

Time Interval After Various Types of Gastrectomy Until Metachronous Multiple Gastric Cancer: Analysis of Data From A Nationwide Japanese Survey

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Abstract

Background

The time interval between initial partial gastrectomy and diagnosis of cancer in the remnant stomach reportedly differs according to the reconstruction procedure used in the initial gastrectomy. However, factors correlated with the time interval from the initial surgery for gastric cancer to the detection of metachronous multiple gastric cancer (MMGC) remain unclear. This study was performed to evaluate the association between the type of initial gastrectomy or reconstruction procedure and the time interval from initial gastrectomy to detection of MMGC as well as the association between the type of initial gastrectomy and the procedure performed for MMGC.

Methods

A questionnaire survey on remnant stomach cancer was conducted by the Japanese Society for Gastro-Surgical Pathophysiology in 2018. Participating facilities were asked to indicate the number of patients who underwent surgery for MMGC between 2003 and 2017, in accordance with the time interval from the initial gastrectomy until treatment for MMGC by type of initial gastrectomy or reconstruction procedure. The number of patients who underwent each treatment procedure (completion total gastrectomy or partial gastrectomy) was also collected.

Results

Analyses were performed using data from 45 facilities. Gastrectomy for MMGC was performed in 1,234 patients during the period. Billroth-II and Roux-en Y accounted for 22.3% (103/462) and 1.3% (6/462), respectively, of patients who underwent surgery for MMGC \geq 10 years from initial DG, while these 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. Likewise, the proportion of each reconstruction procedure differed by the time interval from initial proximal gastrectomy to treatment for MMGC. In terms of the treatments performed for MMGC, the proportion of patients who underwent partial gastrectomy increased in accordance with the size of the remnant stomach after the initial gastrectomy.

Conclusions

The types of gastrectomy or reconstruction procedures for initial gastrectomy differed significantly by time interval between the initial gastrectomy and treatment for MMGC, and their time trends were assumed to be a major cause of the differences. The proportion of patients who underwent completion total gastrectomy decreased as the size of the remnant stomach increased.

Introduction

Gastrectomy for benign disease has decreased over the last four decades as a result of the development of proton pump inhibitors, and thus 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.

Some studies have addressed and reported correlations of the time until the 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 is 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 gastric cancer patients 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, and information on other types of gastrectomy is very limited [5]. Among patients after DG, a characteristic correlation between the type of initial reconstruction and the interval has been reported; 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 number of patients with MMGC [3–5]. A Japanese nationwide survey conducted by Tanigawa et al. included a sufficient number of MMGC patients and supported the findings described above [2]. However, the survey was conducted in 2008 and collected MMGC patients with an adenocarcinoma in the remnant stomach occurring 10 years or more 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 areas of interest are the performed procedure for MMGC and the factors associated with initial gastrectomy. The Japanese nationwide survey mentioned above reported that completion total gastrectomy was performed in more than 80% of patients who underwent initial partial gastrectomy for stomach cancer, irrespective of the reconstruction method, which may be because of the small size of the remnant stomach after gastrectomy for stomach cancer [2]. Although this previous survey included sufficient MMGC patients, it included only MMGC patients who underwent distal gastrectomy with Billroth I or Billroth II reconstruction and who were diagnosed 10 years or more after initial gastrectomy. Therefore, it may also not reflect the current situation of the procedures 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) conducted 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 and the interval between initial gastrectomy for stomach cancer and the detection of MMGC as a 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.

Material And Methods

A nationwide questionnaire survey was planned by the president of the JSGSP 48th Annual Meeting (TK). 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. (Tokyo Japan) and compiled.

The study protocol was approved by the institutional review board of Kanazawa Medical University (Trial No. I267) and conducted in accordance with the Ethical Guidelines of 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. All data were anonymized and assembled for each facility. Patients were able to opt out of the use of their data for research at any point.

