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Pylorus-Preserving Gastrectomy for Gastric Cancer

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Pylorus-preserving gastrectomy (PPG) is a function-preserving surgery for the treatment of early gastric cancer (EGC), aiming to decrease the complication rate and improve postoperative quality of life. According to the Japanese gastric cancer treatment guidelines, PPG can be performed for cT1N0M0 gastric cancer located in the middle-third of the stomach, at least 4.0 cm away from the pylorus. Although the length of the antral cuff gradually increased, from 1.5 cm during the initial use of the procedure to 3.0 cm currently, its optimal length still remains unclear. Standard procedures for the preservation of pyloric function, infra-pyloric vessels, and hepatic branch of the vagus nerve, make PPG technically more difficult and raise concerns about incomplete lymph node dissection. The short- and long-term oncological and survival outcomes of PPG were comparable to those for distal gastrectomy, but with several advantages such as a lower incidence of dumping syndrome, bile reflux, and gallstone formation, and improved nutritional status. Gastric stasis, a typical complication of PPG, can be effectively treated by balloon dilatation and stent insertion. Robot-assisted pylorus-preserving gastrectomy is feasible for EGC in the middle-third of the stomach in terms of the short-term clinical outcome. However, any benefits over laparoscopy-assisted PPG (LAPPG) from the patient's perspective have not yet been proven. An ongoing Korean multicenter randomized controlled trial (KLASS-04), which compares LAPPG and laparoscopy-assisted distal gastrectomy for EGC in the middle-third of the stomach, may provide more clear evidence about the advantages and oncologic safety of PPG.

Key Words: Pylorus-preserving gastrectomy; Stomach neoplasms; Review

Introduction

Due to the initiation of health screening programs in East Asian countries, including Korea and Japan, the proportion of early gastric cancer (EGC) has been increasing.[1] With the excellent outcomes obtained after early treatment of gastric cancer, surgeons are now recognizing postoperative quality of life (QOL) to be as important to consider as survival for these patients.[2,3]

Two surgical approaches are widely used for the treatment of EGC: laparoscopic surgery and function-preserving surgery. Laparoscopic gastrectomy is widely used to manage gastric cancer because of the benefits of the minimally invasive approach, including less postoperative pain, better cosmetic results, early recovery of bowel function, and a rapid return to normal activity.[2,4,5] The oncologic outcomes of laparoscopic gastrectomy for EGC have been found to be comparable.[6] The Korean multicenter randomized controlled trial (RCT) (KLASS-01 study) recently reported that the surgical morbidity rate, particularly the wound complication rate, had decreased in cases undergoing laparoscopic gastrectomy compared with those undergoing open surgery.[7] Thus, laparoscopic gastrectomy is considered as one of the standard procedures for EGC.

In function-preserving surgery, there are several methods for reducing the surgical extent to improve postoperative functional outcomes without compromising oncologic safety, such as pylorus-preserving gastrectomy (PPG), proximal gastrectomy, sentinel node navigation surgery, and vagus nerve-preserving surgery.[8]

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Among these techniques, PPG was initially introduced by Maki et al.[9] for the treatment of peptic ulcers, and was subsequently applied in gastric cancer in Japan and Korea. Although several retrospective case-control studies have described the functional benefits of PPG over distal gastrectomy (DG), a multicenter RCT has not yet been conducted to provide high quality evidence supporting PPG.[10-12]

In the present review, we describe the current status of PPG, the technical information, and advantages and limitations. We also briefly introduce our recent multicenter RCT that compares laparoscopic PPG and laparoscopic DG (KLASS-04 study).

Methods

A PubMed search was conducted using the keywords 'pylorus-preserving gastrectomy' AND 'gastric cancer' for all articles published up to February 2016; only articles written in English were considered. For the analysis, meta-analyses and RCTs were preferentially reviewed. Prospective cohort studies and retrospective case-control studies were also reviewed.

