Time interval after various types of gastrectomy until metachronous multiple gastric cancer: Analysis of data from a nationwide Japanese survey

KOSHI KUMAGAI[1], SANG-WOONG LEE[2], MASAICHI OHIRA[3], MASAKI AIZAWA[4], SATOSHI KAMIYA[5], TAKAOMI TAKAHATA[6], MAKOTO TODA[7], HARUHIKO CHO[8], MASAZUMI TAKAHASHI[9], TAKESHI KUBOTA[10], SHINICHI KINAMI[11] and TAKEO KOSAKA[11]

[1]Department of Gastroenterological Surgery, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo 135-8550; [2]Department of General and Gastroenterological Surgery, Osaka Medical College, Osaka 569-8686; [3]Department of Gastroenterological Surgery, Osaka City University Graduate School of Medicine, Osaka 558-8585; [4]Department of Digestive Surgery, Niigata Cancer Center Hospital, Niigata 951-8566; [5]Department of Gastric Surgery, Shizuoka Cancer Center, Sunto, Shizuoka 411-8777; [6]Department of Surgery, Okayama Saiseikai General Hospital, Kita-ku, Okayama 700-8511; [7]Department of Surgery, Yamagata Prefectural Central Hospital, Yamagata 990-2214; [8]Department of Gastric Surgery, Tokyo Metropolitan Cancer and Infectious Disease Center, Komagome Hospital, Tokyo 113-8677; [9]Department of Surgery, Yokohama Municipal Citizen's Hospital, Yokohama, Kanagawa 221-0855; [10]Division of Digestive Surgery, Department of Surgery, Kyoto Prefectural University of Medicine, Kamigyo-ku, Kyoto 602-8566; [11]Department of Surgical Oncology, Kanazawa Medical University, Uchinada, Ishikawa 920-0293, Japan

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Abstract. The factors influencing the time interval from the initial surgery for gastric cancer to the detection of metachronous multiple gastric cancer (MMGC) remain to be elucidated. The present study was performed to evaluate the association between the type of initial gastrectomy or reconstruction procedure and the time interval from initial gastrectomy to the detection of MMGC. A questionnaire survey on remnant stomach cancer was performed by the Japanese Society for Gastro-Surgical Pathophysiology in 2018. Participating facilities were requested to indicate the number of patients who underwent surgery for MMGC between 2003 and 2017, in association with the time interval from the initial gastrectomy until treatment for MMGC by type of initial gastrectomy or reconstruction procedure. Analyses were performed using data from 45 facilities. Gastrectomy for MMGC was performed on 1,234 patients during this period. Pylorus-preserving gastrectomy (PPG) accounted for only 3.6% (20/557) of the patients who underwent surgery for MMGC ≥10 years from initial gastrectomy, while PPG accounted for 10.1% (40/396) of patients who underwent surgery for MMGC within 5 years after initial gastrectomy. Billroth-II and Roux-en Y reconstruction accounted for 22.3% (103/462) and 1.3% (6/462), respectively, of patients who underwent surgery for MMGC ≥10 years from initial distal gastrectomy (DG), while such patients accounted for 8.0% (23/286) and 21.7% (65/286), respectively, of patients who underwent surgery for MMGC within 5 years after initial DG. Similarly, the proportion of each reconstruction procedure differed according to the time interval from initial proximal gastrectomy to treatment for MMGC. The types of gastrectomy or reconstruction procedure for initial gastrectomy differed significantly according to the time interval between the initial gastrectomy and treatment for MMGC, and the fact that PPG and R-Y reconstruction in DG is a relatively new method were assumed to be a major cause of these differences.

Correspondence to: Dr Koshi Kumagai, Department of Gastroenterological Surgery, Cancer Institute Hospital, Japanese Foundation for Cancer Research, 3-8-31 Ariake, Koto-ku, Tokyo 135-8550, Japan
E-mail: koshi.kumagai@jfcr.or.jp

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Introduction

Gastrectomy for benign disease has decreased over the past four decades as a result of the development of proton pump inhibitors, and hence, cancer in the remnant stomach after this type of gastrectomy, named 'gastric stump cancer', is on the decline. Meanwhile, remnant gastric cancer after partial gastrectomy for gastric cancer, referred to as 'metachronous multiple gastric cancer' (MMGC), has become relatively common.

