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Long-term survival prognosis of function-preserving curative gastrectomy for early gastric cancer

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Abstract. Segmental gastrectomy, mini-distal gastrectomy and local resection of the stomach are function-preserving curative gastrectomies (FPGs), which are used to treat gastric cancer in specialized centers. These surgical options are less invasive and can alleviate postgastrectomy symptoms more than standard gastrectomy; however, their association with prognosis remains to be fully elucidated. The present study aimed to compare the survival prognosis of patients diagnosed as node-negative by sentinel node biopsy (SNB) treated via FPG with reduced lymph node dissection with that of patients who underwent guideline gastrectomy (GL). This retrospective study was conducted between April 1999 and March 2016. The inclusion criteria were a diagnosis of gastric cancer type 0, of ≤5 cm, located in L or M areas, and pT1N0. Patients who underwent distal gastrectomy and pylorus-preserving gastrectomy were included as controls in the GL group. Among the 146 and 300 patients in the FPG and GL groups, respectively, only 1 patient in the GL group experienced recurrence. The overall survival (OS) of the FPG group was 96.6% at 5 years and 92.5% at 10 years, which was significantly higher than that of the GL group (P<0.05). In addition, the cumulative incidence of non-cancer-related deaths, especially pulmonary diseases, was lower in the FPG group than that in the GL group (P<0.05). Notably, the OS and non-cancer death rate in the FPG group remained significantly better after propensity score-matching analysis. In conclusion, for early gastric cancer located in M or L areas, patients treated via FPG guided by SNB have a better prognosis and fewer deaths caused by respiratory disease than those treated via GL. The present clinical trial was registered under the following trial registration numbers: UMIN000010154 (2013/3/4), UMIN000023828 (2016/8/29), jRCTs041180006 (2018/10/9).

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Key words: early gastric cancer, sentinel node biopsy, function-preserving gastrectomy, reconstruction, aspiration pneumonia

Introduction

Gastrectomy with prophylactic lymph node dissection is the standard treatment for early gastric cancer, which is not suitable for endoscopic submucosal dissection (ESD) (1,2). The Japanese gastric cancer treatment guidelines recommend wide-area gastrectomy with nodal dissection up to D1+ (3). The results of this treatment strategy are effective; the 5-year disease-specific survival rate for this procedure is reported to be 97.8%, according to the nationwide registry of the Japan Gastric Cancer Society (4). For gastric cancer occupying the distal two-thirds of the stomach, guidelines for gastrectomy recommend distal partial gastrectomy or pylorus-preserving gastrectomy (PPG). However, unlike ESD, which preserves most of the stomach, guideline gastrectomy (GL) has various disadvantages for patients. Dietary intake is reduced, and various postgastrectomy symptoms occur, followed by weight loss and worsening nutritional status (1,5-8). Additionally, abnormal bowel movement, and diseases such as reflux esophagitis, bone metabolism disorder, anemia and remnant gastric cancer may occur (5). These disadvantages impair the postoperative quality of life of patients and may worsen their prognosis. In older patients, death caused by gastric cancer after GL is uncommon, but overall survival (OS) is not good (4), which suggests that it may be associated with fatalities other than gastric cancer death.

Function-preserving curative gastrectomy (FPG) has been reported to be an alternative to GL to prevent postgastrectomy symptoms, weight loss and malnutrition (1). For gastric cancer occupying the distal two-thirds of the stomach, segmental gastrectomy (SG) and local resection (LR) are FPGs that may be performed (1). FPGs are reported to be less invasive, to prevent malnutrition and to alleviate postgastrectomy symptoms more than GL (9-12). Therefore, FPGs may improve OS; however, to the best of our knowledge, no research has been done on the prognosis after FPG.

For several decades, we have investigated the role of sentinel lymph node biopsy (SNB) in gastric cancer (13-15). Based on the excellent diagnostic ability of SNB, we applied FPG with reduced lymph node dissection in patients diagnosed as node-negative by SNB during surgery (13). The present study aimed to compare the prognosis of patients who underwent FPG with that of patients who underwent GL.

Materials and methods

Patients. This retrospective cohort study investigated the prognosis of patients treated with FPG guided by SNB, which was conducted between April 1999 and March 2016 by the first author (SK). The inclusion criteria for the FPG group were as follows: Age, >20 or <85 years; American Society of Anesthesiologists physical status (ASA-PS) 1-2 (16); tolerated general anesthesia and gastrectomy; superficial type (type 0); long axis, ≤5 cm at preoperative diagnosis; tumor was localized to the L or M areas; FPG was applied with a node-negative intraoperative diagnosis by SNB; T1N0 at final pathological diagnosis; and reliable medical records. The FPG group underwent SG, LR or mini-distal gastrectomy (MDG). Patients were excluded if they had non-early-stage cancer in other organs at the time of surgery, severe comorbidities, Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≥3 (17), or if they underwent FPG without SNB. In addition, the patients from April 1999 to September 2008 were treated at the Department of Surgery II, Kanazawa University Hospital (Kanazawa, Japan), and the patients from October 2009 to March 2016 were treated at the Department of Surgical Oncology, Kanazawa Medical University Hospital (Kahoku, Japan). Notably, the Department of Surgery II is the old facility name of the Department of Gastrointestinal Surgery.

As a control group, data were collected from patients who underwent distal partial gastrectomy (DG) or PPG performed at the same hospitals between April 1999 and March 2016; this group was designated as the GL group. The inclusion criteria were as follows: Age, >20 or <85 years; ASA-PS 1-2; tolerated general anesthesia and gastrectomy; type 0; long axis, ≤5 cm; localized to the L or M areas; pT1N0. The exclusion criteria were as follows: Non-early-stage cancer in other organs at the time of surgery, severe comorbidities, ECOG-PS ≥3. These criteria were the same as those used for the FPG group. In the present study, DG was defined as gastrectomy of 2/3 or more of the distal side, including the pylorus, according to the Japanese Gastric Cancer Treatment Guidelines (3). Patients with an antral cuff length ≤3 cm were selected for PPG.

Surgical procedures. At both Kanazawa University Hospital and Kanazawa Medical University Hospital, gastrectomies were performed by a limited number of specialized surgeons with the same treatment strategy and equivalent surgical skill. The lead surgeon determined the decision to use SNB in the treatment of the patients. SNB was primarily applied in patients for whom SK was the primary surgeon, and guideline-based standard gastrectomy without mapping was mainly applied to patients when other surgeons were in charge.

