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The editor-in-chief

World Journal of Gastrointestinal Surgery

Thank you for giving us the opportunity to submit a revised draft of the manuscript "Comparison of the effects of the six main gastrectomy procedures on patients' quality of life assessed by PGSAS-45" for publication in the World Journal of Gastrointestinal Surgery. We appreciate the time and effort that you and the reviewers dedicated to providing feedback on our manuscript and are grateful for the insightful comments on and valuable improvements to our paper. We have incorporated the suggestions made by the reviewers as much as we can. Please see below, in blue, for a point-by-point response to the reviewers' comments and concerns.

Reviewers' Comments to the Authors:

Reviewer #1

The authors evaluated the post-gastrectomy quality of life by analyzing the questionnaire(PGSAS-45) of 2368 patients received 6 different surgical procedures, found that TGRY had the worst postoperative QOL score, and LR had the highest postoperative QOL score. In addition, the QOL of PG was worse than that of PPG, DGBI, and DGRY, and the postoperative QoL of PPG was slightly better than that of DGBI and DGRY.

Author response: Thank you for taking time out of your busy schedule to review our manuscript.

1. For LR, some patients those not diagnosed as carcinoma were enrolled in this study. For these patients, please state that if the targeted therapy was applied or not;

Author response: Thank you for the important comment. Actually, LR group includes a certain number of gastrointestinal stromal tumor and carcinoid patients other than carcinoma patients, however, the targeted therapy had not applied to any of these patients.

2. The surgical procedure was decided by the tumor stage, site and size, please define the clinical significance of this study of which the QoL of TG, DG or LR were compared.

Author response: We appreciate your precious comment. It's exactly as you said, the type of gastrectomy procedure is usually decided by the tumor stage, site and size. Therefore, previous studies compared surgical outcomes between the rival gastrectomy procedures which applied for the gastric cancer at the similar tumor stage, site and size. As a result, no study has simultaneously assessed various gastrectomy procedures performed for gastric cancer of different sites and compared the severity and characteristics of postgastrectomy syndrome for these procedures to elucidate the broader perspective of the burden of gastrectomy. As one point of view, we assert that it is important for surgeons to understand the general aspects of how the site and extent of gastrectomy affect patient's postoperative QOL. So we described in the limitation section as follows; "First, since the choice of gastrectomy is mainly based on the site and spread of gastric cancer, simultaneously comparing various procedures performed on gastric cancer of different sites has only a little significance on the selection of the type of gastrectomy. However, it is important for surgeons to understand the general aspects of how the site and extent of gastrectomy affect patient's postoperative QOL".

3. The enrolled patients were early gastric cancer according to the inclusion criteria, while the TG (393case) proportion was bigger than PG proportion, please define this.

Author response: We thank your important comment. Proximal gastrectomy is increasingly applied for the upper-third early gastric cancer these days, however, conventional gastrectomy for upper-third early gastric cancer was mainly total gastrectomy until a while ago. Since the PGSAS study was conducted from 2009 to 2010 and the patients underwent gastrectomy several years before the enrollment, for this reason, that the number of total gastrectomy was larger than proximal gastrectomy even for early gastric cancer in the PGSAS study.

4. The enrolled patients comprising open and minimally invasive surgery while the proportion of laparoscopic surgery was different between the six groups, which might affect the result.

Author response: Thank you for pointing it out. Indeed, laparoscopic gastrectomy is considered equally curative and less invasive than open gastrectomy. However, the advantage of laparoscopic gastrectomy in postoperative QOL is not yet clarified. Our colleague, professor Kinami, examined the effect of background factors on postgastrectomy QOL among various type of gastrectomy procedures using multiple regression analysis [Kinami S, *et al.* World J Clin Cases 26:1111, 2018], and reported that the laparoscopic approach had a little advantages in some main outcome measures of PGSAS-45 in DGBI and PPG, whereas any advantage of laparoscopic approach had not proved in the other type of gastrectomy such as TGRY, PG, DGRY and LR as to postoperative QOL. Generally, the only difference between laparoscopic surgery and conventional open surgery is the length of the incision, therefore, we supposed that a large difference in postoperative QOL between laparoscopic and open surgery may be unexpected.

Editorial Office's comments

(1) Science editor:

1 Scientific quality: The manuscript describes an observational study of the comparison of the effects of the six main gastrectomy procedures on patients' quality of life assessed by PGSAS-45. The topic is within the scope of the WJGS.

(1) Classification: Grade C;

Thank you very much for your kind comments.

(2) Summary of the Peer-Review Report: The authors evaluated the post-gastrectomy quality of life, found that TGRY had the worst postoperative QOL score, and LR had the highest postoperative QOL score. In addition, the QOL of PG was worse than that of PPG, DGBI, and DGRY, and the postoperative QoL of PPG was slightly better than that of DGBI and DGRY. The questions raised by the reviewers should be answered; and

Thank you very much for your kind instruction. We carefully check the reviewer's comments and answered the questions accordingly.

(3) Format: There are 4 tables and 2 figures. A total of 47 references are cited, including 7 references published in the last 3 years. There are 12 self-citations (Ref. 1, 12, 13, 15, 16, 18, 19, 20, 21, 22, 43, 44). The topics of the self-citations are related to this study.

Thank you very much for your kind comments. We have read and ascertained above comments carefully. There are 10 self-citations (Ref. 12, 13, 15, 16, 18, 19, 20, 21, 22, 43). We removed Ref. 20 (Tanabe K, *et al*) and 21 (Tanizawa Y, *et al*), because these references were not relevant to this study.

2 Language evaluation: Classification: Grade B. A language editing certificate issued by Editage was provided.

Thank you very much for your kind remark.

3 Academic norms and rules: The authors provided the Biostatistics Review Certificate, the Institutional Review Board Approval Form, and the written informed consent. No academic misconduct was found in the Bing search.

Thank you very much for your kind comments.

4 Supplementary comments: This is an invited manuscript. The study was supported by a grant from Jikei University and a grant from Japanese Society for Gastro-surgical Pathophysiology. The topic has not previously been published in the WJGS.

Thank you very much for your kind remark.

5 Issues raised:

(1) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);

We are sorry regarding this. We uploaded the approved funding agency certificates.

(2) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

We are sorry regarding this. We uploaded the decomposable Figures as "62821-Figures.ppt".

(3) The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text;

We are sorry regarding this. We added the "Article Highlights" section at the end of the main text.