Several studies have addressed and reported correlations of the time until detection of remnant stomach cancer and factors associated with initial gastrectomy. Researchers have

consistently reported that the interval between initial distal gastrectomy (DG) and the diagnosis of stump carcinoma was significantly longer in patients who underwent initial gastrectomy for benign disease than in those who underwent initial gastrectomy for cancer (1-4). The probable reason for the shorter interval for MMGC is that patients with gastric cancer already have precancerous lesions, such as atrophic gastritis and intestinal metaplasia, and they are followed up closely by endoscopic examination. Regarding the correlation of the time interval until the detection of remnant stomach cancer with the initial surgical procedure, most published studies have reported remnant stomach cancer after DG, which is the most commonly performed procedure for both benign and malignant disease in the stomach, while information on other types of gastrectomy is limited (5). A characteristic correlation between the type of initial reconstruction and the interval has been reported in patients after DG; namely, the interval between initial DG and the diagnosis of remnant stomach cancer is significantly longer in patients treated with Billroth II (B-II) reconstruction than in those treated with Billroth I (B-I) reconstruction, while most studies included small numbers of patients with MMGC (3-5). A Japanese nationwide survey performed by Tanigawa *et al* (2) supported the findings described above and included a sufficient number of patients with MMGC. However, the survey was performed in 2008 and collected MMGC patients with adenocarcinoma in the remnant stomach occurring ≥10 years after initial distal gastrectomy reconstructed with B-I or B-II, excluding Roux-en Y (R-Y) reconstruction for cancer, which suggests that the result may not be representative of MMGC in Japan.

Other items of interest are the procedure performed for MMGC and the factors associated with initial gastrectomy. The Japanese nationwide survey mentioned above reported that completion total gastrectomy (CTG) was performed in >80% of patients who underwent initial partial gastrectomy for stomach cancer, irrespective of the reconstruction method, which may be due to the small size of the remnant stomach after gastrectomy for stomach cancer (2). Although this previous survey included a sufficient number of patients with MMGC, it included only patients with MMGC who underwent distal gastrectomy with B-I or B-II reconstruction and who were diagnosed ≥10 years after initial gastrectomy. Therefore, it also may not reflect the procedures currently performed during surgery for MMGC in Japan.

As mentioned above, though it is assumed that the type of initial gastrectomy or reconstruction method correlates with the interval between the initial gastrectomy and detection of MMGC or the required treatment for MMGC, the reported evidence thus far is limited to MMGC after distal gastrectomy.

The Japanese Society for Gastro-Surgical Pathophysiology (JSGSP) performed a questionnaire survey on remnant stomach cancer among Japanese centers that specialize in treating gastric cancer in 2018. This report sought to evaluate the correlation of the type of initial gastrectomy or reconstruction procedure with the interval between initial gastrectomy for stomach cancer and the detection of MMGC as part of the survey. In addition, the correlation between the type of initial gastrectomy or reconstruction procedure and the performed treatment for MMGC was also analyzed.

Materials and methods

Questionnaire. A nationwide questionnaire survey was planned by the president of the JSGSP 48th Annual Meeting (TK) and conducted as a part of the meeting. The questionnaire only collected the number of cases for each questionnaire item and did not collect any individual patient data. The JSGSP members accessed the web-based questionnaire between May 2018 and October 2018 and answered via e-mail. The data were sent to Convention Linkage, Inc. and compiled.

The study protocol was approved by the institutional review board of Kanazawa Medical University (trial no. I267), was performed in accordance with the Ethical Guidelines of the Japan Ministry of Health, Labour and Welfare for Medical and Health Research Involving Human Subjects (6) and conformed to the provisions of the Declaration of Helsinki (7). All data were anonymized and assembled for each facility. Only the statistical numbers of patients were submitted by the doctors and this does not require ethics approval from their own affiliated local review board prior to sharing the data in the questionnaire or consent from the individual patients, as none of their personal/specific data were used.

