Clinical Practice Review

The role of proximal gastrectomy in gastric cancer

Yuki Hirata[1], Hyoung-Il Kim[2], Travis E. Grotz[3], Satoru Matsuda[4], Brian D. Badgwell[1], Naruhiko Ikoma[1]

[1]Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Department of Surgery, Yonsei University College of Medicine, Seoul, Korea; [3]Division of Hepatobiliary and Pancreas Surgery, Mayo Clinic, Rochester, Minnesota, USA; [4]Department of Surgery, Keio University School of Medicine, Tokyo, Japan

Contributions: (I) Conception and design: Y Hirata, N Ikoma; (II) Administrative support: Y Hirata, N Ikoma; (III) Provision of study materials or patients: Y Hirata, N Ikoma; (IV) Collection and assembly of data: Y Hirata, N Ikoma; (V) Data analysis and interpretation: Y Hirata, N Ikoma; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Naruhiko Ikoma, MD, MS. Department of Surgical Oncology, Unit 1484, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, USA. Email: nikoma@mdanderson.org.

Abstract: Over the past 30 years, the prevalence of upper third gastric cancer (GC) and gastroesophageal junction (GEJ) cancer has increased. Total gastrectomy with D2 lymph node dissection is the standard surgical treatment for non-early (T2 or higher) upper third and GEJ cancers, but total gastrectomy often results in post-gastrectomy syndrome (5–50%), consisting of weight loss, dumping syndrome, and anemia. Proximal gastrectomy (PG) has the potential to avoid these postoperative problems by preserving stomach function. However, PG has historically been discouraged by surgeons owing to the high incidence of postoperative reflux esophagitis (20–65%), anastomotic stenosis, and decreased quality of life. In recent years, anti-reflux reconstruction techniques, such as the double flap technique and double-tract reconstruction, have been developed to be performed after PG, and evidence has emerged that these techniques not only reduce the incidence of postoperative reflux esophagitis but also decrease postoperative weight loss and prevent anemia. Prospective studies are underway to determine whether PG with anti-reflux techniques improves patient-reported quality of life. In the present work, we reviewed available evidence for the use of PG for GC and GEJ cancer, including oncologically appropriate patient selection for PG, potential functional benefits of PG over TG, and various types of reconstructions that can be performed after PG, as well as future research on the use of PG.

Keywords: Proximal gastrectomy (PG); gastric cancer (GC); gastroesophageal junction (GEJ) cancer

Submitted Sep 02, 2022. Accepted for publication Oct 21, 2022.
doi: 10.21037/cco-22-82
View this article at: https://dx.doi.org/10.21037/cco-22-82

Introduction

For patients with localized but non-early (T2 or higher) upper third gastric cancer (GC) and gastroesophageal junction (GEJ) cancer with limited esophageal extension, total gastrectomy (TG) with D2 lymph node (LN) dissection is considered the standard surgical treatment (1,2). However, 5–50% of patients who undergo TG experience post-gastrectomy syndrome, which consists of dumping syndrome due to lack of food reservoir, weight loss due to impaired appetite and oral intake, and anemia due to intrinsic factor loss and vitamin B12 malabsorption (3). Proximal gastrectomy (PG) can theoretically mitigate these problems by preserving stomach functions such as the food reservoir and gastric endocrine function (4-6). However, PG has been known to be associated with high incidence of postoperative reflux esophagitis (20–65%) and impaired quality of life (QOL) (7-10). For these reasons, PG is not commonly performed in Western countries.

In East Asia, surgeons developed novel reconstruction techniques to prevent post-PG reflux esophagitis, such as double-tract reconstruction and the double-flap technique (11-16), and PG has been commonly performed for early (clinical T1N0) upper third GC in recent years (1,2).

However, there is still no global consensus on the oncologic and nutritional benefits of PG compared with TG, and the optimal anti-reflux reconstruction technique after PG remains unknown.

In the present article, we review available evidence for the use of PG for GC and GEJ cancer, including oncologically appropriate patient selection for PG, potential functional benefits of PG over TG, and various types of reconstructions that can be performed after PG, as well as future research on the use of PG.

Oncologically appropriate patient selection for PG

Achieving margin-negative resection and clearance of potentially metastatic LNs is critical to provide the best possible oncologic outcomes after gastrectomy for patients with GC. This section describes evidence-based safe indications for PG, focusing on LN dissection for upper third GC and GEJ cancer.

Upper third GC

For early (T1) upper third GC, where the incidence of LN metastasis is negligible (17), PG with perigastric LN dissection is widely accepted as an oncologically safe surgical treatment option (1,2). For example, in Japanese guidelines, the indication for PG is defined as early upper third GC (cT1a/1bN0) in which at least half of the stomach can be preserved and for which endoscopic submucosal dissection is not indicated (1). Equivalent recurrence and survival rates have been consistently reported between patients who underwent PG and those who underwent TG for early upper third GC. One prospective randomized controlled trial also reported similar postoperative complication rates between PG and TG (12,14,18-20).