(4) Authors should always cite references that are relevant to their study. Please check and remove any references that not relevant to this study. Authors cite too many their own articles. Authors should keep the reasonable self-citations that are closely related to the topic of the manuscript, and remove other improper self-citations.

Thank you very much for your valuable comments. There were 10 self-citations (Ref. 12, 13, 15, 16, 18, 19, 20, 21, 22, 43). We ascertained them carefully and removed Ref. 20 (Tanabe K, *et al*) and 21 (Tanizawa Y, *et al*), because these references were not relevant to this study. In addition, incorrectly cited reference for SF-8 and GSRs were corrected in the revised manuscript as Ref. 21, 22, 23.

6 Recommendation: Conditional acceptance.

Thank you very much for your gentle decision.

(2) Editorial office director:

(3) Company editor-in-chief: I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastrointestinal Surgery, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Thank you very much for your kindness. We revised our manuscript according to the reviewer's and editorial office's comments.

We should like to thank the reviewer and Editorial Office for the helpful comments and hope the revised manuscript is suitable for publication in *World Journal of Gastrointestinal Surgery*.

Sincerely,
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Comparison of the effects of the six main gastrectomy procedures on patients' quality of life assessed by PGSAS-45

Running head: Life quality after gastrectomy

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Author contributions: Nakada K, Kinami S, Uenosono Y, Kodera Y designed the study, and collected and managed the data; Kawashima Y, Fukushima R, Yabusaki H, Seshimo A, Hiki N, Koeda K, Kano M collected and managed the data; Oshio A contributed to statistical analysis; Nakada K wrote the paper; all authors have read and approved the final version to be published.

Institutional review board statement: This study was approved by local ethics committees at each institution.

Informed consent statement: Written informed consent was obtained from all enrolled patients.

Conflict-of-interest statement: The authors declare no conflicts of interests related to the publication of this study.

Data sharing statement: No additional data was available.

STROBE statement: The manuscript was revised according to the STROBE statement.

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Abstract

Background: The effects of various gastrectomy procedures on the patient's quality of life (QOL) are not well understood. Thus, this nationwide multi-institutional cross-sectional study aimed to compare the effects of six main gastrectomy procedures on the postoperative QOL using the Postgastrectomy Syndrome Assessment Scale-45 (PGSAS-45), a well-established questionnaire designed to clarify the severity and characteristics of the postgastrectomy syndrome.

Methods: Eligible questionnaires retrieved from 2,368 patients who underwent either of six gastrectomy procedures (total gastrectomy with Roux-en-Y reconstruction [TGRY; n=393], proximal gastrectomy [PG; n=193], distal gastrectomy with Roux-en-Y reconstruction [DGRY; n=475], distal gastrectomy with Billroth-I reconstruction [DGBI; n=909], pylorus-preserving gastrectomy [PPG; n=313], and local resection [LR; n=85]) were analyzed. Among the 19 main outcome measures (MOMs) of PGSAS-45, the severity and characteristics of postgastrectomy syndrome were compared for the aforementioned six gastrectomy procedures using analysis of means.

Results: TGRY and PG significantly impaired the QOL of postoperative patients. Postoperative QOL was excellent in LR (cardia and pylorus were preserved with minimal resection). In procedures removing the distal stomach, diarrhea subscale (SS) and dumping SS were less frequent in PPG than in DGBI and DGRY. However, there was no difference in the postoperative QOL between DGBI and DGRY. The most noticeable adverse effects caused by gastrectomy were meal-related distress SS, dissatisfaction at the meal, and weight loss, with significant differences among the surgical procedures.

Conclusion: Postoperative QOL greatly differed among six gastrectomy procedures. The severity and characteristics of postgastrectomy syndrome should be considered to select gastrectomy procedures, overcome surgical shortcomings, and enhance postoperative care.

Keywords: gastrectomy, quality of life, postgastrectomy syndromes, patient reported outcome measures

Core Tip: For surgeons, to understand the general aspects of how the site and extent of gastrectomy affect patient's postoperative QOL is important. Therefore, we investigated this concern by the nationwide multi-institutional collaborative study called Postgastrectomy Syndrome Assessment Study (PGSAS). The overview of the effects of the six main gastrectomy procedures on the patient's daily living revealed that the postoperative QOL differed greatly depending on the site and extent of gastrectomy. The severity and characteristics of postgastrectomy syndrome should be considered to select gastrectomy procedures, overcome surgical shortcomings, and enhance postoperative care.

INTRODUCTION

Gastrectomy is widely performed and is the most effective treatment for gastric cancer. Recent improvements in early-stage diagnosis and treatment have improved the detection, treatment, and subsequent curing of the disease^[1]. However, postgastrectomy syndrome occurs frequently^[2-7], and the patient's long-term impairments are a concern. In patients with gastric cancer, procedure selection depends on its location, extent, and progression. Daily life impairment caused by gastrectomy varies with the type of surgical procedure. Therefore,

function-preserving gastrectomies such as proximal gastrectomies (PG) and pylorus-preserving gastrectomies (PPG)^[8-10] are performed for early gastric cancer to attenuate the postgastrectomy syndrome associated with gastrectomy by reducing the extent of resection, and local resection (LR) in rare cases^[11].

Currently, a means of assessing the effect of gastrectomy on a patients' daily living does not exist. Therefore, it was difficult to assess the severity and characteristics of postgastrectomy syndrome. In this context, we developed the Postgastrectomy Syndrome Assessment Scale-45 (PGSAS-45)^[12], which is a patient-reported outcome scale, designed to assess the effect of gastrectomy on postoperative patients' daily living. It has been reported to be useful for assessing symptoms, living status, and quality of life (QOL) of postgastrectomy patients^[13-22]. Studies have investigated the postoperative QOL among procedures performed to treat gastric cancer at a specific site. However, no study has simultaneously assessed different gastrectomy procedures used to treat gastric cancer at various sites and compared the severity and characteristics of postgastrectomy syndrome for these procedures to elucidate the broader perspective of the burden of gastrectomy. Therefore, this study aimed to compare the outcomes of the six main gastrectomy procedures with respect to the patient's QOL using PGSAS-45 in order to clarify the severity and characteristics of postgastrectomy syndrome.

MATERIALS AND METHODS

Study population

Fifty-two institutions participated in this study. The PGSAS-45 questionnaire was distributed to 2,922 patients between July 2009 and December 2010. The questionnaires were given to 2,922 patients, and 2,520 responses were mailed to the data center. Among the 2,520

respondents, 152 provided answers that were deemed unsuitable for analysis. Consequently, a total of 2,368 questionnaires returned by mail were analyzed (Fig. 1).