At Kanazawa University Hospital, SN mapping utilized a dye method with blue dye, a radioisotope (RI) method with a RI colloid, and a combination of the dye and RI methods. The tracers used were as follows: Patent Blue or Lymphazurin were used as the blue dye, and 99mTc-tin colloid or 99mTc-phytate were used as the RI colloid. The tracers were administered endoscopically to the submucosal layers at four sites around the tumor. Lymphatics stained with the dye 20 min after intraoperative administration were defined as lymphatic basins, and blue nodes and hot nodes were defined as sentinel lymph nodes. At the Kanazawa Medical University Hospital, the indocyanine green (ICG) fluorescence method was performed. ICG was adjusted to 50 μg/ml (1:100) and administered (0.5 ml) into the submucosa at four sites around the tumor endoscopically on the day before surgery. ICG fluorescence was observed using Photodynamic Eye (Hamamatsu Photonics) during surgery, and the lymphatic system stained with fluorescence was regarded as the lymphatic basin. Lymph nodes with strong fluorescence were regarded as sentinel nodes.

In the present study, the SNB method adopted for all patients was the lymphatic basin dissection method. After *en bloc* dissection of the lymphatic basin, sentinel nodes were harvested at the back table and sent for rapid frozen diagnosis. In cases diagnosed as negative for metastasis by SNB during surgery, FPG was applied, in which lymph node dissection out of the basin was omitted, and the resection area of the stomach was reduced according to the blood supply in each case. Fig. 1 shows a schematic diagram of the three procedures: SG, in which an antral cuff longer than 3 cm was preserved; LR, in which a small lesion of the gastric wall was excised by full-thickness resection and closed with sutures; and MDG, in which the resected area of the stomach, including the pylorus, was <1/2 (1,13). Details regarding SNB and FPG have been discussed in other articles (13-15).

Prognostic surveys. Prognostic information, including survival or death, cause of death, presence or absence of recurrence, and the presence or absence of metachronous multiple gastric cancer (MMGC), was investigated in 2013 for patients at Kanazawa University Hospital and in 2022 for patients at Kanazawa Medical University Hospital. Therefore, except for a few censored patients, the majority were investigated for a time frame spanning >5 years. The causes of death were classified as death due to gastric cancer (recurrence), death from other types of cancer, and death from other diseases. Cancer of the remnant stomach was differentiated between local recurrence and MMGC; the latter was not treated as recurrent gastric cancer. The present study treated OS as all-cause mortality and cancer-specific survival was used to treat gastric cancer death as an event.

All descriptions were made in accordance with the 15th edition of the Japanese Classification of Gastric Carcinoma (JCGC) (18). The diagnosis of lymph node metastasis was determined microscopically using the maximum section of the permanent specimen with hematoxylin and eosin staining (19). As tumor cells were determined to be metastatic regardless of the size of the metastatic focus, isolated tumor cells and micrometastasis were also defined as metastases.

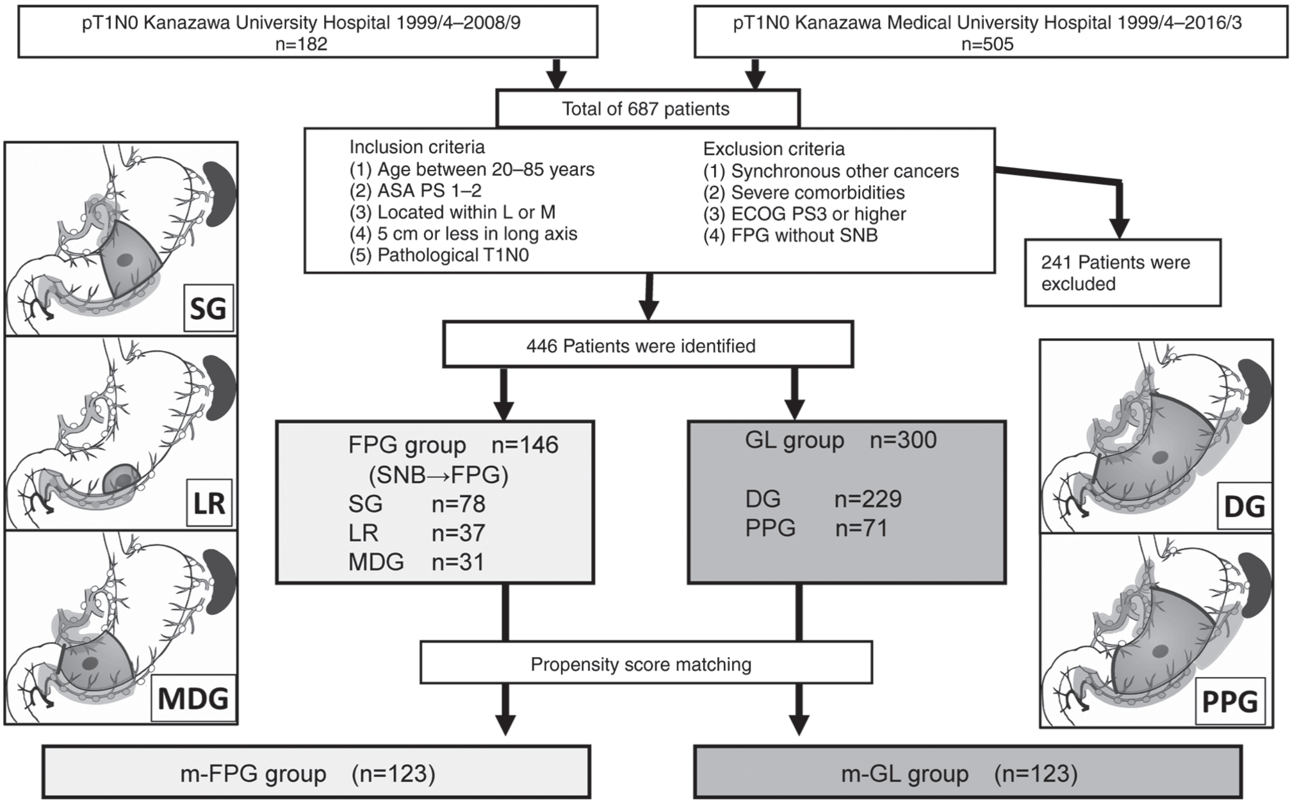

Figure 1. Flow diagram of patient enrollment, schematic diagram of the study procedure and summary of enrolled patients. The FPG group comprised patients who underwent FPG guided by SNB, and the GL group comprised patients who underwent GL with standard lymph node dissection. ASA-PS, American Society of Anesthesiologists physical status; ECOG, Eastern Cooperative Oncology Group; FPG, function-preserving curative gastrectomy; SNB, sentinel node biopsy; SG, segmental gastrectomy; LR, local resection; MDG, mini-distal gastrectomy; GL, guideline gastrectomy; DG, distal gastrectomy; PPG, pylorus-preserving gastrectomy; m-FPG, propensity score-matched function-preserving curative gastrectomy; m-GL, propensity score-matched guideline gastrectomy.

In addition to age, sex and clinicopathological factors, preoperative body mass index (BMI), serum albumin level and ASA-PS were examined and compared as background factors between the two groups. Serum albumin level and body weight in the first postoperative year were further extracted from the medical records, and the change from the preoperative values was compared between the two groups.