For advanced (T2 or higher) upper third GC, safety of PG is still controversial owing to the substantial risk of LN metastasis, and TG with conventional D2 LN dissection is considered standard therapy (1,2). However, for patients with negligible risks of peripyloric LN (#4d, #5, #6) and proper hepatic artery LN (#12) metastases, conventional D2 LN dissection may not be required (21) and these patients can undergo PG with appropriate LN dissection without increasing the risk of regional recurrence (13,22). Indeed, the frequency of peripyloric LN metastasis in advanced GC localized in the upper third of the stomach has been consistently reported to be low. Yura *et al.* investigated the frequency of metastasis at the peripyloric and hepatic artery LNs (i.e., LNs within the extent of conventional D2 LN dissection but that cannot be cleared by PG) and the therapeutic index [calculated by multiplying the frequency of metastasis at each LN station and the 5-year survival rate for those with positive LNs at that station (23)] in 202 patients with advanced upper third GC [pathologic T2–3 (pT2–3)] (24). The incidence rates of metastasis at #4d (distal greater curvature) and #12a (proper hepatic artery) were very low (0.99% and 0.006%, respectively), and the incidence of metastasis at #5 (supra-pyloric) and #6 (infra-pyloric) was zero. As a result, therapeutic indices for #4d, #5, #6, and #12a were zero, indicating no survival benefit from removing these LN stations in patients with pT2–3 upper third GC (24).

Lee *et al.* investigated risk factors for peripyloric LN metastasis in 878 patients with pT2–4 upper third GC who underwent TG. The incidence rate of metastasis at any peripyloric LN (#4d, #5, or #6) was 11.5%. Multivariable analysis showed that tumor epicenter >30 mm from the GEJ (P<0.001), tumor size >70 mm (P<0.001), macroscopic Borrmann type IV tumor (P=0.022), and serosal invasion (pT4; P<0.001) were independent risk factors for peripyloric LN metastasis, and the incidence rate of peripyloric LN metastasis among patients without these risk factors was 0.8% (25).

Ri *et al.* analyzed the frequency of peripyloric and hepatic artery LN metastasis in 167 patients with clinical T2–4 (cT2–4) upper third GC, and they reported similar results. The overall incidence of peripyloric #4d, #5, and #6 metastasis was 4.8%, and the incidence of #12 metastasis was zero. The therapeutic indices at #4d, #5, #6, and #12a were extremely low (<1.4) (26).

Given the very low reported incidence of peripyloric and proper hepatic artery LN metastases from non-early upper third GC, the oncologic benefit of prophylactic dissection of these LNs with TG is likely negligible, unless tumors are bulky, accompanied by serosal invasion, or infiltrating into the mid-lower body of the stomach.

GEJ cancer

The optimal surgical procedure for GEJ cancers, particularly for Siewert type II tumors, has not been standardized, and selection of esophagectomy, TG, or PG greatly differs among nations, institutions, and individual surgeons by specialty (thoracic surgeons, surgical oncologists, and general/gastrointestinal surgeons) (27,28). A recent large Japanese multicenter study prospectively

examined the incidence rates of metastasis at mediastinal and abdominal LN stations, stratified by the length of esophageal extension of the tumor, in patients with cT2–4 GEJ cancer. That study enrolled a total of 371 patients with Siewert type II GEJ cancer who underwent esophagectomy (38%) or gastrectomy (62%) with extended LN dissection. The incidence of metastasis at each peripyloric LN (#4d, #5, #6) and hepatic artery LN (#12a) was less than 5%. However, for tumors with a diameter ≥6 cm, the incidence rate of overall peripyloric LN metastasis was 11%. In addition, the incidence of metastasis for the lower mediastinum LN (#110) was greater than 10% if the esophageal extension exceeded 2 cm (29). Although survival outcomes are not yet available, these results indicate that PG can be safely performed in patients with GEJ cancer with an esophageal extension length of <2 cm and tumor diameter <6 cm.

Similarly, Mine *et al.* retrospectively analyzed 288 patients with pT2–4 GC and investigated the association between the length of the gastric extension of tumor and the incidence of abdominal LN metastasis. They found that in patients in whom the gastric extension was >5 cm, the overall incidence of LN metastasis in the distal greater curvature and peripyloric LNs (#4sb, #4d, #5, and #6) was as high as 20% (30). This result supports the criteria described above for oncologically safe indications of PG for GEJ cancer.

Potential functional benefits of PG

Before encouraging widespread use of PG to treat select patients with upper third GC and GEJ adenocarcinoma, the functional benefits of PG over TG should be established. Theoretically, PG has a functional advantage over TG by preserving the distal half of the stomach. The main problem with TG is decreased postoperative food intake and weight loss, which is driven by the lack of food reservoir and decreased appetite after surgery (3). A relationship between the volume of the remnant stomach and nutritional outcomes after distal gastrectomy (DG) has been consistently reported. For example, Nomura *et al.* investigated the postoperative food intake of 176 patients who underwent laparoscopic DG. The patients were given a survey once in the 6- to 12-month postoperative period assessing their postoperative food intake. In patients who had a smaller gastric remnant after DG (i.e., those who underwent gastrectomy of two-thirds of the stomach compared with half of the stomach), postoperative food intake was significantly decreased from preoperative food intake (67.5% compared with 80% of pre-DG intake, P=0.031) (31).

