10 (62.5%)	7 (26.9%)	
Grade III	2 (12.5%)	9 (34.6%)	
Grade IV	0 (0.0%)	1 (3.8%)	

under the general anesthesia for surgical correction of anastomotic leakage, others were treated with procedures under the local anesthesia such as endoscopic procedures or percutaneous drainage catheter insertion (Table 5). Only in total gastrectomy group, esophagojejunostomy stenosis in two patients (4.8%, $p = 0.495$) and duodenal stump leakage in one patient (2.4%, $p > 0.999$) occurred. On the other hand, patients with intra-abdominal fluid collection were only in proximal gastrectomy group (7.9%, $p = 0.103$) and managed with conservative method.

One patient in proximal gastrectomy group complained of fever and chilling on 15^{th} postoperative day was diagnosed with cholecystitis due to gallstone in the distal common bile duct and finally underwent cholecystectomy with intraoperative cholangiogram. Another patient who had past history of percutaneous coronary stent insertion in total gastrectomy group showed abnormal demonstration on electrocardiogram and elevated cardiac enzyme after gastric surgery. He was diagnosed with Non-ST elevation myocardial infarction and then underwent coronary angiography with stent insertion. The patients with other complications successfully treated with conservative management and there were no differences between two groups. There was no mortality in both groups.

Table 5. Types and management of grade III or higher postoperative morbidity

Grade[1]	Complication	Group[2]	Management
IIIa	Anastomotic leakage	PG	PCD[3], Endoscopic stent
		TG	Endoscopic stent
		TG	Endoscopic stent, E-VAC[4]
	Anastomotic stenosis	TG	Endoscopic dilatation
		TG	Endoscopic dilatation
	Duodenal stump leakage	TG	PCD
	Pleural effusion	TG	PCD
		TG	PCD
	Non-STEMI	TG	Coronary stent insertion
IIIb	Anastomotic leakage	TG	Re-operation
	Cholecystitis due to CBD stone	PG	Cholecystectomy
IV	Anastomotic leakage	TG	Re-operation, ICU[5] admission

[1] according to Clavien-Dindo classification
[2] PG: proximal gastrectomy with double-tract reconstruction,
TG: total gastrectomy with Roux-en-Y esophagojejunostomy
[3] PCD: Percutaneous catheter drainage
[4] E-VAC: Endoscopic vaccum-assisted closure system
[5] ICU: Intensive care unit

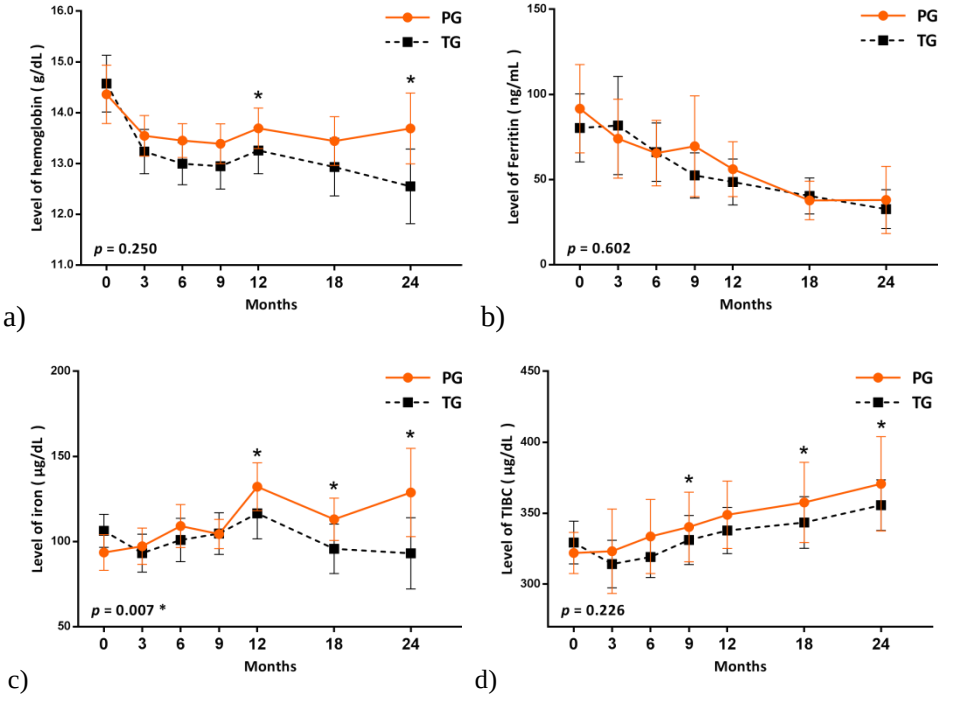
In histopathologic characteristics (Table 6), tumor size, distal margin, and number of retrieved lymph nodes (p = 0.034, <0.001, and 0.005, respectively) showed significant difference as expected due to different extent of resection and lymph node dissection. The proximal gastrectomy group tended to have lower pathologic stage of tumor compared with total gastrectomy group (p = 0.047), while T stage and N stage did not differ between two groups (p = 0.112 and >0.999, respectively).