Eligibility criteria

All patients enrolled in this study fulfilled the following eligibility criteria: (1) pathologically confirmed stage IA or IB gastric cancer (for LR, other tumors, such as gastrointestinal stromal tumors (GISTs) or carcinoids, were included), (2) first-time gastrectomy, (3) age ≥ 20 and ≤ 75 years, (4) no history of chemotherapy, (5) no recurrence or distant metastasis, (6) ≥ 1 year had elapsed since gastrectomy, (7) performance status ≤ 1 on the Eastern Cooperative Group Scale, (8) fully capable of understanding and responding to the questionnaire, (9) absence of other diseases or previous surgeries that may have a greater influence on the results of the questionnaire than gastrectomy, (10) no organ failure or mental disease; and (11) provision of written informed consent by the patient. The patients with dual malignancy or concomitant resection of other organs (co-resection equivalent to cholecystectomy being the exception) were excluded.

Design

We performed continuous sampling from a central registration system for participant enrollment. The questionnaire was distributed to all eligible patients on presentation to the participating clinics. The patients were requested to return the completed forms to the data center by mail. The perioperative data were reported by the attending surgeon to the data center through case report forms. All QOL data from questionnaires were matched with individual patient data collected via the case report forms.

This study was approved by the local ethics committees of each participating institution and was in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964 and later versions. This study was registered with the University Hospital Medical Information Network's Clinical Trials Registry as trial number 000002116.

QOL assessment

We developed the PGSAS-45 as a new integrated QOL questionnaire, comprising an 8-item short-form generic health-related QOL questionnaire (SF-8)^[23] and the Gastrointestinal Symptom Rating Scale (GSRS)^[24, 25]. In addition to the items of the SF-8 (8 items) and GSRS (15 items), 22 newly selected items are included, comprising questions on common postgastrectomy symptoms (8 items), number and type of dumping symptoms (2 items), amount and quality of dietary intake (8 items), daily activity status (1 item), and dissatisfaction with daily life (3 items). Hence, each patient was asked 45 questions in total (Table 1). The details of the PGSAS-45 have been reported previously^[12].

Statistical analysis

Statistical analyses were performed using JMP12.0.1 software (SAS Institute Inc., Cary, NC, USA). The differences in patient characteristics were assessed using analysis of means (ANOM) and the chi-square test, followed by residual analysis. To compare the 19 main outcome measures (MOMs) of PGSAS-45 for the six main gastrectomy techniques, the ANOM method was used, with the alpha level was set at 0.05. Values with $p < 0.05$ were considered significant.

RESULTS

Background (Table 2)

The 2,368 patients who underwent the six main gastrectomy procedures were distributed according to the surgical procedure, as follows: total gastrectomy with Roux-en-Y reconstruction (TGRY), 393 patients; PG, 193 patients, distal gastrectomy with Roux-en-Y reconstruction (DGRY), 475 patients; distal gastrectomy with Billroth-I reconstruction (DGBI), 909 patients; PPG, 313 patients; and LR, 85 patients (Fig 1). The average age of the patients was 62.1 years, and for patients undergoing TGRY, the mean age was significantly higher at 63.4 years. The overall mean postoperative period was 37.7 months. For DGBI, the mean postoperative period was significantly longer at 40.7 months and was significantly shorter at 31.7 months for DGRY. The proportion of men and women in the study population was 66% and 34%, respectively. Among the patients undergoing PPG, the proportion of women was significantly higher at 41%. The overall mean rate for the laparoscopic approach was 38% and was significantly higher for LR (61%) and DGBI (46%), but significantly lower for PG (17%) and TGRY (25%). The overall mean rate of preservation of the celiac branch of the vagus nerve was 24% and was significantly higher for LR (100%), PPG (71%), and PG (44%); however, it was significantly lower for TGRY (3%), DGRY (6%), and DGBI (15%).

Symptoms (Table 3)

When comparing postgastrectomy symptoms of each type of gastrectomy with the overall mean symptom scores, most symptoms were severe for TGRY, while for LR, the symptoms, except for abdominal pain subscale (SS), were mild ($p<0.05$). In PG, meal-related distress SS and esophageal reflux SS were serious complications ($p<0.05$). The meal-related distress SS

was low for both DGBI and DGRY. In addition, the esophageal reflux SS was low for DGRY and the indigestion SS was low for DGBI, respectively ($p<0.05$). The diarrhea SS and dumping SS were reported less severe for PPG ($p<0.05$).

Among the seven symptom SS, after gastrectomy, the most prominent symptom with higher scores were meal-related distress, constipation, and diarrhea. Additionally, as the mean score of symptoms for a specific gastrectomy type significantly differs from the overall mean score of symptoms, the symptom MOMs showing a large difference depending on the procedure were meal-related distress SS (noted in 5 of the 6 gastrectomy procedures), followed by esophageal reflux SS (4 of the 6 gastrectomy procedures).

Living status (Table 3)

Compared with the overall mean living status scores, the postgastrectomy living status for TGRY was clearly worse for all MOMs, except for the quality of ingestion SS, whereas the postgastrectomy living status for the LR was significantly better for all MOMs ($p<0.05$). Moreover, for PG, the ingested amount of food per meal was low, quality of ingestion SS was poor, and weight loss was massive ($p<0.05$). DGBI and PPG were associated with lesser necessity for additional meals and less weight loss; moreover, DGBI was associated with better ability for working ($p<0.05$). Additionally, as the mean score of living status for a specific gastrectomy type significantly differs from the overall mean score of living status, the living status MOMs showing a large difference depending on the procedure were weight loss (noted in 5 of the 6 gastrectomy procedures), followed by necessity for additional meals (4 of the 6 gastrectomy procedures).

QOL (Table 3)

Compared with the overall mean QOL scores, TGRY showed poor scores for all QOL MOMs, except for the mental component summary of SF-8, whereas LR showed excellent scores for all QOL MOMs ($p<0.05$). For PG, a significantly more patients reported dissatisfaction at the meal, dissatisfaction at working, and dissatisfaction for daily life SS ($p<0.05$). The prevalence of dissatisfaction at the meal was lower for DGBI and DGRY, and that of dissatisfaction at working and dissatisfaction for daily life SS was lower for DGBI ($p<0.05$). One of the QOL MOMs notable in gastrectomy was dissatisfaction at the meal. Additionally, as the mean score of QOL for a specific gastrectomy type significantly differs from the overall mean score of QOL, the QOL MOMs showing a large difference depending on the procedure, was dissatisfaction at the meal (noted in 5 of the 6 gastrectomy procedures), followed by dissatisfaction at working and dissatisfaction for daily life SS (4 of 6 gastrectomy procedures).