Although data remain limited, a similar trend has been reported after PG. Ri *et al.* studied the relationship between remnant stomach volume and the incidence of skeletal muscle loss (≥10%) in 158 patients who underwent PG. The remnant stomach volume was estimated by performing a postoperative abdominal X-ray after contrast intake. Results showed that a remnant stomach volume of approximately two-thirds of the original stomach was associated with a lower incidence of skeletal muscle reduction after PG compared with smaller remnant stomach volumes (32). Yamasaki *et al.* prospectively investigated the impact of surgical procedure on postoperative weight loss in 252 patients with upper third GC who underwent PG or TG. The percentage of body weight loss at 1 year after surgery in the PG group was significantly less than that of the TG group (–12.8% compared with –16.9%, P=0.0001) (10).

In addition to mechanical volume of the remnant stomach as a food reservoir, another advantage of PG over TG is maintained endocrine secretion of ghrelin, the so-called appetite hormone (33). Ghrelin is secreted mainly from the gastric body (fundic gland), and approximately 70% of the ghrelin in the circulating blood is produced by the stomach (34). Preserved ghrelin secretion from the remnant stomach may help maintain appetite and body weight. Takiguchi *et al.* reviewed 13 previous reports investigating the relationship between gastrectomy and postoperative ghrelin levels. Across these studies, ghrelin levels were immediately reduced to 12–29% of the preoperative level after TG, compared with 39–71% of the preoperative level after DG. In addition, ghrelin levels gradually recovered to the preoperative level within a few years in most patients after DG, whereas such recovery after TG was rare (35). Kizaki *et al.* examined postoperative plasma ghrelin levels in 74 patients after TG, DG, PG, or pylorus-preserving gastrectomy. They reported that postoperative ghrelin levels were preserved after stomach-preserving procedures such as DG, PG, and pylorus-preserving gastrectomy compared with TG (36). Although ghrelin-producing cells are present in higher densities in the proximal stomach than in the distal stomach, the results of these studies suggest that PG would preserve postoperative ghrelin secretion and contribute to improved appetite level, oral intake, weight retention, and QOL.

PG may also result in improved nutritional metrics compared with TG. Ushimaru *et al.* retrospectively analyzed 192 patients who underwent PG or TG. Postoperative

body weight loss was significantly smaller in the PG group than in the TG group at all observation points (3, 6, 12, 24, and 36 months after surgery), and total protein (at 3, 6, and 12 months after surgery) and serum albumin values (at 3 months after surgery) were significantly higher in the PG group than in the TG group (37). Hayami *et al.* investigated 90 patients with GC and compared short-term outcomes between those who underwent PG and those who underwent TG. They found that 12-month postoperative body weight (P=0.003), hemoglobin levels (P=0.003), and total protein levels (P<0.001) were higher in the PG group than in the TG group (16). A meta-analysis by Xu *et al.* showed that postoperative total cholesterol was better and total protein levels were higher in the PG group than in the TG group at 1 year after surgery, although these values became equivalent between the two groups at 2 years after surgery. However, the TG group had higher loss of bodyweight and lower hemoglobin levels than the PG group, and these values did not recover over time (38).

Anemia is frequently reported after TG (in 60–90% of patients). The iron deficiency is due to decreased gastric acid and lack of food exposure to the duodenum after Roux-en-Y reconstruction, as well as vitamin B12 deficiency due to intrinsic factor loss (3,39,40). The South Korean KLASS-05 randomized control trial (NCT02892643) (6) compared hemoglobin and vitamin B12 levels at 2 years after gastrectomy between patients who underwent TG with those who underwent PG in 137 patients with cT1N0 upper third GC. Results showed no difference in decreased levels of hemoglobin between the groups (P=0.349), but the PG group contained a lower proportion of patients who required vitamin B12 supplementation (15% compared with 58%, P<0.001) (41).

These results indicate that PG may mitigate postoperative weight loss, malnutrition, and incidence of anemia (or need for vitamin B12 supplementation) by maintaining gastric function better than TG.

Reconstruction after PG

Direct esophagogastrostomy (EG) anastomosis is the most straightforward anastomosis after PG and had been performed conventionally. However, performing direct EG without an anti-reflux procedure has been reported to cause severe postoperative reflux esophagitis in 10–30% of patients (18,42). Postoperative reflux esophagitis is associated with body weight loss, anastomotic stricture, and impaired QOL (43), and this is the main reason why PG is not recommended in the United States. To reduce incidence of reflux esophagitis, surgeons developed various post-PG anti-reflux reconstruction techniques, such as the double-flap technique (DFT), double-tract reconstruction (DTR), jejunal interposition, gastric conduit, and fundoplication (7). Among these, DFT and DTR are the two anti-reflux procedures most commonly performed after PG in recent years, and promising outcomes have been reported.

