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REVIEW ARTICLE

Does remnant gastric cancer really differ from primary gastric cancer? A systematic review of the literature by the Task Force of Japanese Gastric Cancer Association

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Abstract Remnant gastric cancer, most frequently defined as cancer detected in the remnant stomach after distal gastrectomy for benign disease and those cases after surgery of gastric cancer at least 5 years after the primary surgery, is often reported as a tumor with poor prognosis. The Task Force of Japanese Gastric Cancer Association for Research Promotion evaluated the clinical impact of remnant gastric cancer by systematically reviewing publications focusing on molecular carcinogenesis, lymph node status, patient survival, and surgical complications. A systematic literature search was performed using PubMed/MEDLINE with the keywords "remnant," "stomach," and "cancer," revealing 1154 relevant reports published up to the end of December 2014. The mean interval between the initial surgery and the diagnosis of remnant gastric cancer ranged from 10 to 30 years. The incidence of lymph node metastases at the splenic hilum for remnant gastric cancer is not significantly higher than that for primary proximal gastric cancer. Lymph node involvement in the jejunal mesentery is a phenomenon peculiar to remnant gastric cancer after Billroth II reconstruction. Prognosis and postoperative morbidity and mortality rates seem to be comparable to those for primary proximal gastric cancer. The crude 5-year mortality for remnant gastric cancer was 1.08 times higher than that for primary proximal gastric cancer, but this difference was not statistically significant. In conclusion, although no prospective cohort study has yet evaluated the clinical significance of remnant gastric cancer, our literature review suggests that remnant gastric cancer does not adversely affect patient prognosis and postoperative course.

Keywords Remnant gastric cancer · Lymph node · Carcinogenesis · Prognosis · Systematic review

Abbreviations
RGC Remnant gastric cancer
PGC Proximal gastric cancer
EBV Epstein–Barr virus

Introduction

Patients who have undergone a partial gastrectomy because of either malignant disease or benign disease are considered to be at an increased risk of carcinogenesis in the remnant stomach, which is known as remnant gastric cancer (RGC) [1–3]. The most frequently used definition is "cancer in the remnant stomach after surgery for benign

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disease and those after surgery for gastric cancer found at least 5 years after the primary surgery." In addition to these criteria, we focused only on cancer found in the proximal stomach after dissection of the distal stomach. Balfour first described the clinical entity of RGC in 1922 [4]. The incidence of metachronous RGC has been reported as 1.0–3.0 % [5–7]. Although Balfour's definition for RGC was occurrence of carcinoma in the remnant after operation for benign disease, later studies included cancer that was detected after 5 years following initial gastrectomy for malignant disease. Although mass screening has improved the early detection rate of gastric cancer in Korea and Japan, RGC is still frequently revealed to be in advanced stages at detection. The risk of RGC is associated with the interval after gastrectomy and the type of reconstruction. These previous studies focused on whether remnant gastric cancer had an increased risk of carcinogenesis [8]. Thereafter, the discussion moved to whether RGC has a poorer prognosis than primary proximal gastric cancer (PGC). Most of the recent publications on this topic included RGC that occurred within 5 years after the primary treatment.

The most important issue is to compare the prognosis of RGC and PGC. Because of extended lymph node metastases and serosal invasion at the time of RGC diagnosis, the patients' prognosis was reported to be poor [9]. Although radical surgery is still the only curative treatment for RGC, such complex surgery remains associated with relatively high rates of morbidity and mortality [10]. Anatomical alterations, intraabdominal adhesions, and the frequent combined resection of other organs render an operation for RGC difficult. Most studies that have investigated this surgical treatment have enrolled only a few patients and have supplied only a brief descriptive analysis of their complications.

In the present study, the Task Force of Japanese Gastric Cancer Association for Research Promotion reevaluated the clinical impact of RGC by systematically reviewing previous publications, focusing mainly on lymph node status, patient survival, and surgical complications. The molecular mechanisms of carcinogenesis were also addressed. Nationwide retrospective cohort studies can be planned based on the results of this systematic review to elucidate the clinical impact of RGC. Based on this review, we sought to develop a basis for the statement of remnant gastric cancer in the next Japanese Gastric Cancer Treatment Guideline.