Indications and Surgical Techniques

1. Indications

The indications for PPG in several centers are EGCs located in the middle-third of the stomach with no evidence of regional lymph node (LN) metastasis. According to the Japanese gastric cancer treatment guidelines, PPG is indicated for the treatment of cT1N0M0 gastric cancers in the middle-third of the stomach, at least 4.0 cm away from the pylorus.[13]

2. Length of the antral cuff

The distance from the lesion to the pylorus needs to be carefully considered as a short antral cuff length may lead to postoperative gastric stasis, a typical complication of PPG. When PPG was initially performed in the treatment of gastric cancer, surgeons usually maintained an antral cuff length of 1.5 cm. With this antral cuff length, incidence of immediate postoperative delayed gastric emptying (DGE) was reported to range between 23% and 40%.[14-16] The relationship between the length of the antral segment and the incidence of DGE was investigated by Nakane et al.[17] in 2002. In that study, the authors found that the incidence of DGE was 35.0% (7/20) in patients with an antral cuff length of 1.5 cm and only 10.0% (1/10) in patients with an antral cuff length of 2.5 cm, at 1 year after surgery. Nunobe et al.[18] reported

Table 1. Early experiences of pylorus-preserving gastrectomy

Author	Institute	No. of cases	Year	Pyloric branch of the vagus nerve & RGA	Length of the antral segment (cm)
Kodama et al.[14]	Akita University	35	1989~1991	Preserved	1.5
Zhang et al.[16]	University of Tokyo	15	1993~1995	Divided	1.5
Imada et al.[15]	Yokohama University	20	1992~1996	Preserved	1.5
Tomita et al.[26]	Nihon University	10	1993~1996	Divided	1.5
Nakane et al.[17]	Kansai University	30	1993~1999	Preserved	1.5 versus 2.5
Hotta et al.[19]	Wakayama University	19	1995~1998	Preserved	1.5
Ohya et al.[24]	Gumma University	13	1995~1998	Preserved	2.0
Nunobe et al.[10]	National Cancer Center	194	1993~1999	Preserved	2.5~6.0
Nagano et al.[22]	Fukui University	72	1991~2000	Preserved	-
Nishikawa et al.[23]	Osaka University	12	1997~2000	Preserved	1.5
Urushihara et al.[27]	Yoshida General Hospital	26	1998~2002	Preserved	3.0
Park et al.[11]	Seoul National University	22	1999~2003	Preserved	3.0
Morita et al.[21]	National Cancer Center	611	1995~2004	Preserved	2.0
Tomikawa et al.[25]	Fukuoka City Hospital	9	2004~2007	Preserved	3.0
Lee et al.[20]	Osaka Medical College	12	2000~2009	NA	≥4.0

RGA = right gastric artery; NA = not available.

an incidence of DGE of 6% to 8% among 90 patients after PPG in whom vagus innervation and blood flow to the pylorus were preserved and the antral cuff length was maintained at 3 cm. In subsequent studies, the length of the antral cuff has tended to be longer than that used during the initial period (Table 1).[10,11,14-17,19-27] However, a Japanese group did not identify antral cuff length as a key factor of the PPG technique, reporting comparable postoperative outcomes among a group of patients with an antral cuff length ≤3 cm and a group of patients with an antral cuff length >3 cm.[28] Considering a sufficient distal resection margin of >1 cm for EGC in addition to the length of the antral cuff, the distance from the lesion to the pylorus should be maintained at >4.0 cm. Although guidelines suggest that the minimum distance from the lesion to the pylorus should be 4.0 cm, the optimal length for the antral cuff remains unclear yet.

3. Lymph node metastasis around the pylorus

An important factor that should be considered prior to performing a PPG is the likelihood of metastasis to LN station 5. This is particularly important as the LN dissection of station 5 is usually omitted during PPG in order to preserve the hepatic branch of the vagus nerve. A review of PPGs performed at 144 institutions in Japan indicated that dissection of LN station 5 was not performed in 53 institutions (36.8%) and was partially performed in 81 institutions (56.2%).[29] At our institution, which is one of the institutions that actively performs PPG, dissection of LN station 5 was performed in only 50% of cases of PPG between 2003 and 2008.[30] In addition to LN station 5, there is also a likelihood of incomplete LN dissection of station 6 during skeletonization of the infra-pyloric artery. For these reasons, the presence or absence of LN metastasis should be carefully evaluated preoperatively using endoscopic ultrasonography and computed tomography (CT). The depth of invasion should also be evaluated, as the probability of LN metastasis increases as the depth of the lesion increases[18,30] Hence, PPG should only be considered only for patients with a cT1N0M0 gastric cancer.