DFT

DFT is a modified EG anti-reflux reconstruction technique (*Figure 1*). Surgeons create an H-shaped seromuscular flap on the anterior wall of remnant stomach, and this flap is used to reinforce the hand-sewn EG anastomosis, creating a one-way valve to prevent reflux (44). DFT has advantages over direct EG reconstruction, such as physiologic alignment by which all food intake flows through the duodenum, but DFT is technically challenging, particularly when performed at a high level within the mediastinum by laparoscopic approach. In addition, the remnant stomach is disconnected from the vagus nerve distribution, thus leading to the risk of delayed gastric emptying (43,45,46).

Hayami *et al.* retrospectively compared outcomes of laparoscopic PG with DFT and laparoscopic TG with Roux-en-Y reconstruction in 90 patients with GC (16). Patients who underwent laparoscopic TG had reflux esophagitis (Los Angeles classification grade B or higher) more frequently than those who underwent laparoscopic PG with DFT (14.9% *vs.* 2.3%, P=0.06) within 12 months after surgery.

Kuroda *et al.* conducted a multicenter retrospective study in 464 patients who underwent PG with DFT [81 patients (17%) underwent laparoscopic DFT]. The overall incidence of reflux esophagitis was 11%, and the incidence of Los Angeles classification grade B or higher reflux esophagitis was 6% (15). The incidence of anastomotic leakage was 2%, and anastomotic strictures occurred in 6% of patients, indicating that the procedure was safe in general. However, the use of a laparoscopic DFT procedure was found to be an independent risk factor for anastomosis-related complications (odds ratio =3.93, 95% confidence interval: 1.93–7.80, P=0.0003). The authors concluded that DFT may prevent reflux esophagitis compared with simple EG, but laparoscopic DFT should be carried out by or under the supervision of experienced surgeons.

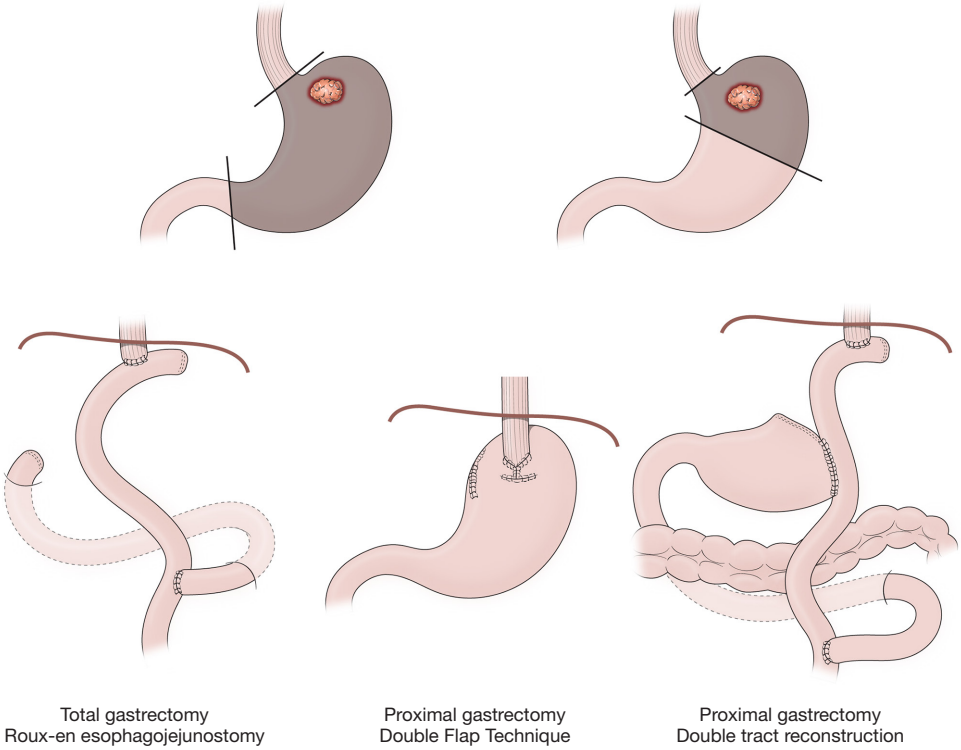

Figure 1 Reconstruction methods of total gastrectomy and proximal gastrectomy.

DTR

Although it requires three anastomoses (esophagojejunostomy, gastrojejunostomy, and jejunojejunostomy; *Figure 1*), DTR is reported a technically safe and effective reconstruction technique (11,13,47,48). DTR avoids direct EG anastomosis by using the Roux-limb to provide interposition between the esophagus and stomach to prevent reflux while maintaining flow through the Roux-limb, which may alleviate symptoms of delayed gastric emptying if it occurs. Technical details such as the ideal distance between EG and gastrojejunostomy to effectively prevent reflux and the size of gastrojejunostomy that allows adequate flow to the gastric remnant are still unknown, and further studies are needed.