The questionnaire consisted of three parts; Fig. 1 shows an English translation of the questionnaire sheet. The first part was a case study of MMGC, and participating facilities were asked 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 asked the facilities to indicate the number of MMGC patients 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 (completion total gastrectomy or partial gastrectomy) was also required. The current report summarizes the data from the first part of the questionnaire.

The chi-squared test was performed with Microsoft Excel 2016 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

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 because of missing or inconsistent data. Thus, subsequent analyses were performed using the

data from 45 institutions, which are shown in the Acknowledgements section with the names of the responsible person (Fig. 2).

Between 2003 and 2017, gastrectomy for remnant stomach cancer was performed in 2,000 patients, with MMGC accounting for 61.7% (1,234 patients) of them (Fig. 2). Table 1 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 Roux-en Y (R-Y, 8.8%, 83/943 cases). In PG for MMGC, most patients underwent jejunal interposition (45.3%, 68/150 cases) or esophagogastric anastomosis (42.7%, 64/150 cases) (Table 1).

Figure 3a summarizes the type of initial gastrectomy by 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 patients who underwent surgery for MMGC within 5 years after initial gastrectomy.

The type of reconstruction procedure in the initial DG and PG by the time interval between the initial gastrectomy and treatment for MMGC are shown in Fig. 3b and Fig. 3c, 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 accounted for 21.7% (65/286) of patients who underwent surgery for MMGC within 5 years after initial DG. Likewise, the proportion of each reconstruction procedure differed by the time interval between initial PG and treatment for MMGC (Fig. 3c). The distribution of the types of gastrectomy ($P < 0.001$; Fig. 3a) or reconstruction procedures ($P < 0.001$; Fig. 3b and $P = 0.022$; Fig. 3c) differed significantly by the time interval between the initial gastrectomy and treatment for MMGC.

Figure 4 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. 4).

Discussion

This multi-institutional questionnaire survey successfully collected data from more than a thousand MMGC patients and shed light on the actual situation of MMGC patients in Japan. As a 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 in 1967 and was developed as a surgical approach for benign peptic ulcer, which aimed to prevent dumping syndrome by preserving the pyloric ring [6]. The feasibility of PPG as a function-preserving gastrectomy for early gastric cancer was first reported by Kodama et al. in 1991 and became prevalent in combination with the generalization of the concept of minimally invasive surgery [7]. 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 2.5% (277/11,261) and 3.1% (397/13,002) of gastrectomies performed in 2001 and 2002, respectively [8–10]. Later, PPGs accounted for approximately 3% of gastrectomies registered in the annual reports [12]. Because patients who underwent surgery for MMGC between 2003 and 2017 were reported in the present survey, the observed low proportion of MMGC patients whose interval between the initial PPG and detection of MMGC was 10 years or longer seemed reasonable.

Several epidemiological studies have reported that B-II in gastrectomy for benign peptic ulcer more significantly correlates with gastric stump carcinoma than B-I, and the incidence increases ≥ 20 years from initial gastrectomy [11, 12]. 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 the reflux, was associated with gastric stump carcinoma, although a consensus has not been reached [13–16]. These characteristics, such as the higher incidence of remnant stomach cancer after B-II and longer interval from initial gastrectomy to detecting remnant stomach cancer, can be applicable to MMGC after B-II. However, we could not prove this in the present study because the number of patients who underwent B-II in each period in 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 in 1893, the use of R-Y in DG became prevalent and its feasibility was published in the 2010s in Japan [17–21]. Therefore, it is also reasonable that the proportion of R-Y procedures increased over time (Fig. 3b). The Japanese Society for the Study of Postoperative Morbidity after Gastrectomy (JSSPMG) conducted a questionnaire survey in 2010 to reveal the status of reconstruction after gastrectomy. The results supported an increase in R-Y in recent years because 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 [22].