The questionnaire consisted of three parts; an English translation of the questionnaire sheet is provided as Supplemental data. In the first part, participating facilities were requested to indicate the number of patients who underwent radical surgery for remnant stomach cancer between 2003 and 2017, as well as the number of cases with MMGC among these patients. The questionnaire also requested that the facilities indicate the number of patients with MMGC in accordance with the time interval from the initial gastrectomy until treatment for MMGC by the type of initial gastrectomy or reconstruction procedure. The number of cases for each treatment procedure (CTG or partial gastrectomy) was also queried. The second part was a cohort study that followed up gastrectomized patients between 2003 and 2012, which required the reporting of the number of cases in which MMGC was observed until the time of observation (8). The third part was regarding the correlation between *Helicobacter pylori* infection and the occurrence of MMGC. Participating institutions were asked to provide information on the institutional policy for eradication after gastrectomy and the occurrence of MMGC after eradication. The current study summarizes the data from the first part of the questionnaire.

Statistical analysis. The χ^2 test was performed with Excel 2016 (Microsoft Corporation) to compare the distribution of the time interval from the initial gastrectomy until the detection of MMGC among different types of initial gastrectomy or reconstruction procedures.

Results

Data collection. At the time of posting of the questionnaire on the website, 204 facilities belonged to the JSGSP. Questionnaire responses were obtained from 63 institutions; responses from 18 institutions were excluded due to missing or inconsistent data. Thus, subsequent analyses were performed using the data from 45 institutions, which are provided in the Acknowledgements section with the names of the responsible contributors (Fig. 1).