4. Techniques for preservation of the pylorus

Although there are minor differences in the surgical techniques according to specific surgeons, the standard technique for PPG includes preservation of the infra-pyloric vessels and the hepatic branch of the vagus nerve for structural and functional preservation of the pylorus.[29] According to a study by Haruta et al.,[31] the infra-pyloric artery originates from the anterior superior pancreatoduodenal artery (distal type, 64.2% of cases), the right gastroepiploic artery (caudal type, 23.1% of cases), or the gastroduodenal artery (proximal type, 12.7% of cases). During dissection of LN station 6, the right gastroepiploic artery is ligated at its root in the distal or proximal types. For cases with a caudal type, the right gastroepiploic artery is ligated at a location distal to the origin of the infra-pyloric artery.[11,29,30,32] The hepatic branch of the vagus nerve that innervates the pylorus usually follows the course of the supra-pyloric LNs (LN station 5) and should be preserved to maintain the motility of the pylorus. In the early years of PPG, surgeons commonly attempted to completely dissect the supra-pyloric LNs.[33] However, today, most surgeons prefer to focus on preservation of the vagus nerve, rather than on supra-pyloric LN dissection during PPG.[12,15,18,23] These important procedures to preserve pyloric function make PPG technically more difficult, when compared with DG.[32]

5. Laparoscopic pylorus-preserving gastrectomy

As most patients who undergo PPG are usually diagnosed with EGC, laparoscopy-assisted pylorus-preserving gastrectomy (LAPPG) is commonly used. Although the operation time is longer in LAPPG than in conventional PPG, LAPPG provides several benefits over PPG, including reduced intraoperative blood loss and postoperative pain, as well as a faster recovery.[18,33,34] Moreover, because LAPPG serves as combination of minimally invasive surgery and function-preserving surgery, LAPPG may appear as an attractive treatment option for patients.[35]

Both extra-corporeal and intra-corporeal methods can be used for anastomosis in LAPPG. For the extra-corporeal method, a hand-sewn anastomosis is usually used, which generally involves an approximately 5.0 cm midline incision after mobilization of the stomach with LN dissection. The distal part of the stomach is retracted through the incision and resected first. After the resection of the proximal part of the stomach, a hand-sewn gastro-gastrostomy is performed.[33-35] Intra-corporeal anastomosis methods using linear staplers have only recently been introduced. For intra-corporeal anastomosis, transection of the stomach in the sagittal direction (i.e., posterior to anterior direction), rather than in the transverse direction (i.e., greater curvature to lesser curvature direction), can facilitate the alignment of the linear staplers.[20,36] After resection of the distal and proximal parts of the stomach, one arm of a 60 mm linear stapler is inserted into each gastric remnant through the gastrostomy on the greater curvature side corner. The stapler has to be fired between the posterior

walls on either side, and then the remaining gastrostomy can be closed using further staplers.

Clinical Outcomes

1. Complications

With regard to the short-term outcomes of PPG, Shibata et al.[37] compared PPG and DG and our group compared LAPPG and laparoscopy-assisted DG (LADG).[12] Both studies indicated that the postoperative hospital stay, postoperative complications, and mortality did not differ between patients undergoing PPG and DG, regardless of the approach.

In a study performed with 307 patients who underwent LAPPG by Jiang et al.,[38] the overall complication rate was 17.3% (53/307) including a major complication rate (grade>IIIa, Clavien-Dindo classification) of only 1.3% (4/307).[39] In another study of complications (again, according to the Clavien-Dindo classification) of 116 patients who underwent LAPPG, the overall complication rate was 14.7% (17/116) and major complications, grade>IIIa, were found in 10 patients (8.6%).[12] In both studies, the most common complication was associated with postoperative impairment in pyloric function; gastric stasis was present in 6.2% in the former study and DGE in 7.8% in the latter.

2. Oncologic safety

Preservation of the vessels and nerves in order to maintain pyloric function may result in insufficient LN dissection at LN stations 5, 6, and 12a, which could consequently compromise the radicality of the curative gastrectomy for gastric cancer. According to the Japanese gastric cancer treatment guidelines (ver. 3), D1+ lymphadenectomy should be performed for patients with cT1N0.[13] LN dissection of station 6 with infra-pyloric artery preservation is a relatively easy technique, and LN station 12a is considered to be beyond the D1+ level in patients with cT1N0M0. However, LN station 5 is considered to be D1 level. In PPG, dissection of LN station 5 is omitted to preserve the hepatic branch of the vagus nerve and preserve pyloric function. This could lead to incomplete D1 LN dissection, which is associated with concerns regarding oncologic safety.