Statistical analysis. The statistical examination was performed using the same method as in our previous article, which examined the prognostic effect of SNB (13). All statistical analyses were performed using EZR version 1.55 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (20). All statistical methods were reviewed by a biostatistician (YI). For background comparisons, age, BMI, serum albumin level and long axis were compared using the Mann-Whitney U test because they were not normally distributed, whereas the other factors were compared using the χ^2 test or Fisher's exact test. OS and survival curves were constructed using the Kaplan-Meier method and were compared using the log-rank test. Multivariate analysis was performed using Cox proportional hazards regression with stepwise variable selection. The Gray test was applied to compare the cumulative incidence, and the Fine-Gray proportional hazard regression was used for multivariate analysis. Propensity scores were calculated using logistic regression analysis with age, sex, BMI, serum albumin level, ASA-PS, location, circumference, macroscopic type, long axis, clinical T status, operation period, surgical approach (open or laparoscopic), pathological T status and pathological diagnosis as variables. The nearest neighbor matching method with greedy matching and one-to-one matching with non-restorative extraction were applied to adjust for the covariates and estimate the causal effects. The caliper of the propensity score was calculated by multiplying the standard deviation of the recommended propensity score estimated value by 0.2, after logit conversion. Balance was evaluated using standardized difference scores. Fisher's exact test was used to analyze the differences in cause of death between the two groups. Welch's two-sample t-test was applied to compare body weight loss and changes in serum albumin level as the F-test proved heteroscedasticity. P<0.05 was considered to indicate a statistically significant difference.

Results

Patient characteristics. A total of 146 and 300 patients were included in the FPG and GL groups, respectively (Fig. 1). Details regarding both of these groups are presented in Table I. Statistical differences were observed between the two groups regarding their background factors, such as location, operation period, surgical approach (conventional open surgery or laparoscopic gastrectomy), and pathological diagnosis. The

Table I. Patient characteristics.

Characteristic	FPG group (n=146)	GL group (n=300)	P-value
Median age, years (range)	65 (28-84)	66 (29-85)	0.139
Sex, male/female	98/48	193/107	0.597
Median BMI, kg/m^2 (range)	23.1 (17.2-34.2)	23.2 (16.0-34.2)	0.721
Median serum albumin, g/dl (range)	4.2 (2.9-5.0)	4.2 (2.9-5.0)	0.895
ASA-PS, 1/2	48/98	102/198	0.832
Location, M/L	99/47	159/141	0.003
Circumference, Less/Ant/Gre/Post	59/24/37/26	149/52/54/45	0.175
Macroscopic type, elevated/depressed	37/109	62/238	0.276
Median long axis, mm (range)	20 (2-50)	21 (4-50)	0.078
Clinical T status, 1a/1b/2	75/60/11	138/140/22	0.521
Operation period, 1999-2008/2008+	124/22	211/89	0.001
Surgical approach, open/laparoscopic	100/46	238/62	0.014
Pathological T status, 1a/1b	93/53	196/104	0.752
Pathological diagnosis, DF/UDF	81/65	205/95	0.009
Surgical procedure			
DG/PPG		229/71	
MDG/SG/LR	31/78/37		
Degree of nodal dissection, D0 or D1/D1+ or D2	146/0	143/157	
Gastric cancer recurrence	0	1	

FPG, function-preserving curative gastrectomy; GL, guideline gastrectomy; BMI, body mass index; ASA-PS, American Society of Anesthesiologists physical status; DF, differentiated type; UDF, undifferentiated type; DG, distal gastrectomy; PPG, pylorus-preserving gastrectomy; MDG, mini-distal gastrectomy; SG, segmental gastrectomy; LR, local resection.

FPG group included 31 patients that underwent MDG, 78 that underwent SG and 37 that underwent LR. The resection sites of the LR were the lesser curvature in 14 patients, greater curvature in 13, anterior wall in 4, and posterior wall in 6. The SNB method included the blue dye method in 29, the RI method in 2, combination mapping in 93, and the ICG fluorescence method in 22 patients. The GL group included 229 patients that underwent DG and 71 patients that underwent PPG. All 446 patients were pathologically node-negative, and all 146 patients that underwent FPG were intraoperatively diagnosed as node-negative using SNB.

OS and cumulative incidence of non-cancer deaths. Among the cases, only 1 patient in the GL group exhibited recurrence of gastric cancer. This patient was a 61-year-old man at the time of surgery, L Less 0 IIc 20 mm pT1b(sm)N0M0 by JCGC, underwent an open DG with D2 and Billroth I reconstruction, and the pathological results were tub2 sm2 INFβ ly0 v0 n0 PM0 DM0. The patient was followed up without adjuvant chemotherapy; however, pulmonary metastases recurred, eventually resulting in death due to gastric cancer 35 months after resection. Therefore, cancer-specific survival for the 446 patients was 98.4% at both 5 and 10 years. The OS for the 446 patients was 93.0% at 5 years and 83.5% at 10 years.

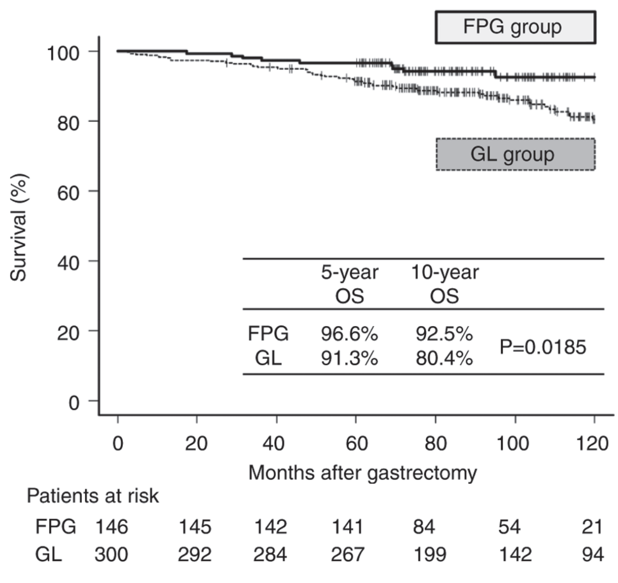

Figure 2. Comparison of OS between the FPG and GL groups. The OS of the FPG group was significantly better than that of the GL group. OS, overall survival; FPG, function-preserving curative gastrectomy; GL, guideline gastrectomy.

The OS curves of the FPG and GL groups are shown in Fig. 2. The prognosis in the FPG group was significantly better than that in the GL group. Table II shows the results of univariate and multivariate analyses of the effect of each factor on OS. OS was favorable in female patients, those aged ≤65 years, not underweight, with normal albumin levels, depressed type tumors, and patients who underwent FPG. The cause of death was examined based on cumulative incidence. Fig. 3 shows the cumulative incidence of non-cancer deaths (other diseases), other types of cancer and recurrence.

Table II. Univariate and multivariate analysis of factors influencing overall survival.