Table 6. Histopathologic characteristics

	Proximal gastrectomy (n = 38)	Total gastrectomy (n = 42)	P value
Tumor location (Tubular)			0.067
EG junction	2 (5.3%)	1 (2.4%)	
Cardia	5 (13.2%)	10 (23.8%)	
Fundus	0 (0.0%)	0 (0.0%)	
Upper body	24 (63.2%)	15 (35.7%)	
Mid body	7 (18.4%)	11 (26.2%)	
Lower body	0 (0.0%)	2 (4.8%)	
Tumor size (mm)	21.4 ± 17.1	32.5 ± 27.1	0.034
Proximal margin (mm)	28.0 ± 22.8	37.6 ± 34.2	0.143
Distal margin (mm)	62.3 ± 26.0	130.7 ± 45.2	<0.001
Histology (Lauren)			>0.999
Intestinal	19 (51.4%)	21 (50.0%)	
Diffuse	17 (45.9%)	18 (42.9%)	
Mixed	0 (0.0%)	1 (2.4%)	
Indeterminate	1 (2.7%)	2 (4.8%)	
T stage			0.112
T1a (m)	17 (44.7%)	17 (40.5%)	
T1b (sm)	20 (52.6%)	17 (40.5%)	
T2 (mp)	1 (2.6%)	8 (19.0%)	
N stage			>0.999
N0	37 (97.4%)	40 (95.2%)	
N1	1 (2.6%)	2 (4.8%)	
Stage			0.045
Stage IA	36 (94.7%)	32 (76.2%)	
Stage IB	2 (5.3%)	10 (23.8%)	
Retrieved lymph nodes	43.9 ± 15.7	56.2 ± 21.7	0.005

2. Hematologic Outcomes

The concentration of hemoglobin, ferritin, TIBC, and transferrin did not statistically differ between two groups (p = 0.250, 0.602, 0.226, and 0.168, respectively), whereas serum iron and transferrin saturation showed significant difference between two groups (p = 0.007 and 0.026, respectively, Figure 2a-f). The cumulative incidence of anemia was lower after proximal gastrectomy than total gastrectomy, however, the difference was not statistically significant (p = 0.690, Figure 2g). Patients in both groups had almost same cumulative incidence of iron deficiency anemia after 18 months (p = 0.971, Figure 2h).