DTR can reduce reflux esophagitis than simple EG by creating an interposition between the esophagus and the remnant stomach. Ahn *et al.* retrospectively reported short-term outcomes 43 patients with GC who underwent laparoscopic PG with DTR. Postoperative reflux was reported in 5% of patients, and anastomotic stricture was reported in 5% (47). Ji *et al.* retrospectively analyzed the short-term outcomes of 64 patients with early GC who underwent PG with DTR or PG with direct EG reconstruction without an anti-reflux procedure, and the rate of postoperative reflux esophagitis was lower in the PG-DTR group (8% *vs.* 31%, P=0.032) (49).

Yamasaki *et al.* conducted a multicenter prospective study of 252 patients comparing the short-term outcomes of TG and PG with various modern reconstruction techniques. Postoperative reflux esophagitis rates were 5% in patients who underwent TG followed by Roux-en-Y reconstruction, 7% in patients who underwent PG followed by DTR, 7% in patients who underwent PG with jejunal interposition, and 19% in patients who underwent PG with direct EG (the details of use of anti-reflux techniques in this group are unknown). Rates of anastomotic stenosis were 5% in the TG with Roux-en-Y group, 0% in the PG with DTR group, 0% in the PG with jejunal interposition group, and 9% in the PG with direct EG group (10).

The short-term results of the above-mentioned prospective KLASS-05 study (LTG compared with LPG in 137 patients with cT1N0 upper third GC) showed no anastomosis-related complications in either group, and the Visick scores for postprandial symptoms at

2 weeks after surgery, including reflux symptoms, were not significantly different between the two groups (P=0.749) (14). These results suggest that DTR results in lower rates of postoperative reflux than does direct EG, at a similar rate to that observed after TG, and that DTR is potentially safer than DFT when implemented as minimally invasive surgery.

In conclusion, both DTR and DFT appear to be safe, feasible, and effective anti-reflux reconstruction methods after PG; however, it remains unclear which method is safer and provides better nutritional and symptomatic outcomes. Although several studies have compared DFT and DTR and reported that DFT is nutritionally superior (50-52), all of these were single-center retrospective studies. In addition, because of the most of these reports are from Eastern countries, whether these techniques are safe and effective for Western patients is unknown. Large, international multicenter prospective studies are warranted, to determine the optimal reconstruction after PG.

Postoperative QOL

All potential benefits of PG discussed above, including nutritional and hematologic metrics and incidence of reflux esophagitis measured by endoscopic findings, are clinically important and meaningful only when they improve patients' symptoms and QOL. Most of the studies reviewed here lack or have very limited patient-reported outcomes data to quantify symptoms and QOL. For example, the presence of reflux esophagitis as an endoscopic finding may not reflect patients' subjective symptoms, and if the patient does not experience symptoms, such an endoscopic finding is not clinically important (43,53).

Kunisaki *et al.* conducted a PGSAS NEXT survey study of patients with upper third GC who underwent TG or PG (5), using a questionnaire developed in Japan for patients who had undergone gastrectomy (PGSAS-45) (4,54). Kunisaki *et al.* enrolled 1,020 TG patients and 518 PG patients. Reconstruction methods used with PG included direct EG (58%; details regarding anti-reflux procedures unknown), DTR (33%), jejunal interposition (6%), and jejunal pouch interposition (3%). PG patients had significantly better scores in several main outcome measures (weight loss, dumping syndrome, necessity for additional meals, ability to work, dissatisfaction with working, and dissatisfaction with daily life subscales; all P<0.05) and generally better scores on the reflux subscale than those who underwent TG. The main limitation of the study was its cross-sectional design, in which timing of survey completion was not standardized.

Karanicolas *et al.* (8) evaluated postoperative QOL in 134 patients with GC who underwent TG, DG, or PG using the European Organization for Research and Treatment of Cancer generic cancer (QLQ-C30) and gastric cancer (QLQ-STO22) modules (55,56). The reconstruction method with PG was direct EG without specific anti-reflux procedures. In that study, patients who underwent PG more frequently reported reflux esophagitis, nausea/vomiting, and global QOL impairment than did patients who underwent DG or TG (8), and the authors concluded that PG with direct EG should be avoided.

Park *et al.* compared postoperative QOL between patients who underwent laparoscopic TG and those who underwent laparoscopic PG followed by DTR in 80 GC patients, using QLQ-C30 and QLQ-STO22 administered longitudinally after surgery (every 3 months during the first year after surgery, every 6 months for 3 years after surgery, and every 12 months for up to 5 years after surgery). Results showed no statistical difference in QOL scores between the two groups (57).

In summary, the advantage of PG over TG in terms of postoperative QOL is not defined, and it may depend on the reconstruction method and survey timing after surgery. The cross-sectional studies lack longitudinal data on patient-reported QOL to assess changes in symptoms over time. A prospective study analyzing longitudinal changes in patient-reported outcomes with standardized reconstruction approaches is warranted.