Overall characteristics

The percentage for the overall mean score of each surgical procedure was calculated for 19 MOMs of PGSAS-45 (Table 4). For every 5% deviation in score from the overall mean score, 1 point was added if the daily living condition was good and 1 point was subtracted if the daily living condition was bad. The total score of the 19 MOMs for each procedure was calculated and compared (Table 4, Fig 2). The overall living condition of patients who underwent the aforementioned gastrectomy procedures was compared: the TGRY had a score of -47 points, which indicated a considerably worse living condition than other procedures, while LR had score of +97 points, which indicated a markedly better living condition compared to the other procedures. PG, where the proximal stomach was resected, had a score of -26 points; therefore, the QOL of patients who underwent PG was poor compared to that of patients who underwent DGRY (3 points), DGBI (5 points), and PPG (10 points), wherein the proximal stomach is presented. The QOL was better for the patients who underwent PPG

where the pylorus was preserved compared to those who underwent DGBI and DGRY, and was almost similar between the patients who underwent DGBI and DGRY.

DISCUSSION

In this study, we developed the PGSAS-45 questionnaire for the assessment of postgastrectomy syndrome. Using this questionnaire, we examined the effects of the six main gastrectomy procedures on patients' daily living. The results revealed that TGRY had the worst postoperative QOL score, whereas LR had the highest postoperative QOL score. For PG, where the proximal stomach is resected, the postoperative QOL was clearly worse than that for PPG, DGBI, and DGRY, where the proximal stomach is preserved. Post-PPG, where the pylorus was preserved, the QOL was slightly better than that of post-DGBI and -DGRY. No significant difference was found between DGBI and DGRY in terms of QOL. Among the 19 MOMs in PGSAS-45, the major differences in the surgical procedures were meal-related distress SS and esophageal reflux SS with respect to the symptoms, weight loss and necessity for additional meals with respect to the living status, and dissatisfaction at the meal, dissatisfaction at working, and dissatisfaction for daily life SS with respect to the QOL. After gastrectomy, the most prominent burdens were meal-related distress SS, constipation SS, diarrhea SS, and dissatisfaction at the meal. To the best of our knowledge, this is the first study to simultaneously examine the effects of various gastrectomy procedures on the patients' daily living postoperatively and to clarify the overall characteristics of postgastrectomy syndrome.

In recent years, the rate of detection of early-stage gastric cancer has increased due to widespread medical screening and improvement of diagnostic techniques^[1]. Advances in treatment also increase the number of patients who can attain long-term postgastrectomy

survival^[1]. On the contrary, various complications, called postgastrectomy syndrome, occur after gastrectomy^[2-7], which become clinical problems that interfere with daily living. Within this context, there has been increasing interest in reducing the incidence of postgastrectomy syndrome and improving postoperative patients' QOL, and the introduction of function-preserving surgery, such as PG and PPG^[8-10], and minimally invasive surgery, such as laparoscopic surgery^[23], has increased. These function-preserving surgical procedures are also accepted by the fourth edition of the gastric cancer treatment guidelines (2017) as an alternative treatment of early-stage gastric cancer (cT1N0M0)^[24].

The primary purpose of gastrectomy is to cure cancer, and then, to allow the patient to live comfortably at the same level as their preoperative condition. To improve the QOL of postgastrectomy patients, it is important to select a gastrectomy procedure considering the patient's postoperative QOL. However, to achieve this, a questionnaire, which accurately measures the postgastrectomy patients' burden in their daily living, is essential. Many studies have compared different gastrectomy procedures^[25-27], but in the absence of a suitable questionnaire to assess the effects of gastrectomy, satisfactory assessment could not be attained. In this light, PGSAS-45^[12], a new questionnaire developed by the Japan Postgastrectomy Syndrome Working Party, was used to assess the gastrectomy procedures, and a nationwide multi-institutional collaborative study called Postgastrectomy Syndrome Assessment Study was conducted to elucidate the effects of the six main gastrectomy procedures on the daily living of postoperative patients.

To date, several studies have compared various gastrectomy procedures as treatment of gastric cancer on a specific site. Total gastrectomy was often performed for upper gastric cancer, but in recent years, PG, which is a function-preserving surgery, has often been performed to treat early-stage gastric cancer for expecting better QOL^[8-10]. A study comparing postoperative QOL between total gastrectomy and PG shows that the latter results in better QOL^[28] with

less diarrhea and dumping symptoms, less weight loss, and less necessity for additional meals^[19]. On the contrary, reflux esophagitis and anastomotic stricture have been reported in PG^[17, 29] and remains a problem. In this study, PG had a total QOL score of -26 points compared with TGRY having -47 points. This shows that PG has lesser worse effects on QOL than TGRY, resulting in less impairment in daily living.

Distal gastrectomy is often performed for middle-third gastric cancer; however, PPG has also been selected as a function-preserving surgery for early-stage gastric cancer^[8-10]. In studies comparing the postoperative QOL of distal gastrectomy and PPG, PPG was reported to have better QOL^[13, 14, 30-32] with fewer occurrences of diarrhea and dumping, less weight loss, and less necessity for additional meals^[13]. In this study, DGBI had QOL score of 5 points, and DGRY had 3 points versus PPG's score of 10 points, indicating that PPG provides better QOL than distal gastrectomy.

Distal gastrectomy is performed as a standard surgical procedure for lower gastric cancer. DGBI and DGRY are mainly performed as reconstructive methods. Many studies have compared DGBI with DGRY^[22, 33-40], each of which has reported benefits, such as lesser weight loss in DGBI^[22] and lower occurrence of residual gastritis and esophageal reflux symptoms in DGRY^[22, 37, 40]. However, there is no definitive view on which of the two reconstructive surgeries is effective. In this study, DGRY (3 points) and DGBI (5 points) had virtually identical scores.

The results of this study were consistent with previous studies comparing various contrasting rival gastrectomy procedures. As mentioned above, various gastrectomy procedures were compared, which revealed an increase of evidence, showing the usefulness of function-preserving surgery. In the future, we anticipate that function-preserving gastrectomy will be applied to a wider extent to address early-stage gastric cancer.