Materials and methods

Research themes and study selection criteria

This review consists of seven research themes: (1) the interval between the initial surgery and diagnosis of RGC; (2) the molecular mechanisms of RGC carcinogenesis; (3) the incidence of lymph node metastases of RGC in comparison with primary gastric cancer; (4) the characteristics of lymph node metastases and optimal dissection for RGC; (5) the prognosis of RGC in comparison with primary PGC; (6) differences in the prognosis of RGC between the first operation for benign disease and that for malignant disease; and (7) postoperative morbidity and mortality rates for RGC resection in comparison with primary gastric cancer. Articles including information related to the research themes were searched electronically through PubMed and Medline by H.S. and K.O. independently in December 2014. In PubMed, the following search terms were used: "remnant," "stomach," and "cancer." In MEDLINE, the following search strategy was used through the advanced search system: "remnant.af. and {(stomach adj5 neoplas$).af. or (stomach adj5 cancer).af. or (stomach adj5 carcinoma).af. or (stomach adj5 malig$) or (gastric adj5 neoplasma) or (gastric adj5 cancer) or (gastric adj5 carcin$) or (gastric adj5 malignant)).af.} and prognos$.af." After removing duplicate publications, articles investigating the clinicopathological characteristics of RGC were selected. Furthermore, case reports, non-English articles, and articles that addressed cancers other than gastric cancer were excluded. All authors (H.S., T.F., Y.H., and K.O.) reviewed all the articles and arrived at a consensus regarding the articles to be selected at a meeting on February 6, 2015. The degree of relevance and quality of the articles were evaluated, with grades of A (high relevance and quality), B (moderate relevance or quality), or C (no relevance or low quality). Articles were excluded from the review if they were given a grade of C.

Data extraction

All research themes, except for the fifth theme (the prognosis of RGC in comparison with PGC), were based on the literature review for each research theme. The key messages and information were extracted from each article and organized by the authors in this part. For evaluation of the prognosis of RGC and PGC, we conducted a publication-based meta-analysis. We extracted the following information from the eligible articles: country of origin; publication year; enrollment period; total sample size; number of patients stratified by tumor stage (if available); number of deaths for each disease; number of patients for each disease; and the summary statistics for the outcome. The primary outcome for the meta-analysis was 5-year mortality.

Statistical analysis

For the meta-analysis, quantitative data were pooled using random effects inverse variance weighted meta-analysis in R version 3.1.1. If the outcome data were missing, we

extracted the summary statistics from the available information and recalculated the number of deaths at 5 years for each study [11]. We used a continuity correction of 0.5 in studies with zero cell frequencies. The relative risks and corresponding 95 % confidence intervals for death were calculated for each study to compare RGC with primary PGC. We also conducted a subgroup analysis based on the tumor stage (I, II or III, IV). Heterogeneity between the trials and groups of studies was measured with I^2 statistics, which indicate the percentage of variance in a meta-analysis that is attributable to study heterogeneity [12]. All p values are two sided and were considered as statistically significant at values of less than 0.05.

Results

Studies included in the present article

We identified 876 titles through PubMed and 278 titles through MEDLINE from the systematic search. Also, we found manually one more eligible paper in addition to the studies from the foregoing searches [13], and this study was included in our analysis. From a total of 198 eligible studies, we excluded 92 studies after the full-text search because the contents were not relevant to our research questions. A final set of 106 studies was included in this literature review. Thirty-eight studies were given an A score, and 68 studies were given a B score. Finally, we conducted a publication-based meta-analysis using 20 studies that compared the 5-year survival rates between RGC and PGC [3, 6, 13–30]. In addition, eight studies included data on TNM staging along with the survival data [3, 6, 13, 14, 16, 17, 23, 29]. The PRISMA flow diagram [31] for this study is shown in Supplement 1.

Interval between the initial surgery and diagnosis of RGC in the papers published after 2000

In 1990, Stalnikowicz and Benbassat conducted the first systematic review to evaluate the association between the interval after gastrectomy and the development of RGC [32]. They reviewed 58 studies, published between 1970 and 1988, to evaluate the association between gastric resection for benign disorders and subsequent cancer of the gastric remnant. Although there were no consistent differences between the expected and observed numbers of cancers occurring within 15 years after gastric resection, the prevalence of cancer was stratified by the length of time since the gastric resection, which indicated a two- to fourfold increase in the risk of gastric cancer in patients who survived for 15 or more years after gastric surgery. In the eligible papers published after 2000, some articles reported the mean or median intervals between the initial surgery and RGC diagnosis. In particular, 7 studies reported the intervals stratified by RGC of the initial surgery for malignant or benign disease, although the background characteristics of patients varied substantially [23, 26, 28, 33–36]. The mean or median intervals between the initial surgery for malignant disease and RGC diagnosis seemed to be shorter than those between the initial surgery for benign disease and RGC diagnosis (Table 1). The mean intervals for malignant and benign disease were around 10 and 30 years, respectively.