Another advantage of the present survey is that a considerable number of patients with MMGC after PG was reported and the same discussion may be applicable to the differences between the three reconstruction procedures after PG. Jejunum interposition (JI) is applicable to the relatively small remnant stomach and can theoretically prevent reflux esophagitis, but it requires procedures that are slightly complicated [23, 24]. Esophagogastric anastomosis (EG) has also been attempted in PG because the procedure is much simpler than jejunum interposition [25, 26]. A major drawback of EG is gastro-esophageal 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 [27–30]. Double-tract reconstruction (DT) after PG is also an emerging procedure, with which surgeons are more familiar than JI because only jejunogastric anastomosis is supposed to be added to R-Y reconstruction [31–34]. A Japanese nationwide survey in 2010 reported that the most preferred reconstruction approach after PG was EG (48% of the responding institutions) followed by JI (28%) and DT (13%) [22]. The small proportion of MMGC found within 5 years after JI in the present survey may be explained by the assumption that JI became common in 1990s, but it has been displaced by DT in the current century.

Although completion total gastrectomy is the standard surgery for advanced cancer in the remnant stomach, partial gastrectomy can be applied to early cancer [35]. The current survey clearly demonstrated that the possibility of avoiding completion total gastrectomy depends on the size of the remnant stomach (Fig. 4).

There are some 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 asked to provide the number of patients who underwent surgery for MMGC between 2003 and 2017. A range of 15 years in the inclusion period 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 published literature on the time trend of the type of gastrectomy or reconstruction procedure. A large-scale prospective study is awaited 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, this multi-institutional questionnaire survey shows that the type of initial gastrectomy and reconstruction procedure differs by the time interval between initial gastrectomy and the detection of MMGC. The proportion of completion total gastrectomy decreased as the size of the remnant stomach increased.

Abbreviations

MMGC, metachronous multiple gastric cancer; DG, distal gastrectomy; PG, proximal gastrectomy, PPG; pylorus-preserving gastrectomy; B-I, Billroth-I; B-II, Billroth-II; R-Y, Roux-en Y; JI, jejunal interposition; EG, esophagogastric anastomosis; DT, double-tract reconstruction; JSGSP, The Japanese Society for Gastro-Surgical Pathophysiology

Declarations

Ethics approval and consent to participate

The study protocol has been approved by the institutional review board of Kanazawa Medical University (Trial No. I267). The 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.

Consent for publication

The requirement to obtain informed consent was waived by the institutional review board of Kanazawa Medical University (Trial No. I267).

Availability of data and materials

All data are available without restriction. Researchers can obtain data by contacting the corresponding author.

Competing interests

The authors declare no competing interest in connection with this study.

Funding

All authors declare that no specific funding was received for this study.

Authors' contributions

Kinami, S. and Kosaka, T. designed the study. Kumagai, K., Aizawa, M., Kamiya, S., Takahata, T., Toda, M., Cho, H., Takahashi, M., and Kubota, T. performed data acquisition, data analysis, and interpretation. Kumagai, K. and Kinami, S. prepared the manuscript. Kinami, S., Lee, SW., and Ohira, M. revised paper critically. All authors read and approved the final manuscript.

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Tables

Table 1. Number of each type of gastrectomy performed in the initial gastrectomy among patients with metachronous multiple gastric cancer

DG		PG		PPG	SG	LR	Total
943		150		79	10	52	1,234
B-I	712	JI	68				
B-II	138	EG	64				
R-Y	83	DT	13				
Others	10	Others	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

Figures

1. How many surgeries for cancer in the remnant stomach were performed between 2003 and 2017?

<input type="text"/>	cases									
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2. How many surgeries were performed for MMGC among these cases?

<input type="text"/>	cases									
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3. Please fill in the blank in the table below with the number of cases.