In the overall characteristics, the worse effects of total gastrectomy on daily life were greater than those in the other five procedures (Table 4, Fig 2) and fatal. In recent years, PG has been frequently performed for early-stage upper gastric cancer, which reduces the incidence of postgastrectomy syndrome, and the postoperative QOL is better than that in total gastrectomy. Alternatively, subtotal gastrectomy is performed, which leaves a portion of the proximal stomach even if the size of the remaining stomach becomes considerably small^[41, 42], and its QOL is reported better than that of TG^[42]. If oncological safety is maintained, avoiding total gastrectomy as much as possible, and actively adopting a procedure that leaves either the distal stomach or a portion of the proximal stomach may help improve postoperative QOL.

In contrast, the QOL after LR was by far better than that after other gastrectomy procedures. Many reports have indicated that QOL after LR was favorable^[15, 43, 44] and that residual stomach functions were retained^[43]. Local gastric resection is often performed for GISTs; however, it has been performed as a surgical treatment for early-stage gastric cancers based on the sentinel lymph node concept^[44, 45]. Endoscopic submucosal dissection (ESD) has been increasingly performed for early-stage gastric cancers, and its applicability continues to increase^[46]. The QOL after ESD is especially favorable^[47], and it would be an ideal treatment method if gastric cancer could be completely cured. Meanwhile, gastrectomy procedures, such as PG, PPG, and DG have been performed in conjunction with the preservation of the celiac branch of the vagus nerve as function-preserving gastrectomy for lesions in early-stage non-ESD applicable gastric cancers. However, there is still a major gap between functional preservation after gastrectomy and ESD with regards to the patients' QOL. In recent years, sentinel node navigation surgery has been incorporated against early-stage non-ESD applicable gastric cancers by safely employing LR while maintaining oncological safety. As the present results show, the QOL after LR is exceedingly favorable compared to that after PPG and PG; therefore, LR may be an effective treatment option for some early-stage non-

ESD applicable gastric cancers. We anticipate the safe introduction of LR against early-stage non-ESD applicable gastric cancers with the accumulation of evidence in the future.

Among the MOMs of PGSAS-45, the major differences according to the type of procedure were meal-related distress SS, change in body weight, and dissatisfaction at the meal. Therefore, the effect of gastrectomy on meal-related MOMs was extremely large, and this was considered the most important factor contributing to the reduction of QOL of postoperative patients. Of the seven symptoms SS of PGSAS-45, meal-related distress SS and dumping SS were reported to have the largest influence on QOL, reducing postgastrectomy QOL^[16]. Therefore, the procedure should be improved to reduce meal-related distress SS and dumping SS.

This study has limitations. First, since the choice of gastrectomy is mainly based on the site and spread of gastric cancer, simultaneously comparing various procedures performed on gastric cancer of different sites has only a little significance on the selection of the type of gastrectomy. However, it is important for surgeons to understand the general aspects of how the site and extent of gastrectomy affect patient's postoperative QOL. Second, this is a retrospective study, and there is a bias in the number of cases between each surgery. However, the overall analysis was based on a large number of cases (n=2,368), and the progression was relatively early as stage IA/IB. Thus, we believe that the difference in the progression of cancer has little influence on the differences between each procedure and mainly reflects the effect of the procedures.

CONCLUSION

This study provided an overview of the severity and characteristics of postgastrectomy syndrome in patients who underwent the six main gastrectomy procedures. It also clarified

that the postoperative QOL differed greatly depending on the site and extent of gastrectomy. To improve postgastrectomy QOL, it is important for surgeons to understand these matters to select the appropriate procedure, to improve the surgical technique to compensate for the shortcomings of each procedure, and to enhance postoperative care by providing appropriate dietary guidance and detecting and addressing postgastrectomy syndromes at an early stage.

ARTICLE HIGHLIGHTS

Research background

No study has simultaneously assessed the effects of the different gastrectomy procedures used to treat gastric cancer at various sites on the postgastrectomy QOL.

Research Motivation

It is important for surgeons to understand the general aspects of how the site and extent of gastrectomy affect patient's postoperative QOL.

Research objectives

The aim of this study was to compare the effects of six main gastrectomy procedures on the postoperative QOL using the Postgastrectomy Syndrome Assessment Scale-45 (PGSAS-45).

Research methods

The 2,368 patients who underwent either of the six main gastrectomy procedures (total gastrectomy with Roux-en-Y reconstruction [TGRY; n=393], proximal gastrectomy [PG; n=193], distal gastrectomy with Roux-en-Y reconstruction [DGRY; n=475], distal gastrectomy with Billroth-I reconstruction [DGBI; n=909], pylorus-preserving gastrectomy [PPG; n=313], and local resection [LR; n=85]) were enrolled in this study. The severity and characteristics of postgastrectomy syndrome were compared among the six gastrectomy procedures by the main outcome measures of PGSAS-45.

Research results

Postoperative QOL was greatly impaired in TGRY and PG, and was excellent in LR. After distal gastrectomy, diarrhea and dumping were less frequent in PPG, and there was no difference between DGBI and DGRY. The most noticeable adverse effects with significant differences among the gastrectomy procedures were meal-related distress SS, dissatisfaction at the meal, and weight loss.

Research conclusions

Postoperative QOL greatly differed depending on the site and extent of gastrectomy.

Research perspectives

To improve postgastrectomy QOL, it is important for surgeons to understand these matters to select the appropriate procedure, to improve the surgical technique to compensate for the

shortcomings of each procedure, and to enhance postoperative care by providing appropriate dietary guidance and detecting and addressing postgastrectomy syndromes at an early stage.