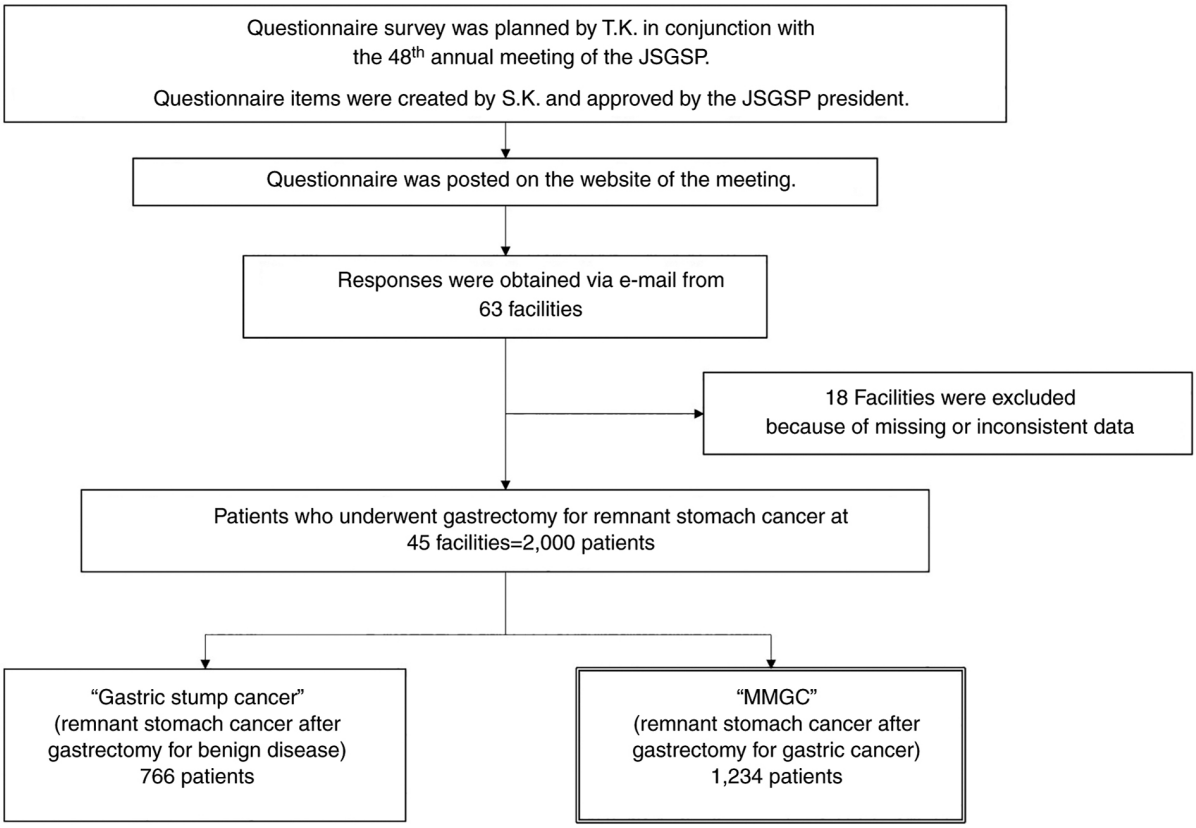

Figure 1. Flow diagram of the questionnaire survey and the subsequent analysis. A total of 1,234 patients with MMGC were analyzed in the current study. MMGC, metachronous multiple gastric cancer; JSGSP, Japanese Society for Gastro-Surgical Pathophysiology.

Between 2003 and 2017, gastrectomy for remnant stomach cancer was performed in 2,000 patients, with MMGC accounting for 61.7% (1,234 patients) (Fig. 1). Table I summarizes the number of each type of gastrectomy and reconstruction procedure performed for the initial gastrectomy among patients with MMGC. DG was the most frequent procedure, accounting for 76.4% (943 cases), followed by proximal gastrectomy (PG) (12.2%, 150 cases) and pylorus-preserving gastrectomy (PPG) (6.4%, 79 cases). B-I was most frequently performed after DG (78.5%, 712/943 cases), followed by B-II (14.6%, 138/943 cases) and R-Y (8.8%, 83/943 cases). In terms of PG for MMGC, most patients underwent jejunal interposition (JI) (45.3%, 68/150 cases) or esophagogastric anastomosis (EG) (42.7%, 64/150 cases) (Table I).

Type of gastrectomy or reconstruction procedure and the time interval between the initial gastrectomy and treatment for MMGC. Fig. 2A summarizes the type of initial gastrectomy according to the time interval between the initial gastrectomy and treatment for MMGC. PPG accounted for only 3.6% (20/557) of the patients who underwent surgery for MMGC ≥10 years from initial gastrectomy, while PPG accounted for 10.1% (40/396) of the patients who underwent surgery for MMGC within 5 years after initial gastrectomy.

The types of reconstruction procedure in the initial DG and PG according to the time interval between the initial gastrectomy and treatment for MMGC are presented in Fig. 2B and C, respectively. B-II accounted for 22.3% (103/462) of the patients who underwent surgery for MMGC ≥10 years from initial DG, while B-II accounted for only 8.0% (23/286) of the patients who underwent surgery for MMGC within 5 years after initial DG. Conversely, R-Y accounted for only 1.3% (6/462) of the patients who underwent surgery for MMGC ≥10 years from initial DG and 21.7% (65/286) of patients who underwent surgery for MMGC within 5 years after initial DG. Similarly, the proportion of each reconstruction procedure differed according to the time interval between initial PG and treatment for MMGC (Fig. 2C). The distribution of the types of gastrectomy ($P<0.001$; Fig. 2A) or reconstruction procedures ($P<0.001$; Fig. 2B and $P=0.022$; Fig. 2C) differed significantly according to the time interval between the initial gastrectomy and treatment for MMGC.

Surgical procedures for MMGC. Fig. 3 summarizes the proportion of performed procedures for MMGC after each type of initial gastrectomy. The proportion of partial gastrectomy increased in accordance with the size of the remnant stomach after the initial gastrectomy (Fig. 3).

Discussion

The present multi-institutional questionnaire survey successfully collected data from >1,000 patients with MMGC and is thus far the largest survey on MMGC. Facility members of the JSGSP are dedicated to gastric cancer surgery and perform a certain number of gastrectomies with strict follow-up. Therefore, the data obtained from these facilities are reliable and may be regarded as representing the actual status of

Table I. Number of each type of gastrectomy performed in the initial gastrectomy among patients with metachronous multiple gastric cancers (n=1,234).