Factor	Univariate analysis (log-rank P-value)	Multivariate analysis		
		Hazard ratio	95% CI	P-value
Age (≤65 vs. >65 years)	<0.0001	3.896	2.026-7.491	<0.0001
Sex (female vs. male)	0.019	2.219	1.143-4.408	0.0185
BMI (<18.5 vs. ≥18.5 kg/m^2)	0.0276	0.296	0.132-0.665	0.0032
Serum albumin (<3.8 vs. ≥3.8 g/dl)	0.0003	0.420	0.233-0.758	0.0039
ASA-PS (1 vs. 2)	0.003			
Location (L vs. M)	0.297			
Circumference (Less vs. AntGrePost)	0.134			
Macroscopic type (dep vs. elev)	0.0004	2.217	1.284-3.830	0.0043
Long axis (≤20 vs. >20 mm)	0.968			
Clinical T status (1a vs. 1b or 2)	0.827			
Operation period (1999-2008 vs. 2008+)	0.399			
Surgical approach (open vs. laparo)	0.01			
Pathological T status (1a vs. 1b)	0.033			
Pathological diagnosis (DF vs. UDF)	0.0060			
Group (GL vs. FPG)	0.0185	0.436	0.212-0.898	0.0243

CI, confidence interval; BMI, body mass index; ASA-PS, American Society of Anesthesiologists physical status; dep, depressed; elev, elevated; laparo, laparoscopic; DF, differentiated type; UDF, undifferentiated type; FPG, function-preserving curative gastrectomy; GL, guideline gastrectomy.

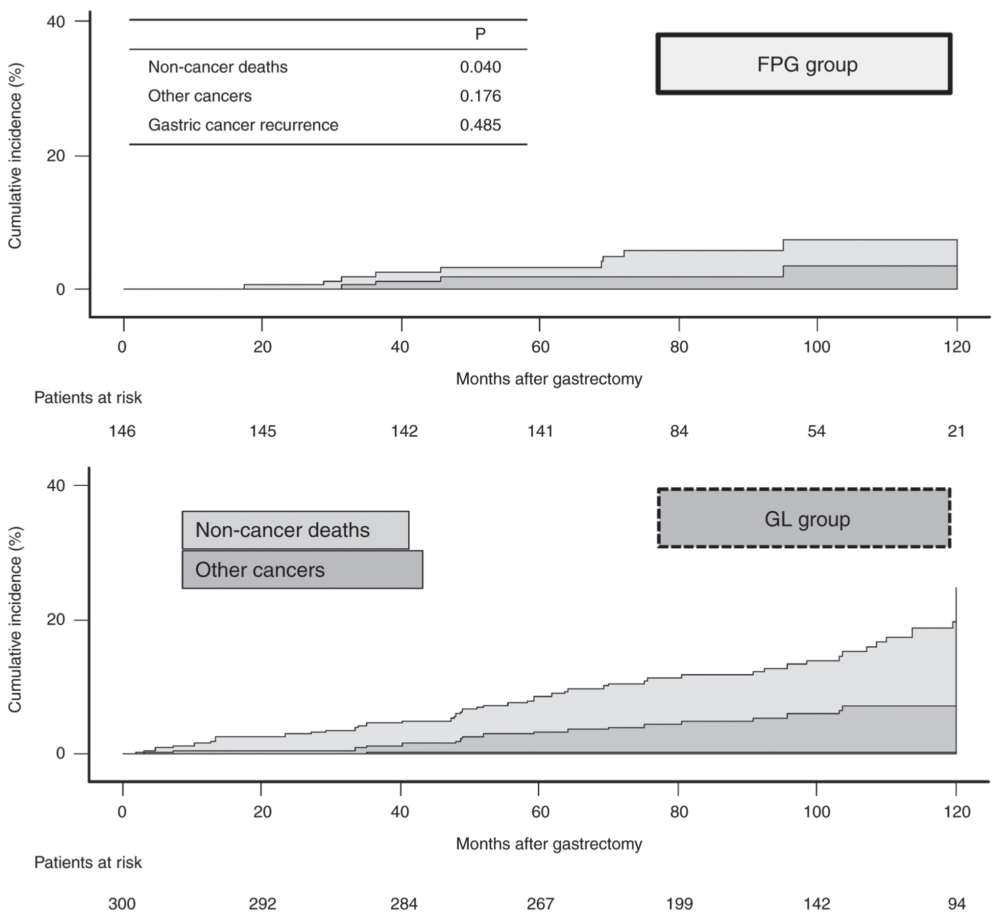

Figure 3. Comparison of cumulative incidence curves of gastric cancer recurrence, other cancers and non-cancer deaths between the FPG and GL groups. The cumulative incidence of non-cancer-related deaths in the FPG group was significantly higher than that in the GL group. FPG, function-preserving curative gastrectomy; GL, guideline gastrectomy.

Table III. Multivariate analysis of factors affecting the cumulative incidence of causes of death or recurrence.

	Non-cancer deaths			Other cancers		
Factor	HR	95% CI	P-value	HR	95% CI	P-value
Age (≤65 vs. >65 years)	1.890	0.810-4.409	0.140	4.393	1.621-11.90	0.004
Sex (female vs. male)	3.272	1.338-8.005	0.009	1.704	0.599-4.851	0.320
BMI (<18.5 vs. ≥18.5 kg/m^2)	0.228	0.072-0.728	0.012	0.365	0.098-1.360	0.130
Serum albumin (<3.8 vs. ≥3.8 g/dl)	0.296	0.151-0.579	0.0004	0.703	0.225-2.202	0.550
ASA-PS (1 vs. 2)	3.635	1.069-12.35	0.039	0.754	0.243-2.341	0.630
Macroscopic type (dep vs. elev)	1.629	0.817-3.248	0.170	2.413	1.050-5.548	0.038
Long axis (≤20 vs. >20 mm)	0.781	0.383-1.596	0.500	0.844	0.351-2.029	0.700
Operation period (1999-2008 vs. 2008+)	1.665	0.591-4.686	0.330	0.731	0.230-2.322	0.600
Surgical approach (open vs. laparo)	0.244	0.055-1.079	0.063	0.596	0.154-2.307	0.450
Pathological T status (1a vs. 1b)	1.629	0.817-3.248	0.170	0.630	0.232-1.711	0.360
Pathological diagnosis (DF vs. UDF)	1.608	0.641-4.031	0.310	0.516	0.134-1.987	0.340
Group (GL vs. FPG)	0.365	0.145-0.921	0.033	0.565	0.189-1.688	0.310

Gastric cancer death was untestable because there was only 1 patient with recurrence in the GL group. HR, hazard ratio; CI, confidence interval; BMI, body mass index; ASA-PS, American Society of Anesthesiologists physical status; dep, depressed; elev, elevated; laparo, laparoscopic; DF, differentiated; UDF, undifferentiated type; GL, guideline; FPG, function-preserving curative gastrectomy.

The cumulative incidence of non-cancer deaths was lower in the FPG group than that in the GL group, and a significant difference was also observed. Table III shows the results of the multivariate analysis using the Fine-Gray proportional hazards regression analysis. Gastric cancer death was untestable because there was only 1 patient with recurrence in the GL group. Non-cancer deaths were worse among male patients, those with a lower weight, low albumin level and ASA-PS 2, and those in the GL group; moreover, deaths due to other types of cancer were poor among the older patients and those with elevated macroscopic type tumors.