Procedure for the initial gastrectomy	Number of cases	Time interval from the initial gastrectomy until diagnosis of MMGC (years)							Treatment for MMGC	
		<1	1-2	2-3	3-4	4-5	5-10	>10	CTG	Partial
DG B-I										
DG B-II										
DG R-Y										
DG others										
PG EG										
PG JI										
PG DT										
PG others										
PPG										
SG										
LR										

Figure 1

Questionnaire used for the analysis (English translation). MMGC, metachronous multiple gastric cancer; DG, distal gastrectomy; B-I, Billroth I; B-II, Billroth II; R-Y, Roux-en Y; PG, proximal gastrectomy; EG,

esophagogastric anastomosis; JI, jejunal interposition; DT, double tract; PPG, pylorus-preserving gastrectomy; SG, segmental gastrectomy; LR, local resection; CTG, completion total gastrectomy; Partial, partial gastrectomy

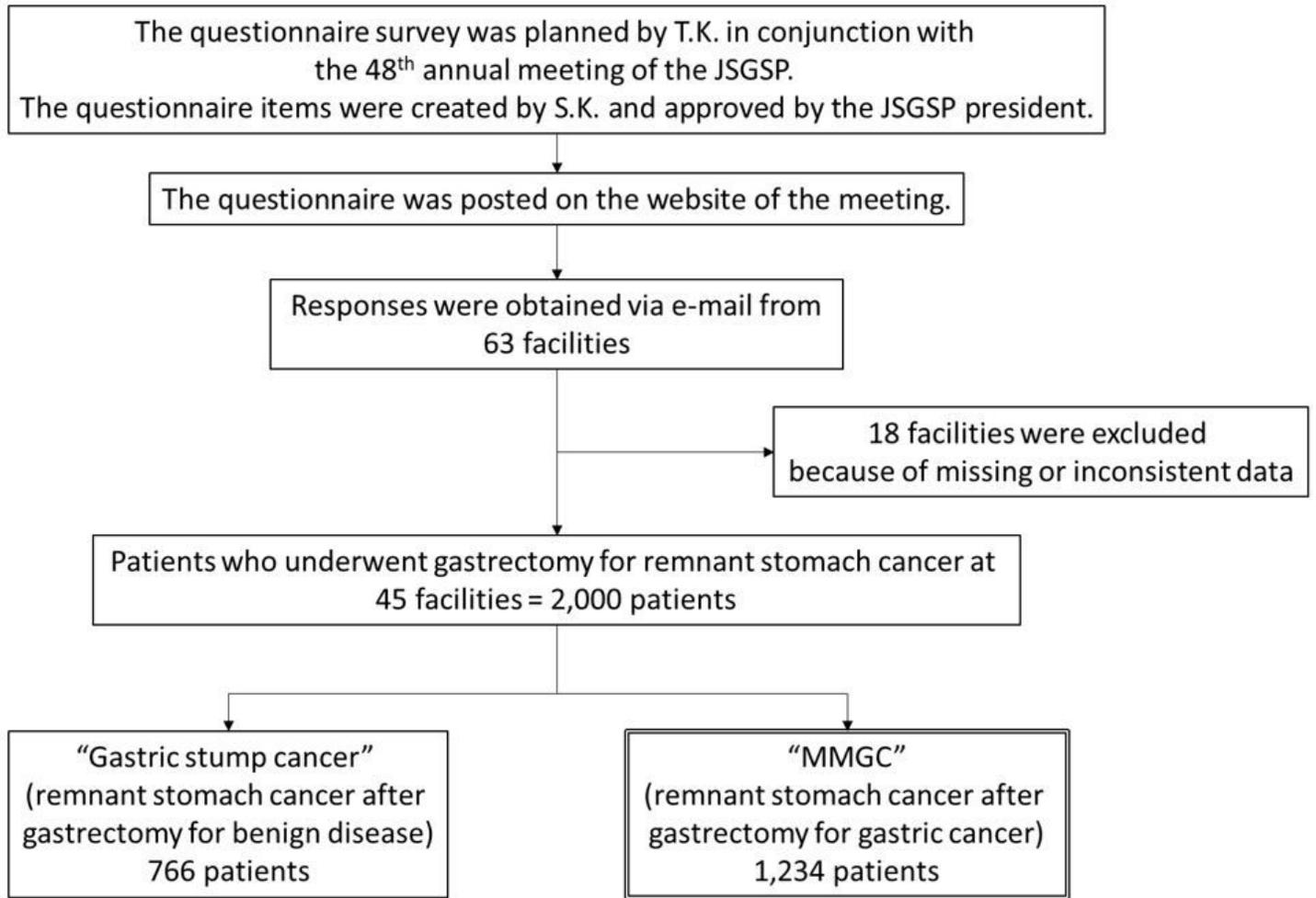


Figure 2

Flow diagram of the questionnaire survey and the subsequent analysis. MMGC, metachronous multiple gastric cancer