Type of surgery/reconstruction or variant	n
DG	943
B-I	712
B-II	138
R-Y	83
Others	10
PG	150
JI	68
EG	64
DT	13
Others	5
PPG	79
SG	10
LR	5

B-I, Billroth-I; B-II, Billroth-II; DG, distal gastrectomy; DT, double tract; EG, esophagogastrostomy; JI, jejunal interposition; LR, local resection; PG, proximal gastrectomy; PPG, pylorus-preserving gastrectomy; R-Y, Roux-en Y; SG, segmental gastrectomy.

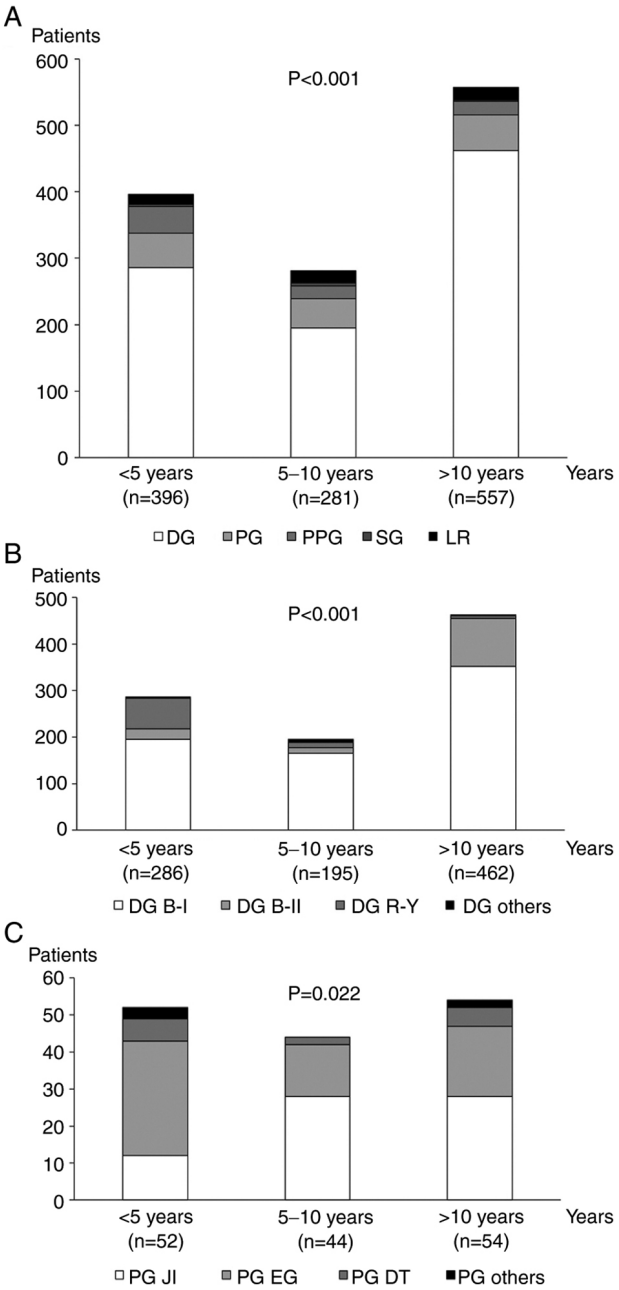

Figure 2. Type of initial gastrectomy and reconstruction procedures after DG and PG according to the time interval between the initial gastrectomy and treatment of MMGC. (A) Types of initial gastrectomy differed depending on the interval between the initial gastrectomy and treatment for MMGC. Reconstruction procedures after (B) DG and (C) PG also differed depending on the interval between the initial gastrectomy and treatment for MMGC. MMGC, metachronous multiple gastric cancer; DG, distal gastrectomy; PG, proximal gastrectomy; B-I, Billroth-I; B-II, Billroth-II; R-Y, Roux-en Y; JI, jejunal interposition; EG, esophagogastrostomy; DT, double tract; PG others, PG with other reconstruction; PPG, pylorus-preserving gastrectomy; SG, segmental gastrectomy; LR, local resection.