To determine the postoperative QOL benefit and safety of minimally invasive PG, we have recently initiated a trans-Pacific international multicenter prospective study comparing patient-reported outcomes after minimally invasive TG with those of minimally invasive PG. In this study, we are enrolling 60 patients who undergo minimally invasive PG followed by DTR or DFT reconstruction or minimally invasive TG, and we will prospectively collect short-term surgical and nutritional outcomes, including ghrelin levels and patient-reported outcomes, longitudinally (1, 3, 6, and 12 months after surgery) using the modified MD Anderson Symptom Inventory Gastrointestinal Cancer Module (MDASI-GI) (58). The primary outcome will be appetite level at 3 months after surgery. MDASI-GI is a validated questionnaire with only 24 question items requiring less than 5 min to complete, assessing symptoms for the past 24 h. We will use a web-based system to distribute the survey and collect results, which will make it feasible to collect patient-reported outcomes frequently. We expect that this pilot study will quantify the impact of

minimally invasive PG on patient QOL and its changes over time, to provide data to support future larger trials (NCT05205343).

Conclusions

PG has the potential for expanded indications for the treatment of advanced upper third GC and GEJ cancer while preserving stomach function. Preserving the stomach may also improve postoperative QOL; however, a well-designed prospective study is needed to verify the impact of this functional benefit. Postoperative reflux esophagitis, the most common disadvantage of PG, could potentially be overcome by improving the anastomosis technique, but international standardization is also warranted.

Acknowledgments

We thank Erica Goodoff, senior scientific editor, Research Medical Library, for editing this article.

Funding: This work was supported by the NIH/NCI (No. P30CA016672), Society of American Gastroenterological Surgery Robotic Surgery Research Grant 2021, and Project Periwinkle Research Grant 2021.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Adam Yopp) for the series "Multimodal Management of Gastric and Gastroesophageal Cancers" published in *Chinese Clinical Oncology*. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cco.amegroups.com/article/view/10.21037/cco-22-82/coif). The series "Multimodal Management of Gastric and Gastroesophageal Cancers" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2018 (5th edition). Gastric Cancer 2021;24:1-21.
2. Guideline Committee of the Korean Gastric Cancer Association (KGCA), Development Working Group & Review Panel. Korean Practice Guideline for Gastric Cancer 2018: an Evidence-based, Multi-disciplinary Approach. J Gastric Cancer 2019;19:1-48.
3. Eagon JC, Miedema BW, Kelly KA. Postgastrectomy syndromes. Surg Clin North Am 1992;72:445-65.
4. Takiguchi N, Takahashi M, Ikeda M, et al. Long-term quality-of-life comparison of total gastrectomy and proximal gastrectomy by postgastrectomy syndrome assessment scale (PGSAS-45): a nationwide multi-institutional study. Gastric Cancer 2015;18:407-16.
5. Kunisaki C, Yoshida K, Yoshida M, et al. Effects of Proximal Gastrectomy and Various Clinical Factors on Postoperative Quality of Life for Upper-third Gastric Cancer Assessed using the Postgastrectomy Syndrome Assessment Scale-45 (PGSAS-45): A PGSAS NEXT Study. Ann Surg Oncol 2022;29:3899-908.
6. Park DJ, Kim HH, Han SU, et al. Multicenter prospective randomized controlled trial of comparing laparoscopic proximal gastrectomy and laparoscopic total gastrectomy for upper third early gastric cancer (KLASS-05). J Clin Oncol 2019;37:TPS184.
7. Nunobe S, Ida S. Current status of proximal gastrectomy for gastric and esophagogastric junctional cancer: A review. Ann Gastroenterol Surg 2020;4:498-504.
8. Karanicolas PJ, Graham D, Gönen M, et al. Quality of life after gastrectomy for adenocarcinoma: a prospective cohort study. Ann Surg 2013;257:1039-46.
9. Rosa F, Quero G, Fiorillo C, et al. Total vs proximal gastrectomy for adenocarcinoma of the upper third of the stomach: a propensity-score-matched analysis of a multicenter western experience (On behalf of the Italian Research Group for Gastric Cancer-GIRCG). Gastric Cancer 2018;21:845-52.