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Figure legends

Fig. 1 CONSORT flowchart of the PGSAS study

Fig. 2 General QOL scores after the six main gastrectomy procedures

Table 1. Structure of PGSAS-45

| Domains | Subdomains | Items | | | Subscales |
|----------|---------------------|-------|---------------------------------------|---------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| QOL | SF-8 (QOL) | 1 | Physical functioning* | five or six-point Likert scale | Physical component summary* (item 1-8) Mental component summary* (item 1-8) |
| | | 2 | Role physical* | | |
| | | 3 | Bodily pain* | | |
| | | 4 | General health* | | |
| | | 5 | Vitality* | | |
| | | 6 | Social functioning* | | |
| | | 7 | Role emotional* | | |
| | | 8 | Mental health* | | |
| Symptoms | GSRS (Symptoms) | 9 | Abdominal pains | seven-point Likert scale except item 29 and 32 | Esophageal reflux subscale (item 10, 11, 13, 24) Abdominal pain subscale (item 9, 12, 28) Meal-related distress subscale (item 25-27) Indigestion subscale (item 14-17) Diarrhea subscale (item 19, 20, 22) Constipation subscale (item 18, 21, 23) Dumping subscale (item 30, 31, 33) |
| | | 10 | Heartburn | | |
| | | 11 | Acid regurgitation | | |
| | | 12 | Sucking sensations in the epigastrium | | |
| | | 13 | Nausea and vomiting | | |
| | | 14 | Borborygmus | | |
| | | 15 | Abdominal distension | | |
| | | 16 | nausea and vomiting | | |
| | | 17 | Increased flatus | | |
| | | 18 | Decreased passage of stools | | |
| | | 19 | Increased passage of stools | | |
| | | 20 | Loose stools | | |
| | | 21 | Hard stools | | |
| | | 22 | Urgent need for defecation | | |
| | | 23 | Feeling of incomplete evacuation | | |
| | PGSAS (Symptoms) | 24 | Bile regurgitation | | Total symptom scale (above seven subscales) |
| | | 25 | Sense of foods sticking | | |
| | | 26 | Postprandial fullness | | |

| | | | | | |
|---------------|-----------------------|----|-------------------------------------------|-------------------------|------------------------------------------------------|
| | | 27 | Early satiation | | |
| | | 28 | Lower abdominal pains | | |
| | | 29 | Number and type of early dumping symptoms | | |
| | | 30 | Early dumping general symptoms | | |
| | | 31 | Early dumping abdominal symptoms | | |
| | | 32 | Number and type of late dumping symptoms | | |
| | | 33 | Late dumping symptoms | | |
| Living status | Meals (amount) 1 | 34 | Ingested amount of food per meal* | five-point Likert scale | - |
| | | 35 | Ingested amount of food per day* | | |
| | | 36 | Frequency of main meals | | |
| | | 37 | Frequency of additional meals | | |
| | Meals (quality) | 38 | Appetite* | | Quality of ingestion subscale* (item 38-40) |
| | | 39 | Hunger feeling* | | |
| | | 40 | Satiety feeling* | | |
| | Meals (amount) 2 | 41 | Necessity for additional meals | | - |
| | Social activity | 42 | Ability for working | | - |
| QOL | Dissatisfaction (QOL) | 43 | Dissatisfaction with symptoms | | Dissatisfaction for daily life subscale (item 43-45) |
| | | 44 | Dissatisfaction at the meal | | |
| | | 45 | Dissatisfaction at working | | |

In items or subscales with * ; higher score indicating better condition.

In items or subscales without * ; higher score indicating worse condition.

Each subscale is calculatec as the mean of composed items or subscales except physical component summary and mental component summary of SF-8.

Item 29 and 32 don't have score. Then, they were analyzed separately.

Table 2. Patients' background

| Types of gastrectomy | TGRY (n=393) | PG (n=193) | DGRY (n=475) | DGBI (n=909) | PPG (n=313) | LR (n=85) | Overall (n=2368) | P-value |
|---------------------------------------------------|----------------------------------------|----------------------------------------|---------------------------------------|-----------------------------------------|----------------------------------------|---------------------------------------|------------------|----------------------|
| Age (years)* | 63.4±9.2 ^a | 63.7±7.7 | 62.0±9.1 | 61.6±9.1 | 61.5±8.7 | 60.8±9.8 | 62.1±9.1 | |
| Sex: Male/Female (n) [Male, %] | 276/113 [71] | 139/53 [72] | 318/154 [67] | 594/311 [66] | 183/126 ^b [59] | 48/37 [56] | 1558/794 [66] | 0.003 ^c |
| Postoperative period (months)* | 35.0±24.6 | 40.5±28.1 | 31.7±18.0 ^a | 40.7±30.7 ^a | 38.4±27.7 | 42.9±34.2 | 37.7±27.4 | |
| Approach: Laparoscopic/Open (n) [Laparoscopic, %] | 97 ^b /293 ^b [25] | 33 ^b /159 ^b [17] | 152/320 [32] | 415 ^b /489 ^b [46] | 136/173 [44] | 52 ^b /33 ^b [61] | 885/1467 [38] | <0.0001 ^c |
| Celiac branch of vagus Saving/Cut (n) [Saving, %] | 12 ^b /371 ^b [3] | 83 ^b /105 ^b [44] | 28 ^b /442 ^b [6] | 133 ^b /754 ^b [15] | 213 ^b /87 ^b [71] | 84 ^b /0 ^b [100] | 553/1759 [24] | <0.0001 ^c |

* Mean±SD

a p<0.05 vs. overall mean (ANOM)

b p<0.05 vs. expected value (residual analysis)

c Chi-square test

TGRY: Total gastrectomy with Roux-en-Y reconstruction; PG: Proximal gastrectomy; DGRY: Distal gastrectomy with Roux-en-Y reconstruction;

DGBI: Distal gastrectomy with Billroth I reconstruction; PPG: Pylorus preserving gastrectomy; LR: Local resection of the stomach.

Table 3. Comparison of main outcome measures of PGSAS-45 among six types of gastrectomy using ANOM