Propensity score matching (PSM) analysis. Several background factors influenced OS and cumulative mortality; therefore, PSM was applied to eliminate these factors. After PSM, 123 patients were included in both groups. The profiles of both groups are shown in Table IV, and the backgrounds of both groups were uniform after PSM.

OS analysis after PSM is shown in Fig. 4. OS in the matched (m)-FPG group remained significantly better than that in the m-GL group. Cumulative mortality analysis after PSM is shown in Fig. 5. The cumulative mortality from non-cancer deaths in the m-FPG group remained significantly better than that in the m-GL group.

Details of the cause of non-cancer deaths. Table V lists the possible causes of non-cancer deaths. These causes of death were classified into cardiovascular disease, cerebrovascular disease, respiratory disease, accident and others. Accidents included 2 falling accidents, 1 traffic accident and 1 case of asphyxia. A total of 8 patients died due to other causes: 1 patient in the FPG group and 1 in the GL group died due to unknown causes; renal failure (2 patients), esophageal rupture, systemic lupus erythematosus, spondylitis and old age (1 patient each) were the cause of death in the remaining patients. When comparing the FPG and GL groups, 9 patients in the GL group died of respiratory disease, whereas no patient died of pneumonia in the FPG group, indicating a significant difference. The incidence of respiratory disease also tended to be lower in the m-FPG group than in the m-GL group. Table VI provides a detailed profile of the 9 patients in the GL group who died of respiratory disease. The causes of death included 1 case of exacerbation of chronic obstructive pulmonary disease (COPD); however, most cases were of aspiration pneumonia secondary to reflux esophagitis or vomiting. All patients were post-DG; the reconstruction methods used were Billroth I in 5, Roux-en Y in 3, and Billroth II in 1 patient. This cohort of 9 cases included two with COPD, while the remaining 7 had no history of respiratory complications. The number of patients with preoperative respiratory comorbidities, such as a history of COPD, asthma or pneumonia was 6 (4.1%) in the FPG group and 10 (3.3%) in the GL group.

Body weight and serum albumin levels after 1 year. To compare the postoperative nutritional status between the two groups, the serum albumin levels and body weight of patients were examined 1 year after surgery; the changes from the preoperative values are shown in Table VII. Unfortunately, some outpatient medical records were lost, and data were available for only 75 patients in the FPG group and 229 patients in the GL group. Weight loss averaged 7.6% in the GL group compared with only 2.6% in the FPG group. Conversely, serum albumin levels were nearly restored to preoperative levels in both groups.

MMGC in the remnant stomach. MMGC was distinguished from local recurrence of primary gastric cancer in the present study. None of the patients were diagnosed with local recurrence in the present study; by contrast, 3 patients in the FPG group and 7 in the GL group developed MMGC (Fig. 6). The

Table IV. Patient characteristics after propensity score matching.

Characteristic	m-FPG group (n=123)	m-GL group (n=123)	P-value
Median age, years (range)	65 (28-84)	65 (29-85)	0.350
Sex (male/female)	83/40	82/41	1.000
Median BMI, kg/m^2 (range)	22.9 (17.2-32.5)	23.1 (16.3-32.5)	0.757
Median serum albumin, g/dl (range)	4.1 (2.9-5.0)	4.2 (2.9-4.8)	0.821
ASA-PS, 1/2	38/85	43/80	0.587
Location, M/L	80/43	74/49	0.510
Circumference, Less/Ant/Gre/Post	53/23/25/22	48/22/31/22	0.836
Macroscopic type, elevated/depressed	30/93	28/95	0.881
Median long axis, mm (range)	20 (2-50)	20 (4-50)	0.898
Clinical T status, 1a/1b/2	58/55/10	57/59/6	0.614
Operation period, 1999-2008/2008+	101/22	100/23	1.000
Surgical approach, open/laparoscopic	99/24	95/28	0.881
Pathological T status, 1a/1b	78/45	69/54	0.298
Pathological diagnosis, DF/UDF	75/48	74/49	1.000
Surgical procedure			
DG/PPG		93/30	
MDG/SG/LR	30/61/32		
Degree of nodal dissection, D0 or D1/D1+ or D2	123:0	65:58	
Gastric cancer recurrence	0	0	

m-FPG, matched function-preserving curative gastrectomy; m-GL, matched guideline gastrectomy; BMI, body mass index; ASA-PS, American Society of Anesthesiologists physical status; DF, differentiated type; UDF, undifferentiated type; DG, distal gastrectomy; PPG, pylorus-preserving gastrectomy; MDG, mini-distal gastrectomy; SG, segmental gastrectomy; LR, local resection.

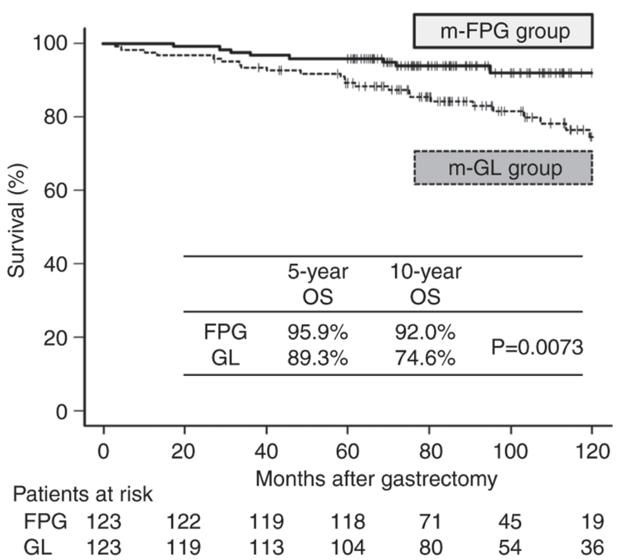

Figure 4. Comparison of OS between the FPG and GL groups after propensity score matching. The OS in the FPG group was significantly better than that in the GL group after propensity score matching. OS, overall survival; m-FPG, propensity score-matched function-preserving curative gastrectomy; m-GL, propensity score-matched guideline gastrectomy.

10-year cumulative incidence of MMGC was 2.1% in the FPG group and 2.4% in the GL group, with no significant difference between the groups. A total of 3 patients in the FPG group and 5 in the GL group underwent ESD, whereas 2 patients in the GL group underwent gastrectomy. No recurrence of MMGC was observed in these 10 patients.

Discussion

The present study showed that for patients with pT1N0 gastric cancer ≤5 cm in size, located in the M or L regions, and with no indications for ESD, FPG had a better prognosis and lower mortality due to respiratory disease than GL. The Japanese gastric cancer treatment guidelines introduced LR and SG as limited surgeries and defined them as investigational procedures, as they require a reduction in lymph node dissection (1,3). Limited facilities perform these procedures, and, to the best of our knowledge, there has been no research on their association with prognosis, especially in young people with fewer comorbidities. To the best of our knowledge, the present study is the first to directly compare the long-term prognosis, including the presence of other types of cancer and the occurrence of non-cancer deaths, following FPG with GL surgeries.