In a study about a new index evaluating the therapeutic value of LN dissection for gastric cancer, Sasako et al.[40] reported that the index (estimated via multiplication of the incidence of metastasis and the 5-year survival rate of patients with metastasis to LN station 5) was only 0.8 in patients with cancer of the middle-third of the stomach. In particular, a few studies have also focused on the probability of metastasis to LN station 5 from EGC of middle-third of the stomach. Kodera et al.[41] reported that the metastasis rate to LN station 5 was <5% and our group reported that the metastasis rate to LN station 5 was 4.2% (52/1,245) (Fig. 1).[30] In both studies, most of the patients with LN metastasis in station 5

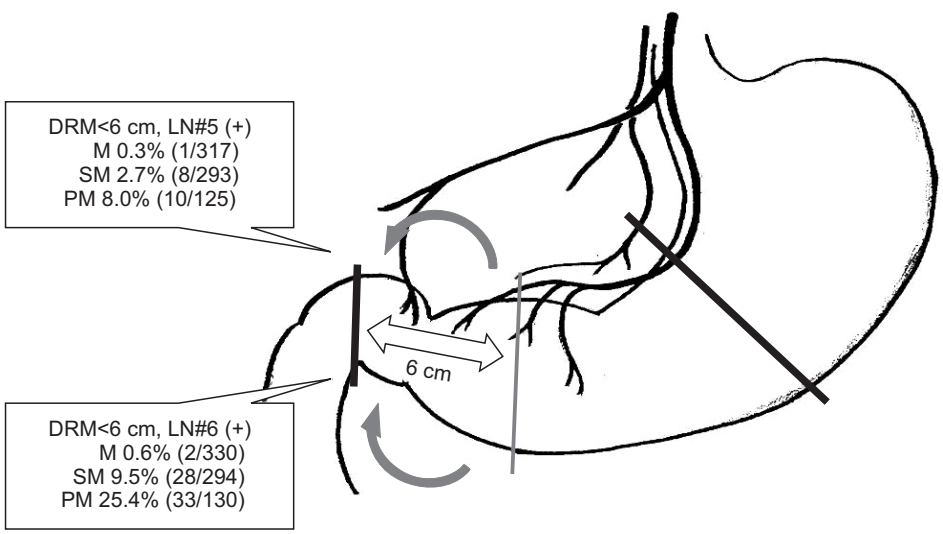

Fig. 1. Station 5 and 6 lymph node metastases of gastric cancer in the middle-third of the stomach. Kong et al.[30] examined the metastasis rate to each lymph node (LN) station in 1,802 patients with gastric cancer who underwent curative subtotal gastrectomy. Among patients with a distal resection margin (DRM) <6.0 cm, the metastasis rate to LN station 5 was 0.3% (1 of 317) for patients with a T1a cancer, 2.7% (8 of 293) for patients with a T1b cancer, and 8.0% (10 of 125) for patients with a T2a cancer. For metastasis to LN station 6, the rate was 0.6% (2 of 330) for patients with a T1a cancer, 9.5% (28 of 294) for patients with a T1b cancer, and 25.4% (33 of 130) for patients with a T2a cancer. M = mucosa; SM = submucosa; PM = proper muscle.

were finally confirmed as having at least T2 cancer after surgeries, whereas the metastasis rates to LN station 5 were very low for T1 cancer. Furthermore, Hiki et al.[42] and Nunobe et al.[18] reported supra-pyloric LN metastasis rates of 0.2% and 0.5%, respectively, for T1 cancer located in the middle-third of the stomach. Our group reported that LN dissection during PPG was adequate by using the Maruyama index, which is calculated as the sum of the likelihood of undissected nodal disease in each LN station.[43]

3. Survival and recurrence

The long-term outcomes of PPG have been evaluated in many retrospective studies. Hiki et al.[44] reported that the 5-year survival rate of patients who underwent PPG for a cT1N0 gastric cancer was 98% with no cases of recurrence. Morita et al.[21] reported a 5-year survival rate of 96.3%, with 5 cases of recurrence, among patients who underwent PPG for EGC. Our group recently reported a 3-year recurrence-free survival rate of 98.2% for LAPPG for EGC, which is comparable with the rate for LADG.[12] One of two meta-analyses on PPG also reported that a 5-year survival rates were similar in patients underwent PPG or DG.[45]