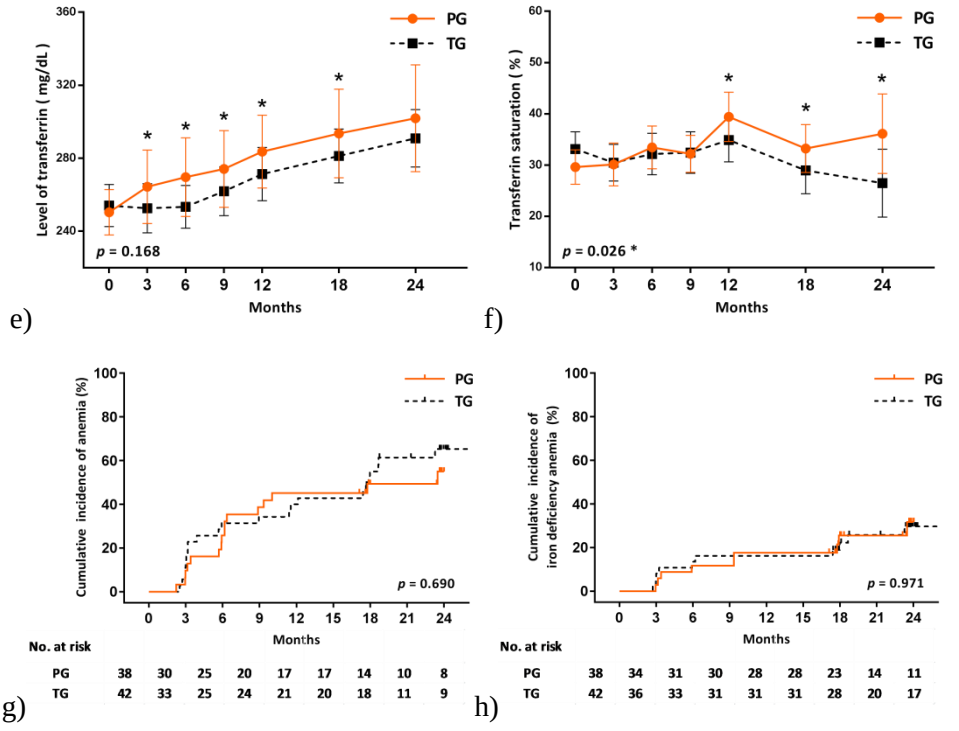


Figure 2. Changes in hematologic parameters. Level of a) hemoglobin, b) ferritin, c) iron, d) total iron-binding capacity, e) transferrin, and f) transferrin saturation. Cumulative incidence of g) anemia and h) iron deficiency anemia. *PG* proximal gastrectomy with double-tract reconstruction, *TG* total gastrectomy with Roux-en-Y esophagojejunostomy, *TIBC* Total iron-binding capacity.

3. Vitamin B12 metabolism

For accurate analysis, we excluded patients who supplemented with vitamin B12 from the analysis at the time of supplementation and thereafter. In both groups, levels of vitamin B12 were over 600 pg/mL preoperatively. However, it decreased markedly below 300 pg/mL at 3 months after surgery and converged to 200 pg/mL until 9 months after surgery. At 12 months after surgery, there was no available value in total gastrectomy group because all of the patients who underwent total gastrectomy supplemented with vitamin B12 after 18 months. The mean changes of vitamin B12 level did not differ

between two groups (p = 0.095, Figure 3a).

Figure 3b shows cumulative incidence of vitamin B12 deficiency after surgery. Proximal gastrectomy group had lower cumulative incidence of vitamin B12 deficiency compared with total gastrectomy group: approximately 85% of patients in proximal gastrectomy group suffered from vitamin B12 deficiency at 24 months after surgery. On the contrary, although the difference was not statistically significant, 100 % of the patients in total gastrectomy group experienced vitamin B12 deficiency within 21 months after surgery (p = 0.087).