10. Yamasaki M, Takiguchi S, Omori T, et al. Multicenter prospective trial of total gastrectomy versus proximal gastrectomy for upper third cT1 gastric cancer. Gastric Cancer 2021;24:535-43.
11. Yang K, Bang HJ, Almadani ME, et al. Laparoscopic Proximal Gastrectomy with Double-Tract Reconstruction by Intracorporeal Anastomosis with Linear Staplers. J Am Coll Surg 2016;222:e39-45.
12. Jung DH, Lee Y, Kim DW, et al. Laparoscopic proximal gastrectomy with double tract reconstruction is superior to laparoscopic total gastrectomy for proximal early gastric cancer. Surg Endosc 2017;31:3961-9.
13. Ikoma N, Badgwell BD, Mansfield PF. Robotic Proximal Gastrectomy with Double-Tract Reconstruction for Gastroesophageal Junction Cancer. J Gastrointest Surg 2021;25:1357-8.
14. Hwang SH, Park DJ, Kim HH, et al. Short-Term Outcomes of Laparoscopic Proximal Gastrectomy With Double-Tract Reconstruction Versus Laparoscopic Total Gastrectomy for Upper Early Gastric Cancer: A KLASS 05 Randomized Clinical Trial. J Gastric Cancer 2022;22:94-106.
15. Kuroda S, Choda Y, Otsuka S, et al. Multicenter retrospective study to evaluate the efficacy and safety of the double-flap technique as antireflux esophagogastrostomy after proximal gastrectomy (rD-FLAP Study). Ann Gastroenterol Surg 2018;3:96-103.
16. Hayami M, Hiki N, Nunobe S, et al. Clinical Outcomes and Evaluation of Laparoscopic Proximal Gastrectomy with Double-Flap Technique for Early Gastric Cancer in the Upper Third of the Stomach. Ann Surg Oncol 2017;24:1635-42.
17. Tanizawa Y, Terashima M. Lymph node dissection in the resection of gastric cancer: review of existing evidence. Gastric Cancer 2010;13:137-48.
18. Ichikawa D, Komatsu S, Kubota T, et al. Long-term outcomes of patients who underwent limited proximal gastrectomy. Gastric Cancer 2014;17:141-5.
19. Ahn SH, Lee JH, Park DJ, et al. Comparative study of clinical outcomes between laparoscopy-assisted proximal gastrectomy (LAPG) and laparoscopy-assisted total gastrectomy (LATG) for proximal gastric cancer. Gastric Cancer 2013;16:282-9.
20. Nozaki I, Hato S, Kobatake T, et al. Long-term outcome after proximal gastrectomy with jejunal interposition for gastric cancer compared with total gastrectomy. World J Surg 2013;37:558-64.
21. Cui M, Xing JD, Yang W, et al. D2 dissection in laparoscopic and open gastrectomy for gastric cancer. World J Gastroenterol 2012;18:833-9.
22. Haruta S, Shinohara H, Hosogi H, et al. Proximal gastrectomy with exclusion of #3b lesser curvature lymph node dissection could be indicated for patients with advanced upper-third gastric cancer. Gastric Cancer 2017;20:528-35.
23. Sasako M, McCulloch P, Kinoshita T, et al. New method to evaluate the therapeutic value of lymph node dissection for gastric cancer. Br J Surg 1995;82:346-51.
24. Yura M, Yoshikawa T, Otsuki S, et al. Oncological safety of proximal gastrectomy for T2/T3 proximal gastric cancer. Gastric Cancer 2019;22:1029-35.
25. Lee S, Son WJ, Roh YH, et al. Indication of Proximal Gastrectomy for Advanced Proximal Gastric Cancer Based on Lymph Node Metastasis at the Distal Part of the Stomach. Ann Surg Open 2021;2:e107.
26. Ri M, Kumagai K, Namikawa K, et al. Is proximal gastrectomy indicated for locally advanced cancer in the upper third of the stomach? Ann Gastroenterol Surg 2021;5:767-75.
27. Mariette C, Piessen G, Briez N, et al. Oesophagogastric junction adenocarcinoma: which therapeutic approach? Lancet Oncol 2011;12:296-305.
28. Yamashita H, Seto Y, Sano T, et al. Results of a nation-wide retrospective study of lymphadenectomy for esophagogastric junction carcinoma. Gastric Cancer 2017;20:69-83.
29. Kurokawa Y, Takeuchi H, Doki Y, et al. Mapping of Lymph Node Metastasis From Esophagogastric Junction Tumors: A Prospective Nationwide Multicenter Study. Ann Surg 2021;274:120-7.
30. Mine S, Kurokawa Y, Takeuchi H, et al. Distribution of involved abdominal lymph nodes is correlated with the distance from the esophagogastric junction to the distal end of the tumor in Siewert type II tumors. Eur J Surg Oncol 2015;41:1348-53.
31. Nomura E, Lee SW, Bouras G, et al. Functional outcomes according to the size of the gastric remnant and type of reconstruction following laparoscopic distal gastrectomy for gastric cancer. Gastric Cancer 2011;14:279-84.
32. Ri M, Nunobe S, Makuuchi R, et al. Key Factors for Maintaining Postoperative Skeletal Muscle Mass After Laparoscopic Proximal Gastrectomy with Double-Flap Technique Reconstruction for Early Gastric Cancer. J Gastrointest Surg 2021;25:1569-72.
33. Adachi S, Takiguchi S, Okada K, et al. Effects of ghrelin administration after total gastrectomy: a prospective,