Patients in the FPG group underwent reduction in lymph node dissection guided by SNB. In the FPG group, no patients with false-negative SNBs were included and there was no recurrence of gastric cancer. This was a retrospective study that selected pT1N0 tumors, and the results of SNB could not be evaluated in this study. The details of our SNB results are presented in another study, with a sensitivity of 84% and an accuracy rate of 98.6% (13). Gastric cancer is the most common type of gastrointestinal carcinoma for which SNB has been attempted (1). The feasibility of the

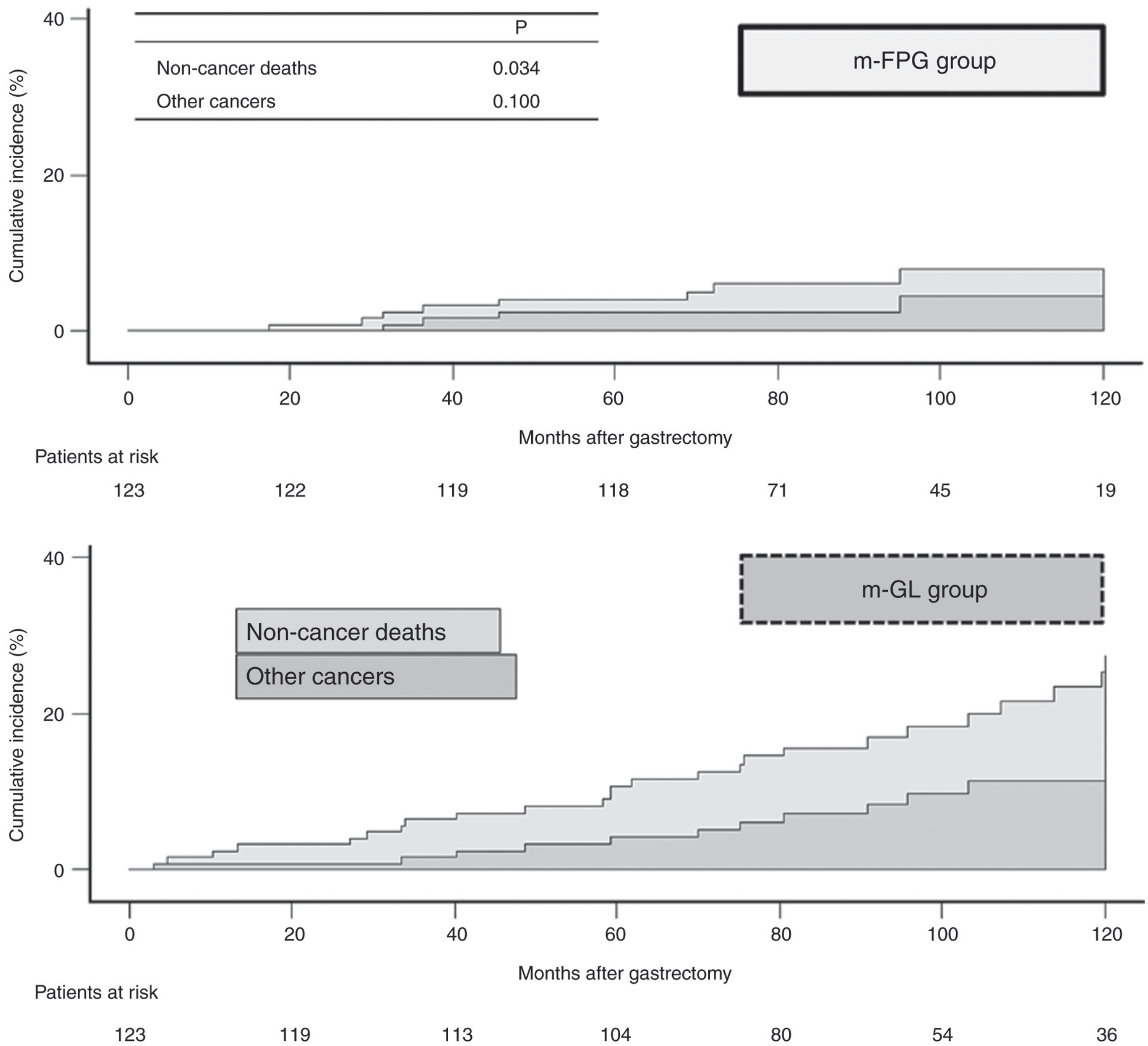

Figure 5. Comparison of cumulative incidence curves for other cancers and non-cancer deaths between the FPG and GL groups after propensity score matching. No recurrence of gastric cancer was observed in this series of matched patients. The cumulative incidence of non-cancer deaths in the FPG group was significantly better than that in the GL group after propensity score matching. m-FPG, propensity score-matched function-preserving curative gastrectomy; m-GL, propensity score-matched guideline gastrectomy.

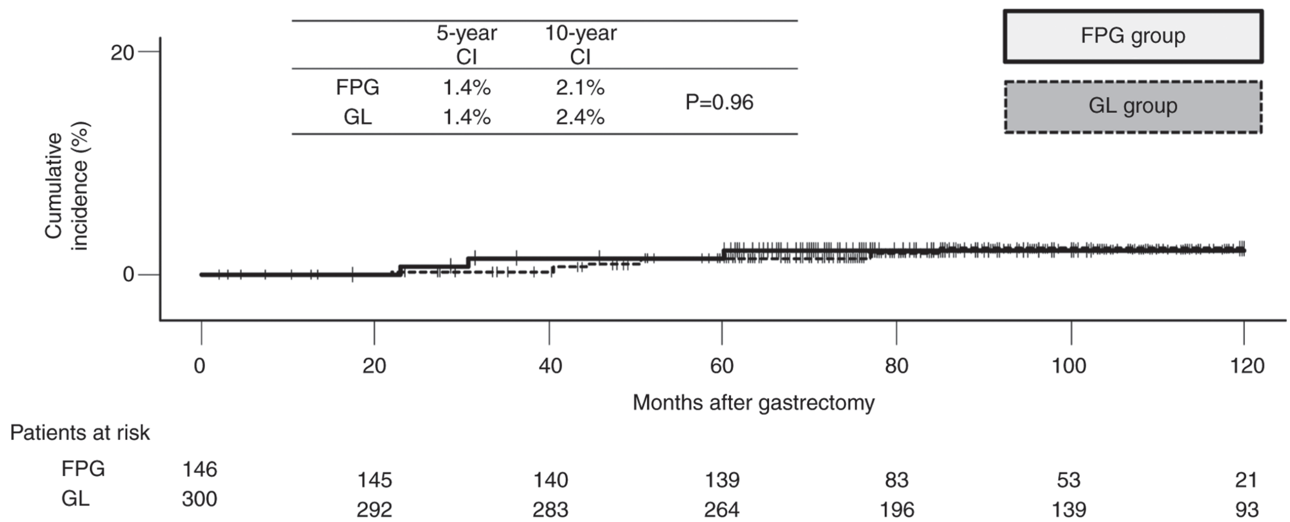

Figure 6. Cumulative incidence of metachronous multiple gastric cancer in the remnant stomach. There was no difference in the incidence of metachronous multiple gastric cancer between the FPG and GL groups. CI, cumulative incidence; FPG, function-preserving curative gastrectomy; GL, guideline gastrectomy.