| | Types of gastrectomy | TGRY (n=393) | PG (n=193) | DGRY (n=475) | DGBI (n=909) | PPG (n=313) | LR (n=85) | Overall (n=2368) | |
|---------------|------------------------------------------|--------------|--------------|--------------|--------------|-------------|-------------|------------------|---|
| Domain | Main outcome measures | Mean±SD | Mean±SD | Mean±SD | Mean±SD | Mean±SD | Mean±SD | Mean±SD | N |
| Symptoms | Esophageal reflux SS | 2.0±1.0† | 2.0±1.0† | 1.5±0.7* | 1.7±0.8 | 1.7±0.8 | 1.4±0.5* | 1.7±0.9 | 4 |
| | Abdominal pain SS | 1.8±0.8 | 1.7±0.7 | 1.7±0.8 | 1.7±0.7 | 1.6±0.7 | 1.5±0.6 | 1.7±0.8 | 0 |
| | Meal-related distress SS | 2.6±1.1† | 2.6±1.1† | 2.1±0.9* | 2.1±0.9* | 2.1±0.9 | 1.5±0.6* | 2.2±1.0 | 5 |
| | Indigestion SS | 2.3±0.9† | 2.2±0.8 | 2.0±0.8 | 2.0±0.8* | 2.0±0.9 | 1.5±0.6* | 2.0±0.9 | 3 |
| | Diarrhea SS | 2.3±1.2† | 2.0±1.0 | 2.1±1.1 | 2.1±1.1 | 1.8±1.0* | 1.5±0.8* | 2.1±1.1 | 3 |
| | Constipation SS | 2.1±0.9 | 2.3±1.1 | 2.1±1.0 | 2.2±1.0 | 2.2±1.1 | 1.9±0.9* | 2.2±1.0 | 1 |
| | Dumping SS | 2.2±1.1† | 2.0±1.0 | 2.0±1.0 | 2.0±1.0 | 1.8±0.9* | 1.3±0.4* | 2.0±1.0 | 3 |
| | Total symptom score | 2.2±0.7† | 2.1±0.7 | 1.9±0.7 | 2.0±0.7 | 1.9±0.7 | 1.5±0.4* | 2.0±0.7 | 2 |
| | Change in BW | -13.8%±7.9%† | -10.9%±8.2%† | -8.4%±6.6% | -7.9%±8.1* | -6.9%±7.0%* | -1.6%±5.7%* | -8.9%±8.0% | 5 |
| Living status | <u>Ingestion amount of food per meal</u> | 6.4±1.9† | 6.5±1.9† | 7.2±2.0 | 7.1±2.0 | 7.0±1.9 | 9.0±1.8* | 7.0±2.0 | 3 |
| | Necessity for additional meals | 2.4±0.8† | 2.0±0.8 | 1.9±0.8 | 1.9±0.8* | 1.8±0.8* | 1.4±0.6* | 1.9±0.8 | 4 |
| | <u>Quality of ingestion SS</u> | 3.8±1.0 | 3.6±1.0† | 3.8±0.9 | 3.8±0.9 | 3.8±0.9 | 4.0±0.8* | 3.8±0.9 | 2 |
| | Ability for working | 2.0±0.9† | 2.0±0.9 | 1.8±0.9 | 1.8±0.9* | 1.8±0.9 | 1.4±0.6* | 1.8±0.9 | 3 |
| | Dissatisfaction with symptoms | 2.1±1.0† | 2.0±0.9 | 1.8±0.9 | 1.8±0.9 | 1.8±0.9 | 1.2±0.4* | 1.8±0.9 | 2 |
| | Dissatisfaction at the meal | 2.8±1.1† | 2.7±1.1† | 2.2±1.1* | 2.2±1.1* | 2.2±1.1 | 1.3±0.6* | 2.3±1.1 | 5 |
| | Dissatisfaction at working | 2.1±1.1† | 2.0±1.1† | 1.7±1.0 | 1.7±0.9* | 1.7±0.9 | 1.1±0.4* | 1.8±1.0 | 4 |
| | Dissatisfaction for daily life SS | 2.3±0.9† | 2.2±0.9† | 1.9±0.9 | 1.9±0.8* | 1.9±0.8 | 1.2±0.4* | 2.0±0.9 | 4 |
| | <u>PCS of SF-8</u> | 49.6±5.6† | 49.5±6.1 | 50.8±5.6 | 50.5±5.5 | 51.1±5.3 | 52.4±3.8* | 50.5±5.6 | 2 |
| QOL | <u>MCS of SF-8</u> | 49.2±6.0 | 49.0±6.0 | 49.8±5.7 | 49.9±5.7 | 50.0±6.1 | 51.6±4.6* | 49.7±5.8 | 1 |

* p<0.05; better than overall mean (ANOM)

† p<0.05; worse than overall mean (ANOM)

In items or subscales with underline, higher score indicates better condition

In items or subscales without underline, higher score indicates worse condition

N: the number of the type of gastrectomy mean differ from the overall mean

TGRY: Total gastrectomy with Roux-en-Y reconstruction; PG: Proximal gastrectomy; DGRY: Distal gastrectomy with Roux-en-Y reconstruction;

DGBI: Distal gastrectomy with Billroth I reconstruction; PPG: Pylorus preserving gastrectomy; LR: Local resection of the stomach.

Table 4. The percentage and point against overall mean of the main outcome measures of PGSAS-45 among six types of gastrectomy

| | Types of gastrectomy | TGRY | | PG | | DGRY | | DGBI | | PPG | | LR | | Overall |
|---------------|------------------------------------------|----------------|---------------------|----------------|---------------------|----------------|---------------------|----------------|---------------------|----------------|---------------------|----------------|---------------------|----------------|
| Domain | Main outcome measures | % ^a | points ^b | % ^a | points ^b | % ^a | points ^b | % ^a | points ^b | % ^a | points ^b | % ^a | points ^b | % ^a |
| Symptoms | Esophageal reflux SS | 115.5% | -3 | 116.4% | -3 | 86.6% | 2 | 99.1% | 0 | 99.1% | 0 | 79.6% | 4 | 100% |
| | Abdominal pain SS | 105.0% | -1 | 99.5% | 0 | 98.9% | 0 | 100.5% | 0 | 97.7% | 0 | 87.6% | 2 | 100% |
| | Meal-related distress SS | 120.8% | -4 | 120.2% | -4 | 95.2% | 0 | 93.7% | 1 | 96.3% | 0 | 67.3% | 6 | 100% |
| | Indigestion SS | 112.0% | -2 | 105.5% | -1 | 99.8% | 0 | 97.0% | 0 | 98.0% | 0 | 72.5% | 5 | 100% |
| | Diarrhea SS | 110.4% | -2 | 94.9% | 1 | 99.9% | 0 | 102.8% | 0 | 89.3% | 2 | 73.6% | 5 | 100% |
| | Constipation SS | 96.2% | 0 | 105.9% | -1 | 97.2% | 0 | 102.2% | 0 | 103.0% | 0 | 85.6% | 2 | 100% |
| | Dumping SS | 116.3% | -3 | 103.3% | 0 | 99.5% | 0 | 99.4% | 0 | 88.6% | 2 | 64.2% | 7 | 100% |
| | Total symptom score | 111.0% | -2 | 105.8% | -1 | 97.2% | 0 | 99.4% | 0 | 95.6% | 0 | 74.4% | 5 | 100% |
| Living status | <u>Change in BW</u> | 153.1% | -10 | 121.8% | -4 | 99.4% | 0 | 88.2% | 2 | 76.6% | 4 | 18.1% | 16 | 100% |
| | <u>Ingestion amount of food per meal</u> | 91.4% | -1 | 92.2% | -1 | 102.9% | 0 | 101.3% | 0 | 99.8% | 0 | 127.6% | 5 | 100% |
| | Necessity for additional meals | 121.6% | -4 | 105.3% | -1 | 98.3% | 0 | 96.3% | 0 | 90.7% | 1 | 73.3% | 5 | 100% |
| | <u>Quality of ingestion SS</u> | 99.8% | 0 | 94.7% | -1 | 99.8% | 0 | 100.7% | 0 | 99.8% | 0 | 107.1% | 1 | 100% |
| | Ability for working | 112.3% | -2 | 107.5% | -1 | 100.5% | 0 | 96.2% | 0 | 97.2% | 0 | 77.4% | 4 | 100% |
| | Dissatisfaction with symptoms | 112.7% | -2 | 108.8% | -1 | 97.8% | 0 | 98.1% | 0 | 97.2% | 0 | 64.9% | 7 | 100% |
| QOL | Dissatisfaction at the meal | 122.2% | -4 | 116.6% | -3 | 94.6% | 1 | 95.0% | 1 | 96.9% | 0 | 54.7% | 9 | 100% |
| | Dissatisfaction at working | 121.1% | -4 | 115.2% | -3 | 97.2% | 0 | 94.7% | 1 | 94.2% | 1 | 62.5% | 7 | 100% |
| | Dissatisfaction for daily life SS | 118.9% | -3 | 113.6% | -2 | 96.4% | 0 | 95.9% | 0 | 96.1% | 0 | 60.2% | 7 | 100% |
| | <u>PCS of SF-8</u> | 98.3% | 0 | 98.1% | 0 | 100.6% | 0 | 100.1% | 0 | 101.1% | 0 | 103.9% | 0 | 100% |
| | <u>MCS of SF-8</u> | 98.8% | 0 | 98.5% | 0 | 100.2% | 0 | 100.2% | 0 | 100.5% | 0 | 103.6% | 0 | 100% |
| | QOL scores (Total poins) | | -47 | | -26 | | 3 | | 5 | | 10 | | 97 | |
| | | | | | | | | | | | | | | |