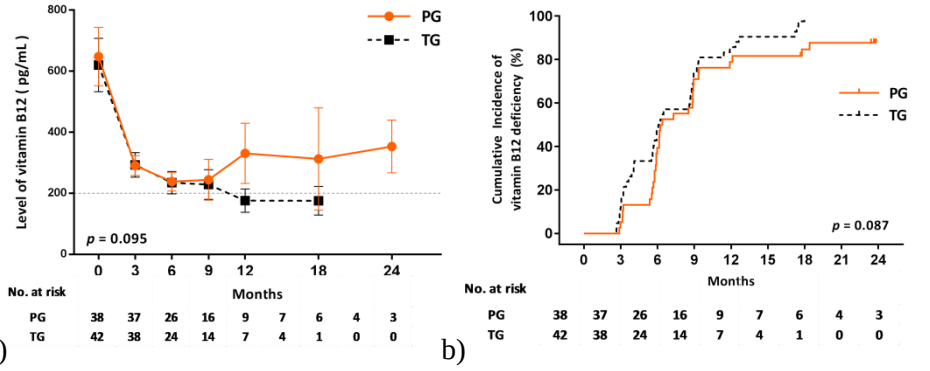


Figure 3. Comparison of vitamin B12 metabolism between PG and TG. a) Changes in vitamin B12 level without supplementation. b) Cumulative incidence of vitamin B12 deficiency. *PG* proximal gastrectomy with double-tract reconstruction, *TG* total gastrectomy with Roux-en-Y esophagojejunostomy.

4. Weight and nutritional parameters

Mean changes in BMI from baseline are shown in Figure 4. In both groups, BMI decreased more than 2.5 kg/m^2 from baseline until 12 months after surgery. After that, BMI in proximal gastrectomy group tended to recover while those in total gastrectomy group remained at the plateau. However, its difference was not statistically significant between two groups (p = 0.591).

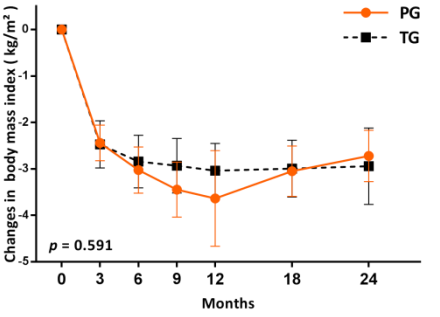


Figure 4. Mean changes in body mass index from baseline. *PG* proximal gastrectomy with double-tract reconstruction, *TG* total gastrectomy with Roux-en-Y esophago-jejunostomy

In nutritional aspect, the proximal gastrectomy group showed similar level of total protein, albumin and similar total lymphocyte count compared to the total gastrectomy group (p = 0.678, 0.743, 0.938 and 0.144, respectively, Figure 5).

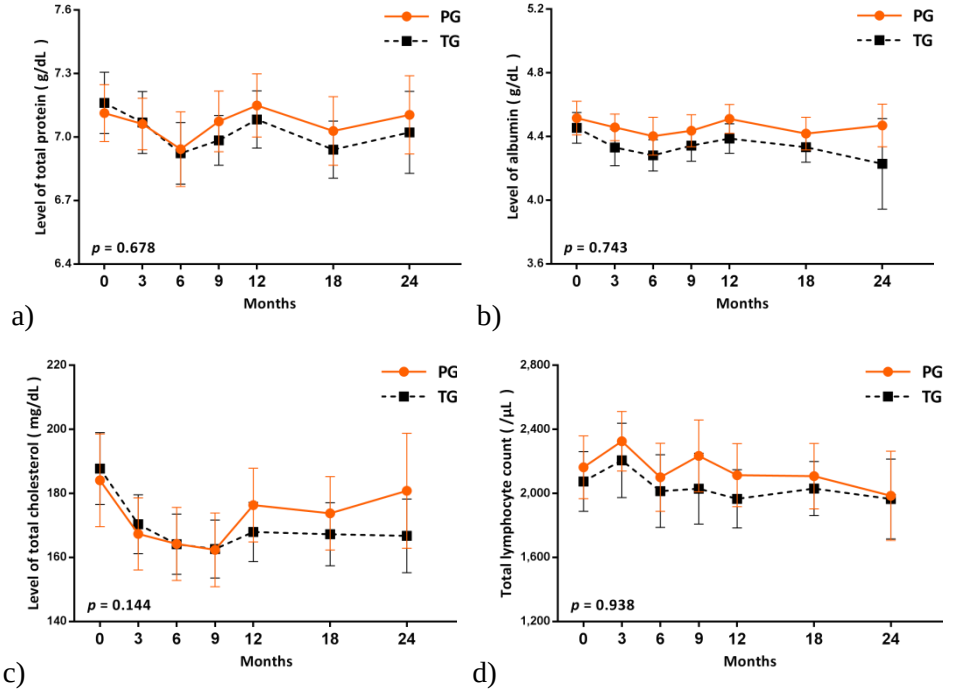


Figure 5. Changes in nutritional parameters. Level of a) total protein, b) albumin,

c) cholesterol. d) Total lymphocyte count. *PG* proximal gastrectomy with double-tract reconstruction, *TG* total gastrectomy with Roux-en-Y esophagojejunostomy.