MMGC in Japan. This survey included a much larger number of MMGC patients compared with another cohort study performed concurrently. In the present study, 1,234 patients with MMGC who underwent gastrectomy were retrospectively analyzed, while another prospective cohort study comprised 718 patients who developed MMGC and received any treatment during the follow-up period, including 386 patients who underwent surgery (8). In other words, the present study included more than three times the number of patients with MMGC who underwent surgery.

The present study provides the following novel findings: i) A current overview of MMGC in Japan; ii) information on MMGC after PG and PPG, which are relatively new function-preserving surgeries; and iii) a definite correlation between the time interval from the initial gastrectomy until the detection of MMGC and the types of gastrectomy or reconstruction applied in the initial surgery. In addition, regarding the procedure performed for MMGC, it was indicated that the proportion of CTGs decreased as the size of the remnant stomach increased. As part of the survey, the present study revealed that the type of gastrectomy and reconstruction procedure used in the initial gastrectomy differed in accordance with the interval length between the initial gastrectomy and the detection of MMGC.

PPG was first described by Maki *et al* (9) in 1967 and was developed as a surgical approach for benign peptic ulcer that aimed to prevent dumping syndrome by preserving the pyloric ring. The feasibility of PPG as a function-preserving gastrectomy for early gastric cancer was first reported by Kodama and Koyama (10) in 1991 and became prevalent in combination with the generalization of the concept of minimally invasive surgery. A report from The Japanese Gastric Cancer Association Registration Committee, which summarized the treatment results of 8,308 gastric cancer patients treated at 113 major Japanese hospitals in 1991, did not report any PPG cases, while PPG accounted for 3.4% (4,026/118,367) of gastrectomies performed between 2001 and 2007 (11,12). As patients who underwent surgery for MMGC between 2003 and 2017 were reported in the present survey, the observed low proportion of patients with MMGC whose interval between the

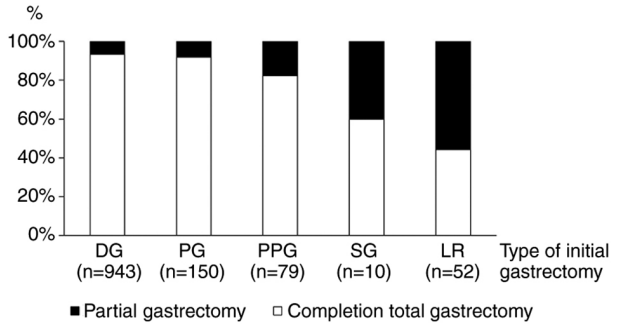

Figure 3. Statistics on the procedure performed for metachronous multiple gastric cancer after each type of initial gastrectomy. The proportion of partial gastrectomy increased in accordance with the size of the remnant stomach after the initial gastrectomy. DG, distal gastrectomy; PG, proximal gastrectomy; PPG, pylorus-preserving gastrectomy; SG, segmental gastrectomy; LR, local resection.

initial PPG and detection of MMGC was ≥10 years appeared reasonable.

Several epidemiological studies have reported that B-II in gastrectomy for benign peptic ulcer is more highly correlated with gastric stump carcinoma than B-I and the incidence increases ≥20 years from initial gastrectomy (13,14). Previous studies reported that reflux of bile and pancreatic juice may be important factors for cancer development in the remnant stomach. Studies also assumed that atypical hyperplasia, called 'gastritis cystica polyposa', proximal to the gastrojejunal anastomosis in B-II reconstruction caused by reflux, was associated with gastric stump carcinoma (15-18), although a consensus has not been reached. However, several animal model experiments provided evidence supporting that pancreatic juice alone or in combination with bile acids, the main component duodenal juice, may cause carcinogenesis in the remnant stomach (19). These characteristics, such as the higher incidence of remnant stomach cancer after B-II and the longer interval from initial gastrectomy to detecting remnant stomach cancer, may be applicable to MMGC after B-II. However, it was not possible to prove this in the present study, as the number of patients who underwent B-II in each period at participating facilities was unknown and because the most probable cause of the observed difference in the interval is the trend in the use of each reconstruction procedure, as with that for the type of gastrectomy. R-Y reconstruction in DG is a relatively new method compared with B-I or B-II (2). Although R-Y was invented and reported by Roux (20) in 1893, the use of R-Y in DG became prevalent and its feasibility was published in the 2010s in Japan (21-25). Therefore, it is also reasonable that the proportion of R-Y procedures increased over time. The Japanese Society for the Study of Postoperative Morbidity after Gastrectomy performed a questionnaire survey in 2010 to reveal the status of reconstruction after gastrectomy. The results supported an increase in R-Y in recent years, as the most common reconstruction method after DG was B-I in 112 (77%) of the 145 responding institutions, R-Y in 30 (21%) and B-II in one (0.7%), in 2010 (26).