In items or subscales with underline, higher score indicates better condition

In items or subscales without underline, higher score indicates worse condition

a; % to the overall mean

b; if the QOL is better more than 5% compared to the overall mean, +1 point is given for every 5%

if the QOL is worse less than 5% compared to the overall mean, -1 point is given for every 5%

TGRY: Total gastrectomy with Roux-en-Y reconstruction; PG: Proximal gastrectomy; DGRY: Distal gastrectomy with Roux-en-Y reconstruction;

DGBI: Distal gastrectomy with Billroth I reconstruction; PPG: Pylorus preserving gastrectomy; LR: Local resection of the stomach.

Fig. 1 CONSORT flowchart of the PGSAS

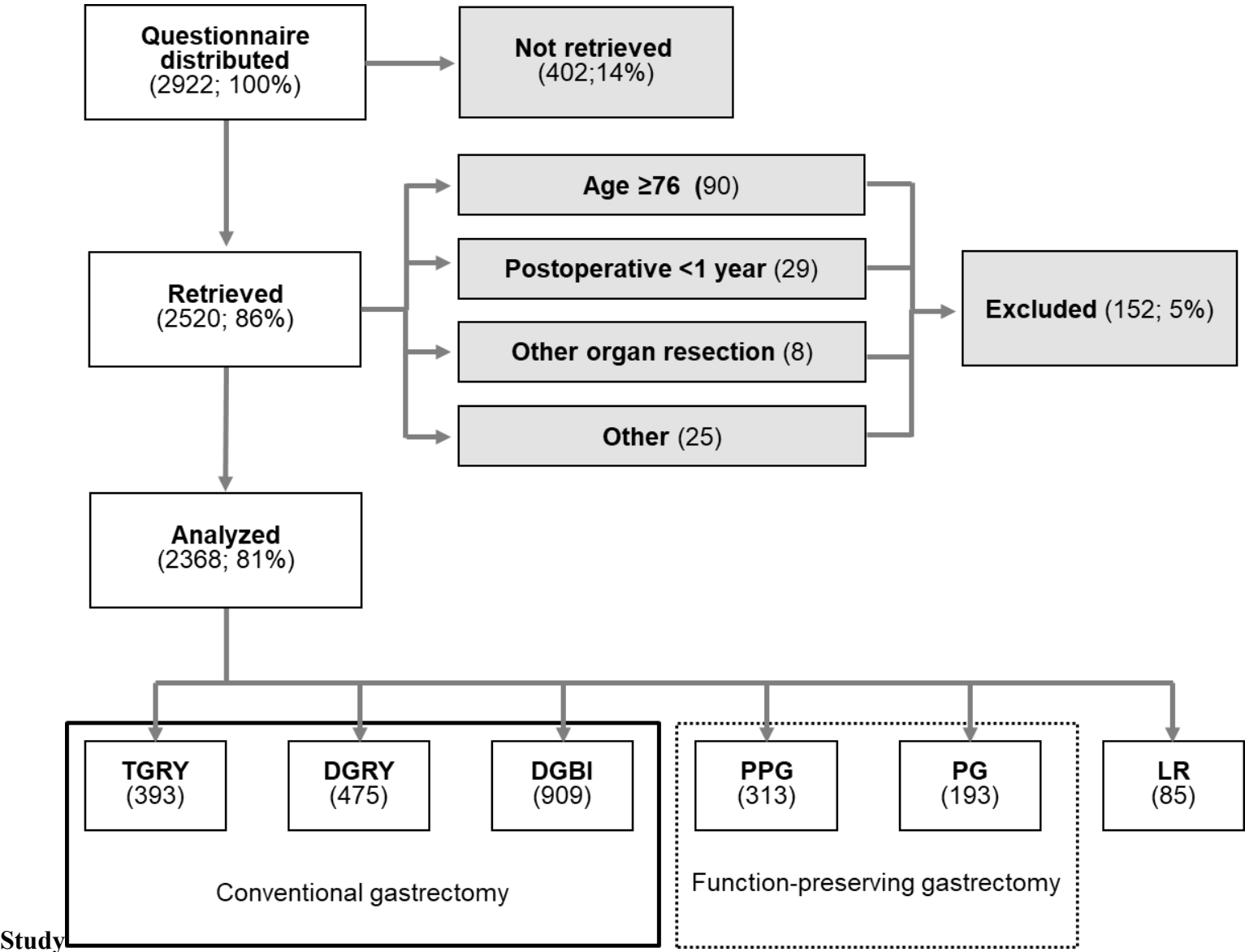


Fig. 2 General QOL scores after the six main gastrectomy procedures