IV. DISCUSSION

In our study, minimally invasive proximal gastrectomy with double-tract reconstruction had comparable outcomes to minimally invasive total gastrectomy with Roux-en-Y esophagojejunostomy in terms of surgical, hematologic and nutritional aspects. Analyses of the hematologic parameters, including hemoglobin, ferritin, and transferrin saturation also showed that postoperative levels did not differ between two groups. Although the cumulative incidence of anemia was lower in proximal gastrectomy group than total gastrectomy group, the difference was not statistically significant. Furthermore, two groups showed similar cumulative incidence of iron deficiency anemia. The nutritional parameters showed comparable levels in both groups.

Proximal gastrectomy followed by various reconstruction methods except double-tract reconstruction completely preserves food passage into the duodenum, whereby it have been reported to have better outcome for iron metabolism compared to total gastrectomy[13-16,35-38]. On the other hand, double-tract reconstruction only preserves duodenal food passage partially because it literally has two ways of food passage. Nonetheless, this reconstruction is also expected to be beneficial on iron metabolism. Although most studies have analyzed mean level of hematologic parameters, it have showed favorable or comparable outcomes on iron metabolism following double-tract reconstruction for proximal gastrectomy compared with total gastrectomy[12,22].

In the present study, the mean levels of hemoglobin and ferritin were higher in proximal gastrectomy group compared with those in total gastrectomy group as expected. However, the values in both groups still remained within the normal range and difference was not statistically significant. Moreover, the cumulative incidence of anemia and iron deficiency anemia were not different

between the two groups. Partial preservation of duodenal food passage by diversion in double-tract reconstruction makes amount of iron absorption much reduced. While accurate proportion of food passage through the duodenum in proximal gastrectomy with double-tract reconstruction has never been reported, one study described that contrast material passes into the duodenum and 60% of ingested food was found in remnant stomach after double-tract reconstruction[12]. This partial passage of ingested food into the duodenum through jejunogastrostomy would be insufficient to prevent iron deficiency.

Iron deficiency might be due to not only reconstruction method but gastrectomy itself, since decreased oral intake caused by reduction of volume of the stomach after gastrectomy affects decreased iron intake. Similar phenomenon was also observed even after distal subtotal gastrectomy with gastroduodenostomy (Billroth I anastomosis) which completely preserves food passage to the duodenum. Iron deficiency occurred in more than half of the patients after distal subtotal gastrectomy with gastroduodenostomy (Billroth I anastomosis) in 3 years after gastrectomy[11]. Preservation of distal stomach after proximal gastrectomy would not be sufficient to prevent iron deficiency. In addition, decreased chief cell mass on stomach and vagotomy decreases gastric acidity resulted in decreased efficacy of iron absorption. Therefore, iron deficiency after proximal gastrectomy with double-tract reconstruction would be inevitable.

With regard to vitamin B12 metabolism, distal stomach preservation in proximal gastrectomy have been reported to have beneficial effect[12,22,35]. Most studies regarding proximal gastrectomy with double-tract reconstruction reported just mean level of vitamin B12 after surgery without exact incidence of vitamin B12 deficiency. When we compared cumulative incidence of vitamin B12 deficiency after proximal gastrectomy with double-tract reconstruction, it was similar to that after total gastrectomy.