Advantages and Pitfalls

The benefits of PPG, when compared with DG, include the lower incidence of dumping syndrome, bile reflux, and gallstone formation, and better nutritional advantages such as a relatively small body weight change.[11,46] A large scale retrospective study on dumping syndrome after gastrectomy involving 1,153 patients found that PPG was a preventive factor for early and late dumping syndromes.[47] In another questionnaire-based study on QOL after gastrectomy, PPG was found to have significantly lower scores in terms of diarrhea as well as dumping syndrome, when compared with DG.[48] In addition, the study from our institution reported a lower incidence of gallstone formation among patients who underwent LAPPG (0%) compared with those who underwent LADG (6.5%). The study also showed that patients who underwent LAPPG had a better nutritional status as compared with those who underwent LADG, including a smaller decrease in serum protein levels, serum albumin levels, and abdominal fat.[12] Two recently published meta-analyses on PPG specifically evaluated the postoperative QOL among patients who underwent PPG or DG. Both the meta-analysis conducted by Song et al.[49] (involving 1,774 patients in 15 studies) and the meta-analysis conducted by Xiao et al.[45] (involving 1,213 patients in 16 studies) reported PPG to be a preventive factor of dumping syndrome, bile reflux, gastritis, and gallstone formation, while acting as a beneficial factor in weight regain.

As mentioned previously, gastric stasis is a typical complication of PPG. The pathophysiologic mechanism of gastric stasis after PPG has not been definitively identified, but it is known to be caused to some extent by anastomotic edema and neurologic dysfunction due to intraoperative damage.[23,26,50] During initial experiences with PPG, the incidence of gastric stasis was as high as 40%.[26] Recently published studies have reported the incidence of gastric stasis or DGE after PPG of 6.2% to 10.3%.[12,18,21,34,38,50] However, this value is still considered to be high, given that the rate of these complications in DG is approximately 1.0%.[7]

Gastric stasis can be easily diagnosed based on a combination of symptoms, such as post-prandial epigastric fullness or indigestion, and simple imaging, such as radiography or an upper gastrointestinal series.[51] Patients who developed gastric stasis after PPG may show improvement via conservative management and radiological interventions.[38,51,52] Bae et al.[51] reported that the standardization of the surgical procedure for LAPPG in order to preserve blood flow and the hepatic branch of the vagus nerve can reduce the severity of gastric stasis. Moreover, cases of mild gastric stasis with a Clavien-Dindo classification[39] grade $\leq$II responded to gastric balloon dilatation. However, in 26.7% (12/45) of patients who developed gastric stasis after PPG, gastric balloon dilatation was not sufficient to improve the obstructive symptoms due to recoiling of the pyloric canal. In these patients, retrievable stent insertion could resolve the obstructive symptoms. The mean duration of stent retention was 10.4$\pm$5.0 days and none of the patients showed a recurrence of gastric stasis over 26.2 months of follow-up. Among 50 cases of balloon dilatation, only 1 case of a transmural tear was noted, and among 12 stent insertions, 3 cases of stent migration were observed. This finding is important for the determination of an effective treatment option for gastric stasis due to pyloric spasm after PPG. However, considering the relatively invasive properties of the procedure itself and the possibility of stent migration, stent insertion should only be performed after balloon dilatation has been attempted.

Robotic Surgery

Robotic surgery is reported to have several benefits including three-dimensional and highly magnified imaging, a steady fixed camera, and absence of a surgeon's tremors when compared with

laparoscopic surgery.[5] However, the benefits of robotic surgery in patients with gastric cancer remain controversial. In a recently published multicenter prospective case-matched study by the Korean Robot Gastrectomy Study Group of the KLASS, robotic gastrectomy was not found to be superior to laparoscopic gastrectomy in terms of perioperative clinical outcomes, even though it may provide a superior operating environment.[53] Although several studies on robotic surgery for gastric cancer have been published, studies focused on robot assisted pylorus-preserving gastrectomy (RAPPG) are rare and there is no RCT comparing RAPPG and LAPPG thus far. Recently, Han et al.[52] reported on the surgical outcomes of RAPPG for gastric cancer. Based on a propensity score matching analysis of RAPPG and LAPPG, there were no differences in complication rates or the number of examined LNs between the two groups. The only difference between RAPPG and LAPPG was the operation time, which was longer in RAPPG than in LAPPG (258.3 versus 193.9 minutes). As such, RAPPG may provide another treatment option for EGC in the middle-third of the stomach; however, the benefits of RAPPG over LAPPG from patients' perspective are yet to be determined.