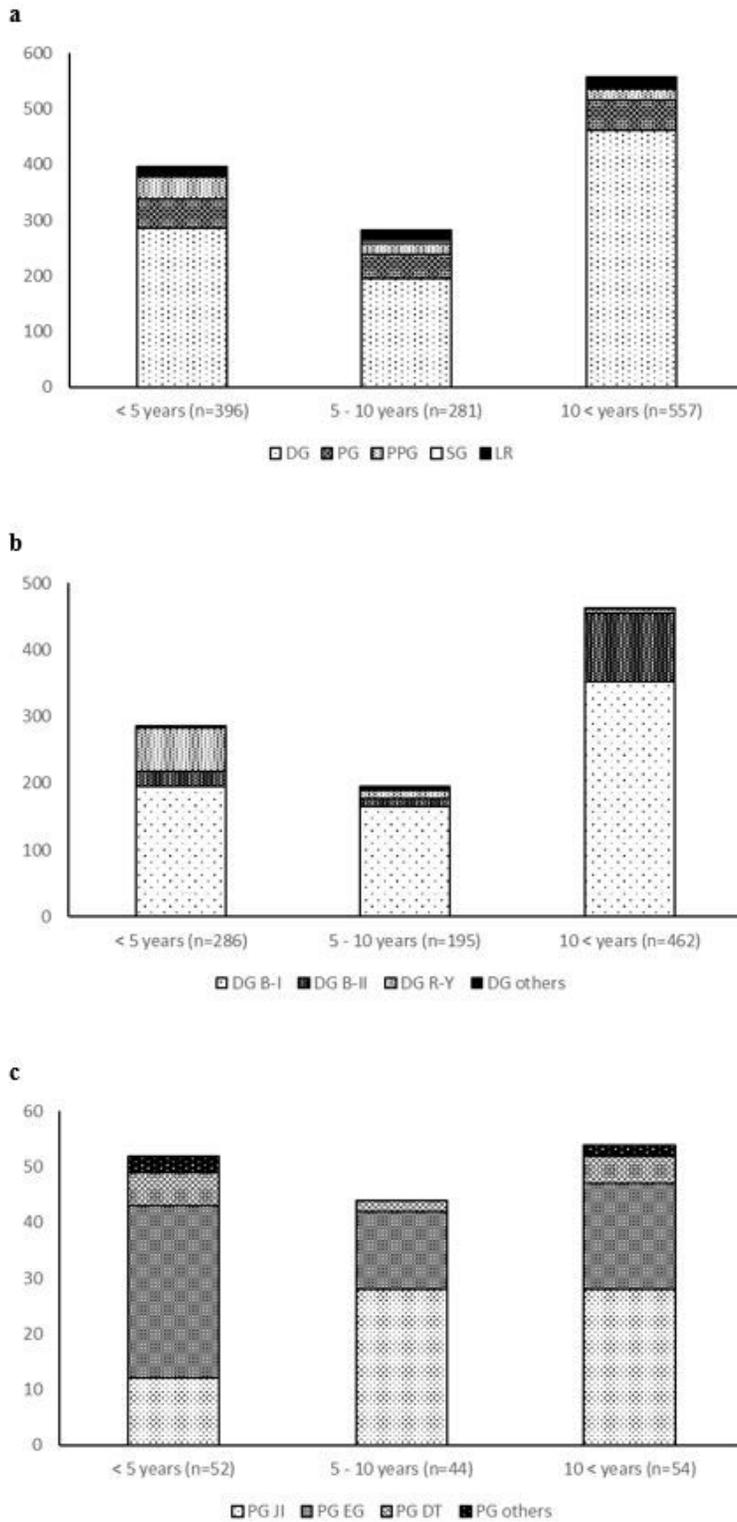


Figure 3

Type of initial gastrectomy (a) and reconstruction procedures after DG (b) and PG (c) by time 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; JI, jejunal interposition; EG, esophagogastrostomy; DT, double tract