The parietal cell is most important factor for vitamin B12 metabolism because absorption of vitamin B12 is mediated by intrinsic factor released from gastric

parietal cell. Since gastric parietal cells mainly located in anatomical body of the stomach[39], the patient who underwent proximal gastrectomy might have small parietal cell volume due to paucity of parietal cell in gastric antrum and pylorus. The parietal cell volume after gastrectomy could be related to the volume of gastric remnant. In addition, volume of parietal cell would be influenced by pathologic change of remnant gastric mucosa after proximal gastrectomy with double-tract reconstruction such as atrophic gastritis or intestinal metaplasia[40,41]. Therefore, vitamin B12 deficiency after proximal gastrectomy with double-tract reconstruction would also be inevitable.

In our institution, as mentioned above, stomach was transected above the angle, and only two or three branches of right gastric and gastroepiploic arteries were preserved. That means volume of the remnant stomach is about half of entire stomach. This small volume of remnant stomach might have affected our results. Compared with a study reported superior clinical and nutritional outcomes after proximal gastrectomy with double-tract reconstruction compared with total gastrectomy[22], distal resection margin in proximal gastrectomy group of our study (6.2 cm) was much greater than that study (2.8 cm). While the mean value of tumor size and proximal resection margin are similar, the volume of the gastric remnant in our study is smaller than theirs. We may suppose that disparities in the volume of the gastric remnant make different hematologic and nutritional outcomes.

Moreover, the remnant gastric volume is also a factor affecting recovery of the amount of food intake and gastrointestinal symptoms after surgery. Thus, small remnant gastric volume could make these similar outcomes of proximal gastrectomy compared with total gastrectomy. With regard to remnant volume of the stomach, patients with a larger remnant stomach (1/2 resected group) showed higher postoperative/preoperative body weight ratios compared to those with small remnant stomach (2/3 resected group) and with no remnant stomach (total gastrectomy group)[25]. In this study, the changes in BMI from baseline were not significantly different between proximal gastrectomy with double-tract reconstruction group and total gastrectomy group. Considering

that food intake has a significant impact on body weight, relatively small volume of remnant stomach as a reservoir could cause insufficient food intake. However, according to a nationwide questionnaire survey in Japan, about 30% of institutions answered that they preserve less than half of entire stomach or decide the volume of remnant depending on case during performing proximal gastrectomy[20]. Thus, further research to indicate the appropriate volume of the gastric remnant is required.

Rate of anastomosis-related complication was lower in proximal gastrectomy group compared to total gastrectomy group, although it was not significantly different between two groups. It might be postulated by reduced tension to the esophagojejunostomy by jejunogastrostomy as supporting structure for Roux-limb, or by deconcentrating of food passage pressure to the alternative way of gastric remnant via jejunogastrostomy. However, it is unclear whether the proximal gastrectomy with double-tract reconstruction may reduce anastomosis-related complications.

Since we have relatively small number of included patients, it was difficult to show statistical differences. However, our study population was relatively larger among studies comparing proximal gastrectomy with double-tract reconstruction to total gastrectomy. Short duration of follow-up is another limitation. We could not evaluate oncologic outcomes such as survival rate or recurrences. Therefore, for further understanding of proximal gastrectomy, well-organized study of large scale in current indication is needed. A multicenter prospective randomized controlled trial of comparing laparoscopic proximal gastrectomy with double-tract reconstruction with total gastrectomy for upper third early gastric cancer (KLASS-05, NCT02892643)[42] is in progress in Korea. We expect confirmative results regarding efficacy of proximal gastrectomy with double-tract reconstruction on clinical, surgical and functional outcomes from KLASS-05 trial.

Despite these limitations, our results showed the similar short-term outcomes of proximal gastrectomy with double-tract reconstruction compared with total gastrectomy. Additional research of vitamin B12 metabolism associated with

parietal cell distribution in remnant stomach and iron metabolism associated with duodenal food passage would be necessary to further understand the consequences after proximal gastrectomy with double-tract reconstruction.

V. CONCLUSION

Proximal gastrectomy with double-tract reconstruction and total gastrectomy has similar outcomes in hematolotic and nutritional aspects, especially in vitamin B12 deficiency and iron-deficiency anemia. For patients with gastric cancer located in upper third of the stomach, proximal gastrectomy with double-tract reconstruction can be considered as an alternative option with comparable outcomes of total gastrectomy, if oncological safety is assured.

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