randomized, placebo-controlled phase II study. Gastroenterology 2010;138:1312-20.
34. Jeon TY, Lee S, Kim HH, et al. Changes in plasma ghrelin concentration immediately after gastrectomy in patients with early gastric cancer. J Clin Endocrinol Metab 2004;89:5392-6.
35. Takiguchi S, Takata A, Murakami K, et al. Clinical application of ghrelin administration for gastric cancer patients undergoing gastrectomy. Gastric Cancer 2014;17:200-5.
36. Kizaki J, Aoyagi K, Sato T, et al. Production of ghrelin by the stomach of patients with gastric cancer. Kurume Med J 2014;60:99-104.
37. Ushimaru Y, Fujiwara Y, Shishido Y, et al. Clinical Outcomes of Gastric Cancer Patients Who Underwent Proximal or Total Gastrectomy: A Propensity Score-Matched Analysis. World J Surg 2018;42:1477-84.
38. Xu Y, Tan Y, Wang Y, et al. Proximal versus total gastrectomy for proximal early gastric cancer: A systematic review and meta-analysis. Medicine (Baltimore) 2019;98:e15663.
39. Lim CH, Kim SW, Kim WC, et al. Anemia after gastrectomy for early gastric cancer: long-term follow-up observational study. World J Gastroenterol 2012;18:6114-9.
40. Jeong O, Park YK, Ryu SY. Prevalence, severity, and evolution of postsurgical anemia after gastrectomy, and clinicopathological factors affecting its recovery. J Korean Surg Soc 2012;82:79-86.
41. Park DJ, Han S-U, Hyung WJ, et al. Laparoscopic proximal vs. total gastrectomy for upper third EGC: KLASS-05 randomized clinical trial. Houston, TX: International Gastric Cancer Congress; March 6-9, 2022.
42. Nakamura M, Yamaue H. Reconstruction after proximal gastrectomy for gastric cancer in the upper third of the stomach: a review of the literature published from 2000 to 2014. Surg Today 2016;46:517-27.
43. Hiki N, Nunobe S, Kubota T, et al. Function-preserving gastrectomy for early gastric cancer. Ann Surg Oncol 2013;20:2683-92.
44. Kuroda S, Nishizaki M, Kikuchi S, et al. Double-Flap Technique as an Antireflux Procedure in Esophagogastrostomy after Proximal Gastrectomy. J Am Coll Surg 2016;223:e7-e13.
45. Kano Y, Ohashi M, Ida S, et al. Laparoscopic proximal gastrectomy with double-flap technique versus laparoscopic subtotal gastrectomy for proximal early gastric cancer. BJS Open 2020;4:252-9.
46. Mine S, Kurokawa Y, Takeuchi H, et al. Postoperative complications after a transthoracic esophagectomy or a transhiatal gastrectomy in patients with esophagogastric junctional cancers: a prospective nationwide multicenter study. Gastric Cancer 2022;25:430-7.
47. Ahn SH, Jung DH, Son SY, et al. Laparoscopic double-tract proximal gastrectomy for proximal early gastric cancer. Gastric Cancer 2014;17:562-70.
48. Berlth F, Tagkalos E, Mann C, et al. Minimally invasive proximal gastrectomy and double tract reconstruction. Ann Laparosc Endosc Surg 2022;7:8.
49. Ji X, Jin C, Ji K, et al. Double Tract Reconstruction Reduces Reflux Esophagitis and Improves Quality of Life after Radical Proximal Gastrectomy for Patients with Upper Gastric or Esophagogastric Adenocarcinoma. Cancer Res Treat 2021;53:784-94.
50. Nishimura E, Irino T, Matsuda S, et al. Comparison of changes in body fat mass and reflux esophagitis between reconstruction methods after proximal gastrectomy. Asian J Surg 2022. [Epub ahead of print]. doi: 10.1016/j.asjsur.2022.04.110.
51. Yu B, Park KB, Park JY, et al. Double tract reconstruction versus double flap technique: short-term clinical outcomes after laparoscopic proximal gastrectomy for early gastric cancer. Surg Endosc 2022;36:5243-56.
52. Saze Z, Kase K, Nakano H, et al. Functional benefits of the double flap technique after proximal gastrectomy for gastric cancer. BMC Surg 2021;21:392.
53. Tokunaga M, Ohyama S, Hiki N, et al. Endoscopic evaluation of reflux esophagitis after proximal gastrectomy: comparison between esophagogastric anastomosis and jejunal interposition. World J Surg 2008;32:1473-7.
54. Nakada K, Ikeda M, Takahashi M, et al. Characteristics and clinical relevance of postgastrectomy syndrome assessment scale (PGSAS)-45: newly developed integrated questionnaires for assessment of living status and quality of life in postgastrectomy patients. Gastric Cancer 2015;18:147-58.
55. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365-76.
56. Vickery CW, Blazeby JM, Conroy T, et al. Development of an EORTC module to improve quality of life assessment in patients with gastric cancer Br J Surg 2000;87:362-73.
57. Park JY, Park KB, Kwon OK, et al. Comparison of laparoscopic proximal gastrectomy with double-tract

reconstruction and laparoscopic total gastrectomy in terms of nutritional status or quality of life in early gastric cancer patients. Eur J Surg Oncol 2018;44:1963-70.
58. Wang XS, Williams LA, Eng C, et al. Validation and application of a module of the M. D. Anderson Symptom Inventory for measuring multiple symptoms in patients with gastrointestinal cancer (the MDASI-GI). Cancer 2010;116:2053-63.

Cite this article as: Hirata Y, Kim HI, Grotz TE, Matsuda S, Badgwell BD, Ikoma N. The role of proximal gastrectomy in gastric cancer. Chin Clin Oncol 2022;11(5):39. doi: 10.21037/cco-22-82