Another advantage of the present survey is that a considerable number of patients with MMGC after PG were reported. Significant differences in the proportion of each reconstruction procedure according to the time interval between initial PG and treatment for MMGC were found and the reason for the difference may be explained as follows: JI is applicable to the relatively small remnant stomach and may theoretically prevent reflux esophagitis, but it requires procedures that are relatively complex (27,28). EG has also been attempted in PG, as the procedure is much simpler than JI (29,30). A major drawback of EG is gastroesophageal reflux after surgery. To compensate for this, the hand-sewn double-flap technique and other techniques using linear staples have been introduced and a better postoperative quality of life was increasingly reported in the late 2010s (31-34). Double-tract reconstruction (DT) after PG is also an emerging procedure, with which surgeons are more familiar than JI, as only jejuno-gastric anastomosis is supposed to be added to R-Y reconstruction (35-38). A Japanese nationwide survey performed in 2010 indicated that the most preferred reconstruction approach after PG was EG (48% of the responding institutions) followed by JI (28%) and DT (13%) (26). The small proportion of MMGC detected within 5 years after JI in the present survey may be explained by the assumption that JI became common in the 1990s but has been replaced by DT in the current century.

Although CTG is the standard surgery for advanced cancer in the remnant stomach, partial gastrectomy may be applied to early cancer (39). The current survey clearly demonstrated that the possibility of avoiding CTG depends on the size of the remnant stomach.

There are several limitations to the current survey that should be addressed. First, the retrospective nature of the data collection is an issue, and individual patient data, including the detailed surgical treatments of the initial gastrectomy and MMGC, were not collected to protect patient privacy. In the present survey, each institution was requested to provide the number of patients who underwent surgery for MMGC between 2003 and 2017. There are potential risks of selection bias due to the retrospective nature of the data collection, although the participating facilities were requested to report all MMGC patients who underwent surgery during this period. The 15-year inclusion period and the lack of published literature on the time trend of the type of gastrectomy or reconstruction procedure made it difficult to assess the correlation between the time trend of the type of gastrectomy or reconstruction procedure and the time interval from the initial gastrectomy until the detection of MMGC. Another limitation is the lack of universality of the results of the study. R-Y is mainly performed in Western countries, while B-I or B-II is rarely performed following DG due to the potential risk of gastroesophageal reflux in obese individuals. In addition, PG or PPG, which are indicated for early gastric cancer, are also seldomly performed in the West, as most patients with gastric cancer have advanced disease. The vast majority of the patients included in the present study were thought to be Japanese and information on ethnicity was not collected in this study. Therefore, the results of the present study are not universal and are specific to Japanese patients. Furthermore, the type of gastrectomy depends on several clinicopathological factors that may be confounding factors, which affect the time interval from the initial gastrectomy to the detection of MMGC. However, the questionnaire used in the present study only included the number of patients subjected to each procedure and the time interval between the initial gastrectomy and the detection of MMGC, as this survey comprised >1,000 patients and it was necessary to

simplify the questionnaire. Hence, the retrospective nature is one of the limitations of the current study.

A large-scale prospective study is esteemed to elucidate factors other than the time trend of gastrectomy or reconstruction procedure that may correlate with the time interval from initial gastrectomy until the detection of MMGC.

Despite the limitations discussed above, the present multi-institutional questionnaire survey study demonstrated that the type of initial gastrectomy and reconstruction procedure differs according to the time interval between initial gastrectomy and the detection of MMGC. The proportion of CTG decreased as the size of the remnant stomach increased.