Table V. Comparison of the causes of death by non-cancer other diseases.

	Full cohort analysis			After propensity score matching		
Cause of death	FPG group (%)	GL group (%)	P-value	m-FPG group (%)	m-GL group (%)	P-value
Cardiovascular disease	2 (1.4)	6 (2.0)	1.000	1 (0.8)	2 (1.6)	1.000
Cerebrovascular disease	0	5 (1.7)	0.178	0	3 (2.4)	0.247
Respiratory disease	0	9 (3.0)	0.034	0	5 (4.1)	0.060
Accident	2 (1.4)	2 (0.6)	0.600	2 (1.6)	2 (1.6)	1.000
Other cause	1 (0.7)	7 (2.3)	0.283	1 (0.8)	2 (1.6)	1.000

FPG, function-preserving curative gastrectomy; GL, guideline gastrectomy; m-FPG, matched function-preserving curative gastrectomy; m-GL, matched guideline gastrectomy.

Table VI. Details of nine patients who died of respiratory disease.

No.	Age, years	Sex	BMI, kg/m^2	ASA-PS	Comorbidity	Surgery	Survival[a]	Cause of death
1	70	M	21.2	2	COPD	DG B1	2	Aspiration pneumonia after vomiting
2	68	M	16.0	2	COPD	DG B2	13	Exacerbation of COPD
3	62	M	23.8	1	None	DG RY	13	Aspiration pneumonia
4	85	M	19.3	2	HT AP	DG B1	27	Aspiration pneumonia after vomiting
5	66	M	27.7	2	Sarcoidosis	DG RY	58	Bacterial pneumonia
6	57	M	24.5	1	None	DG RY	76	*Aspergillus* pneumonia
7	73	F	26.2	2	HT DM	DG B1	99	Aspiration pneumonia after vomiting
8	76	M	19.6	2	HT AP	DG B1	109	Aspiration pneumonia after vomiting
9	64	M	22.5	2	HT	DG B1	113	Bacterial pneumonia

Age, BMI, ASA-PS and comorbidity refer to preoperative status. [a]Months from initial surgery until death. BMI, body mass index; ASA-PS, American Society of Anesthesiologists physical status; COPD, chronic obstructive pulmonary disease; HT, hypertension; AP, history of angina pectoris; DM, diabetes mellitus; DG, distal gastrectomy; B1, Billroth I reconstruction; B2, Billroth II reconstruction; RY, Roux-en Y reconstruction

Table VII. Comparison of body weight and serum albumin levels between the two groups after 1 year.

Variable	FPG group (n=75)	GL group (n=229)	P-value
Change of body weight, %	-2.58±4.38	-7.57±5.43	<0.0001
Change in serum albumin level, g/dl	0.04±0.68	-0.05±0.34	0.303

Body weight and serum albumin levels 1 year after surgery were compared with the corresponding preoperative values. Values are expressed as the mean ± SD. FPG, function-preserving curative gastrectomy; GL, guideline gastrectomy.

sentinel node concept has been confirmed in a nationwide large-scale prospective study in Japan (21). It has also been confirmed that curability is not impaired, even if the extent of lymph node dissection is reduced from D1+ using SNB (13). Prospective clinical trials confirming this have been conducted in South Korea and Japan (12,22). The Korean trial was designed to prove the non-inferiority of the treatment outcomes of function-preserving surgery performed using SNB as an index. Unfortunately, non-inferiority was not demonstrated because of the failure to distinguish MMGC from gastric cancer recurrence (12). The risk of MMGC naturally increases as the residual gastric mucosa widens; however, most MMGC cases can be treated by ESD or gastrectomy, and are not directly related to death from gastric cancer (23). Therefore, MMGC should be distinguished from local recurrence of gastric cancer. In the present study, gastric cancer recurrence and MMGC were assessed separately, and no local recurrence was observed. The final judgment on the strategy to reduce the extent of dissection using SNB must be based on the results of the

Japanese trial (22); however, the oncological safety of this therapy does not appear to be problematic.

The FPG surgical procedures in the present study included MDG, SG and LR. It is important to differentiate between SG and PPG, though this is not defined in the guidelines (3), varies among researchers and there is no consensus. Some investigators include all SGs in PPG (24,25). However, a number of researchers define PPG as cases in which a cuff of 1.5-3 cm is secured, and SG as cases in which blood flow is preserved and a more extended cuff is secured by omitting the dissection area than the range of PPG prescribed by the guidelines (9,26-29). Our research group has long categorized both procedures based on the length of the antral cuff, classifying cuffs of ≤3 cm as PPG and those >3 cm as SG (1,13,30). The surgical method was chosen for each patient, focusing mainly on the extent of lymph node dissection and the distribution of the preserved perigastric arteries. When an intraoperative node-negative diagnosis was made using SNB, prophylactic lymphadenectomy was reduced to the lymphatic basin only. Lymphatic basins receive direct lymphatic flow from the tumor, as sentinel nodes are found only in these lymphatic basins. Although the distribution of the lymphatic basins depends on the gastric cancer lesion and varies from case to case, in most cases, it is limited to two basins. Even with lymphatic basin dissection, gastric blood flow can be partially maintained and FPG is possible. Presumably, there is a difference in postoperative complaints between the three surgical procedures for FPG, and prior research has shown that LR is associated with the least complaints and the best quality of life (9,10). In the future, as long as gastric blood flow is maintained, FPG strategies should be oriented toward LR, such as laparoscopic endoscopic cooperative surgery (1,31-35).

The inclusion criterion of the present retrospective study was pT1N0; therefore, the target patients seemed to have few recurrences of gastric cancer. Only 1 of the 446 patients had a recurrence of gastric cancer. By contrast, the 10-year survival rate was 83.5%. When the cause of death was divided into other cancer deaths and non-cancer deaths, there was no difference in the mortality rate from other types of cancer between the FPG and GL groups; however, non-cancer deaths in the FPG group were significantly lower than those in the GL group. The similarity in the occurrence of other cancers in both groups indicated that the genetic backgrounds of the two groups were generally the same. Therefore, it should be noted that the FPG group had fewer non-cancer deaths.