KLASS-04 Study: A Multicenter Prospective Randomized Controlled Trial

Although a few studies have evaluated the optimal surgical procedures to treat EGC of the middle-third of the stomach, comparing LAPPG and LADG, most studies on PPG have been performed at a single center with a limited number of patients and in a retrospective manner. For the application of LAPPG in the clinical setting, it is essential to first perform a comparative analysis of the short- and long-term outcomes from a large volume of prospective randomized data. In order to determine whether the postoperative QOL and nutritional status are better, and if survival is comparable after LAPPG, the KLASS group has initiated a multicenter RCT (KLASS-04 study) to compare LAPPG and LADG for EGC of the middle-third of the stomach (NCT No.02595086).

A total of 256 patients, diagnosed with a cT1N0M0 primary gastric adenocarcinoma located in the middle-third of the stomach by endoscopic ultrasonography or CT, will be enrolled (128 patients in each group) (Table 2). The primary endpoint is the incidence of dumping syndrome, assessed using the Sigstad score (≥7) at 1 year after surgery. The secondary endpoints are: the 3-year relapse-free survival and overall survival; the 30-day op-

Table 2. Indications and contraindications for KLASS-04 study

Indications
① 20≤age (yr)≤80
② Histologically proven gastric adenocarcinoma
③ Performance status of 0 or 1 on the Eastern Cooperative Oncology Group scale
④ 1≤American Society of Anesthesiologists class≤3
⑤ cT1N0M0 (by endoscopic ultrasonography or computed tomography scan)
⑥ Located at the middle-third of the stomach at least 5 cm away from the pylorus and resectable by distal gastrectomy
⑦ Written informed consent
Contraindications
① Pyloric deformity due to ulcerative disease
② History of gastric surgery (e.g., gastrojejunostomy or primary closure)
③ Synchronous early gastric cancer or adenoma in the antrum
④ Prior treatment with chemotherapy or radiotherapy against early gastric cancer diagnosed this time
⑤ Need for combined resection (e.g., cholecystectomy)
⑥ History of prior treatment (e.g., surgery, chemotherapy, or radiotherapy) against any other malignancies within the last 5 years (excluding cured basal cell carcinoma and in situ cervical cancer)
⑦ Lack of decision-making capacity
⑧ Pregnant or breast-feeding women
⑨ Currently involved or participated in another clinical trial within the last six months

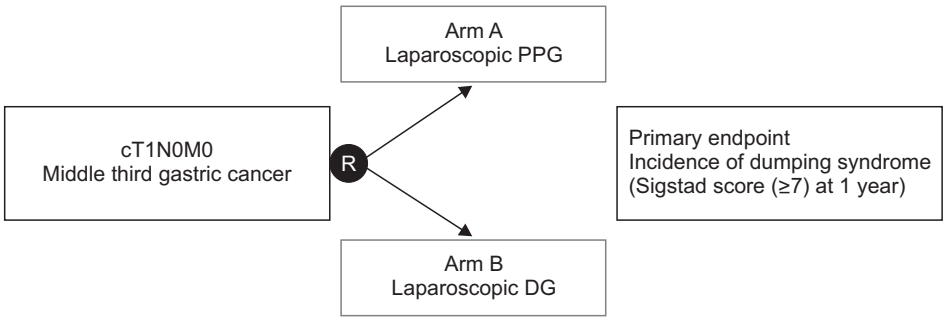

Fig. 2. Schematic diagram of the KLASS-04 study. PPG = pylorus-preserving gastrectomy; DG = distal gastrectomy.

erative morbidity and mortality; changes in body weight and fat volume on abdominal CT; changes in hemoglobin, protein, albumin, and pre-albumin levels; symptoms and QOL measurement using the JSGIS-Q, EORTC C30, and STO22; the incidence of gallstones; and the gross and microscopic findings on gastroscopy (Fig. 2).

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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