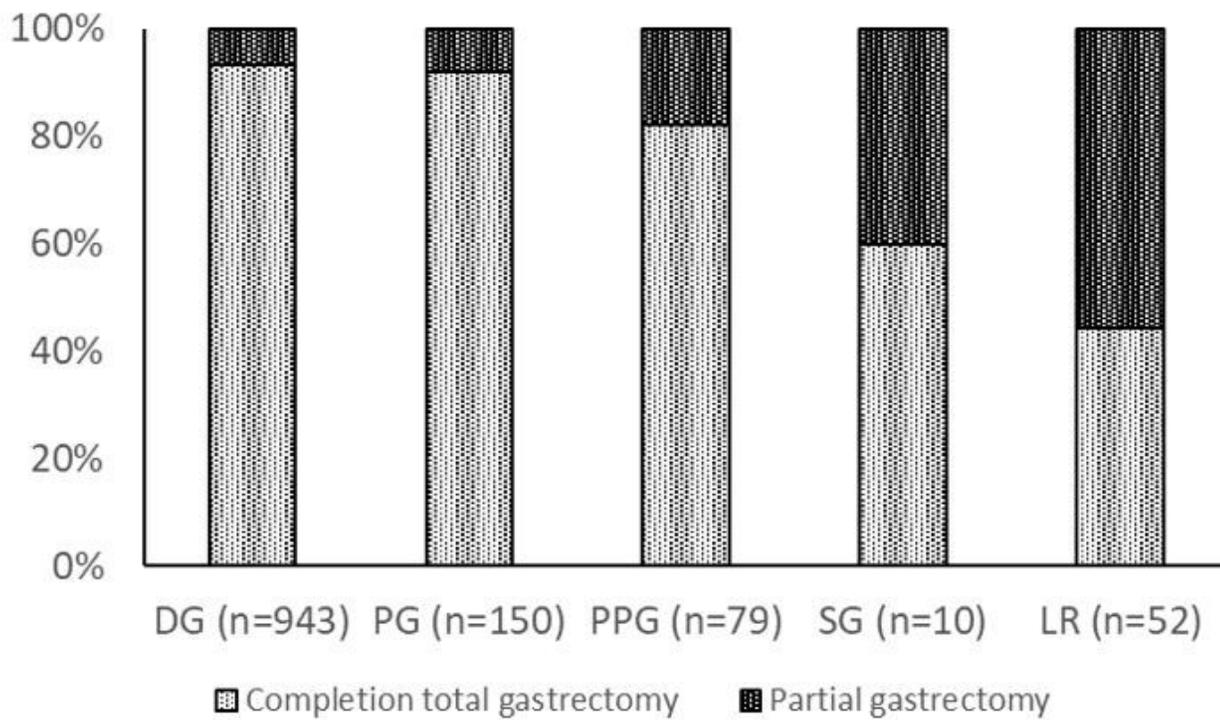


Figure 4

Performed procedure for MMGC after each type of initial gastrectomy. MMGC, metachronous multiple gastric cancer; DG, distal gastrectomy; PG, proximal gastrectomy; PPG, pylorus-preserving gastrectomy; SG, segmental gastrectomy; LR, local resection