No deaths due to pneumonia occurred in the FPG group. Two main factors may explain the difference in the incidence of pneumonia between the two groups. First, the FPG group had a larger stomach volume and a lower risk of aspiration pneumonia caused by reflux of gastric or duodenal juices. It is well known that bilious vomiting is recognized as a postoperative sequela of the Billroth II reconstruction (36). Duodenogastric reflux was observed even after Billroth I reconstructions. In addition, the angle of His becomes blunted after the Billroth I method. Reflux esophagitis and subsequent aspiration pneumonia occur after gastrectomy because of these factors. Conversely, in the FPG group, sufficient gastric capacity was preserved, and the pylorus was also preserved in the SG and LR methods, meaning regurgitation of duodenal juice would be less than that in the patients that underwent DG. Another possible factor is the lower risk of infectious complications secondary to the weakened immune system in the FPG group, where the nutritional status was maintained. Besides aspiration pneumonia, bacterial pneumonia and *Aspergillus* pneumonia were found among the cases of respiratory death. Dietary intake is maintained and body weight loss is lower following FPG compared with GL (1,9-11,37). Unfortunately, because the present study was retrospective, some of the outpatient medical records were discarded, making assessment of postoperative nutritional status difficult, and only body weight and serum albumin levels for the first year after surgery were available for some cases. The level of weight loss was lower in the FPG group than that in the GL group, which is consistent with the results of the nationwide PGSAS study (6-8,37). Conversely, albumin levels returned to preoperative levels in both groups, indicating that albumin levels may not be used to assess nutritional status. Prospective studies will need to investigate other indicators that can directly determine immunity.

The present study has a potential impact on the treatment of gastric cancer in the older population. The appropriate treatment for older patients with early gastric cancer that does not indicate ESD is currently D1+ gastrectomy in Japan; however, OS after gastrectomy in older patients is not good (4). Currently, there are two measures to improve this situation: Performing ESD without surgery or not treating it at all; however, these measures cannot overcome the risk of gastric cancer recurrence. The present results may offer a third therapeutic strategy of FPG guided by SNB for older patients with no recurrence of gastric cancer and fewer non-cancer deaths than GL surgery. In the present study, in addition to GL surgery, several factors were revealed to worsen OS in patients after early gastric cancer surgery, including older age, male sex, low BMI, lower serum albumin level, and elevated type tumors. In addition, sex, BMI, nutritional status, ASA-PS and function preservation were identified as independent factors influencing non-cancer deaths. Therefore, it could be suggested that the selection of FPG procedures may contribute to improving prognosis not only in the elderly, but also in patients who are male, malnourished or have a number of comorbidities. However, this strategy should be used with caution in young patients in whom the rate of death due to respiratory diseases is low.

FPG has some disadvantages, including an increased risk of MMGC (23) and delayed gastric emptying (DGE) (30). The wider the remnant stomach mucosa, the higher the incidence of MMGC (23). Nevertheless, it has been confirmed that the majority of MMGC cases can be treated with ESD after FPG (23). As such, there is no need to delay carrying out FPG because of the increased risk of MMGC; however, it is essential to conduct surveillance with MMGC in mind (23). The cumulative incidence of MMGC did not differ between the FPG and GL groups in the present study. This is because the indication for SNB was limited to instances of single gastric tumors, and synchronous multiple gastric cancer cases were often included in the GL group. Therefore, the risk of MMGC may initially be low in the FPG group, which may offset the size-dependent risk for MMGC.

Complications of DGE are severe and associated with pylorus-preserving procedures, such as PPG, SG and LR (30). Furthermore, DGE is known to develop after PPG, delayed food intake and prolonged hospital stays (24,25,30,38). This condition is known to cause esophagogastric reflux, increase the chances of pneumonia and lead to death from other diseases. However, none of the patients who underwent the pylorus-preserving procedure died of pneumonia in the present study. Unfortunately, the details of postoperative complications at Kanazawa University Hospital could not be accessed due to the unavailability of detailed medical records. However, at Kanazawa Medical University Hospital, DGE occurred in 1.6% of DG cases, 7.7% of PPG cases and 5.9% of WR cases; no DGE was encountered following MDG/SG. Furthermore, there are currently no evidence-based measures to prevent DGE occurrence after PPG (39-41). Empirically, vagal preservation (hepatic branch, celiac branch, hepatic plexus and pyloric branch), securing the long antral cuff, and intraoperative pyloric bougie are considered effective at preventing DGE occurrence (39-41). SK, when performing the pyloric preservation procedure, always stretches the pylorus with a finger bougie or intestinal forceps and preserves the autonomic nerves as much as possible. This may explain why patients who underwent SG in the present study did not suffer from DGE. In addition, the subjective symptoms of DGE improved over time, and none of the patients developed DGE symptoms or pneumonia over the long-term follow up period. In our experience, although preventive measures are needed, DGE does not lead to death by pneumonia. Therefore, hesitation to perform gastric preservation because of concerns over DGE may be unwarranted.

The present study has some limitations. Firstly, this was a retrospective study, and some potential selection bias may have occurred in the FPG group. The final results regarding the effects of FPGs on survival prognosis will be determined through the ongoing prospective trial (22). The study also did not investigate postgastrectomy symptoms, which will also become evident in a prospective study. Another limitation is the long study period. During this period, diagnostic and therapeutic techniques advanced, which may have affected prognosis. Patients with a good ECOG-PS and no severe comorbidities were selected; however, we could not investigate their preoperative nutritional status and postoperative complications. In addition, because of missing medical records for some patients, smoking history could not be assessed and was thus not considered in this analysis. Furthermore, patients with cancer located in the U area were excluded from the present study because the surgical procedures for such patients were total gastrectomy and proximal gastrectomy, and they had more postoperative complications than those included in this study.

In conclusion, for early gastric cancer located in the M or L areas, and not applicable for ESD, FPG guided by SNB may achieve a better prognosis and significantly fewer respiratory disease-related deaths than GL. The present study suggested the curability and safety of FPG, and may help influence the treatment of early gastric cancer in older patients.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

SK was responsible for the scientific conception of the study and writing of the manuscript. SK, DK, KO and TF contributed to the surgery and data collection. YI was responsible for the statistical analysis. YI and HT confirm the authenticity of all the raw data. HT and NI contributed to interpretation of data, and the drafting, editing and critical revision of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the ethics committees of Kanazawa University Hospital, Kanazawa Medical University and the University Hospital Medical Information Network Clinical Trials Registry (UMIN registry). ICG fluorescent mapping was approved by the Ethics Committee of the Japan Registry of Clinical Trials (jRCT). The trial/approval numbers are R093 (2009/8/28), M288 (2013/2/25) and M404 (2016/7/25) for the local ethics committees of Kanazawa Medical University; UMIN000010154 (2013/3/4) and UMIN000023828 (2016/8/29) for the UMIN registry; and jRCTs041180006 (2018/10/9) (https://jrct.niph.go.jp/latest-detail/jRCTs041180006) for the jRCT. This study was conducted in accordance with the Good Clinical Practice guidelines and Declaration of Helsinki. All patients provided written informed consent for surgical treatment and the use of their data. Regarding data use, patients were allowed to opt-out of the study at any time.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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