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Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan), Mr. Hiroshi Kusanagi (Department of Gastroenterological Surgery, Kameda Medical Center, Chiba, Japan), Professor Shinichi Kinami (Department of Surgical Oncology, Kanazawa Medical University, Ishikawa, Japan), Mr. Takahisa Yamaguchi (Department of Gastroenterological Surgery and Division of Cancer Medicine, Graduate School of Medical Science, Kanazawa University, Ishikawa, Japan), Ms. Marie Washio (Department of Upper Gastrointestinal Surgery, Kitasato University School of Medicine, Kanagawa, Japan), Mr. Kojiro Eto (Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan), Ms. Hiromi Yasuda (Departments of Gastrointestinal and Pediatric Surgery, Division of Reparative Medicine, Institute of Life Sciences, Mie University Graduate School of Medicine, Mie, Japan), Mr. Hiroyuki Sagawa (Department of Gastroenterological Surgery, Nagoya City University Graduate School of Medical Sciences, Aichi, Japan), Ms. Chie Tanaka (Department of Gastroenterological Surgery, Nagoya University Graduate School of Medicine, Aichi, Japan), Mr. Sohei Matsumoto (Department of Surgery, Nara Medical University, Nara, Japan), Mr. Akio Kaito (Gastric Surgery Division, National Cancer Center Hospital East, Chiba, Japan), Mr. Masaki Aizawa (Department of Digestive Surgery, Niigata Cancer Center Hospital, Niigata, Japan), Mr. Takuya Noguchi (Department of Gastroenterological Surgery, Oita Kouseiren Tsurumi Hospital, Oita, Japan), Mr. Hiroshi Isozaki (Department of Surgery, Oomoto Hospital, Okayama, Japan), Mr. Ryo Tanaka (Department of General and Gastroenterological Surgery, Osaka Medical College, Osaka, Japan), Mr. Yoshitaka Toyomasu (Department of Digestive Tract and General Surgery, Saitama Medical Center, Saitama Medical University, Saitama, Japan), Professor Shinichi Sakuramoto (Division of Gastroenterological Surgery, Saitama Medical University International Medical Center, Saitama, Japan), Mr. Satoshi Kamiya (Department of Gastric Surgery, Shizuoka Cancer Center, Shizuoka, Japan), Mr. Hirokazu Yamaguchi (Department of Gastroenterological Surgery, Showa General Hospital, Tokyo, Japan), Mr. Kimiyasu Yamazaki (Department of General and Gastroenterological Surgery, Showa University School of Medicine, Tokyo, Japan), Mr. Shinya Mikami (Division of Gastroenterological and General Surgery, St. Marianna University School of Medicine, Kanagawa, Japan), Mr. Takashi Kiyokawa (Department of Surgery, Teikyo University School of Medicine, Tokyo, Japan), Mr. Muneharu Fujisaki (Department of Surgery, Jikei University School of Medicine, Tokyo, Japan), Professor Hiroharu Yamashita (Department of Gastrointestinal Surgery, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan), Mr. Yoko Oshima (Department of Surgery, School of Medicine, Toho University, Tokyo, Japan), Professor Eiji Nomura (Department of Surgery, Tokai 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School of Medicine, Yokohama City University, Kanagawa, Japan), Mr. Hiroshi Miyamoto (Department of Surgery, Gastroenterological Center, Yokohama City University, Kanagawa, Japan), Mr. Masazumi Takahashi (Department of Surgery, Yokohama Municipal Citizen's Hospital, Kanagawa, Japan).

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

SKi and TKo designed the study. KK, MA, SKa, TT, MTo, HC, MTa and TKu performed data acquisition, data analysis and interpretation. KK and SKi checked and approved the authenticity of the raw data and prepared the manuscript. SKi,

SWL and MO revised the paper for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol was approved by the institutional review board of Kanazawa Medical University (Ishikawa, Japan; trial no. I267). This study was conducted in accordance with the Ethical Guidelines of the Japan Ministry of Health, Labour and Welfare for Medical and Health Research Involving Human Subjects and conformed to the provisions of the Declaration of Helsinki. The requirement to obtain informed consent was waived by the institutional review board of Kanazawa Medical University (Ishikawa, Japan; approval no. I267).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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