Table 1 Interval to remnant gastric cancer after primary gastrectomy for initially malignant disease and benign disease

Reference no.	Author, year	Initial surgery for malignant disease (in years)	Initial surgery for benign disease (in years)
[23]	An, 2007	18.8 ± 9.7	28.6 ± 10.2
[33]	Ahn, 2008	6.8 ± 6.7	32.4 ± 7.2
[34]	Hu, 2009	10.4 ± 5.5	29.2 ± 12.7
[35]	Lee, 2010	7 ± 5	36 ± 6
[36]	Namikawa, 2010	10.0 (1–48)	24.5 (8–40)
[26]	Komatsu, 2012	12 (2–36)	32 (5–51)
[28]	Li, 2013	16.8 ± 11.4	16.8 ± 11.4

Pathogenesis of the remnant cancer may differ significantly, depending on the period after the primary surgery. Remnant cancer that develops through etiologies that are identical to that of the primary cancer may emerge relatively early after the primary surgery, whereas cancer caused by reflux of the duodenal contents may emerge late. Based on the frequency of location of primary gastric cancer, particularly depending on *Helicobacter pylori*-induced carcinogenesis [37], the incidence of metachronous multiple cancers may be higher after proximal gastrectomy. Perhaps proximal gastrectomy may induce additional risk for RGC when compared with distal gastrectomy.

Molecular carcinogenesis of RGC

There could be molecular changes that are related to metachronous multiple carcinogenesis not influenced by surgery-induced reflux and those that may reflect chemical carcinogenesis resulting from the reflux. Each molecular mechanism could be described in relationship to the two major types of carcinogenesis. However, there were not any articles describing these differences in molecular mechanisms rather than the differences between RGC and PGC. Duodenogastric reflux, including the reflux of bile and pancreatic juice, after a Billroth II procedure for benign disease is frequently discussed as an important factor related to the development of stump carcinoma.

Many experiments have implicated bile acids, the main component of the duodenal juice, in gastric carcinogenesis. In particular, rat models without the use of the carcinogen *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine showed adenocarcinoma in the remnant stomach that was related to the severity of the duodenogastric reflux. A relationship between gastritis cystica polyposa and gastric-type adenocarcinoma has been suggested [38].

During the past 10 years, several reports have showed the molecular carcinogenesis of RGC. In a retrospective study with 130 patients, Leivonen et al. analyzed the cell proliferation rate of biopsy specimens from gastric remnants by immunohistochemical staining of Ki-67 [39]. The Ki-67 labeling index of the tumors was significantly higher in the remnant stomach group, as is known to be associated with bile reflux and reconstruction without bile reflux. Recently, Sasaki et al. confirmed that the surrounding gastric mucosa in the RGC group was significantly less atrophic than that of the group with gastric cancer restricted to the upper part of the stomach [40]. The surrounding gastric mucosa was significantly less atrophic in RGC than in chemotherapy-naïve gastric cancer, which indicates that RGC may have a different pathogenesis.

Clarke et al. found that bcl-2 protein overexpression in the gastric remnant mucosa and gastric cancer 15 or more years after partial gastrectomy suggest the bcl-2 proto-oncogene is involved in malignant progression [41]. van Rees et al. reported that K-ras codon 12 point mutations are rare in both RGC and primary gastric cancer [42]. On the other hand, Baba et al. found that p53 overexpression by tumors was almost twice as common in the group with gastric cancer of the remnant stomach as that in the group that underwent distal gastrectomy for benign disease [43]. p53 mutation may have an important role in the high proliferative activity of RGC, and *Helicobacter pylori* infection may be closely related to carcinogenesis in patients with RGC. Kawabe et al. found a significant relationship between the expression of COX-2 and p53 in RGC [44]. For those with adjacent noncancerous mucosa, the rate of positive COX-2 expression was significantly higher in patients with RGC than in patients with primary gastric cancer. Therefore, the authors suggested that the COX-2 selective inhibitor to RGC may have synergistic effects with chemotherapy.

Kaizaki et al. found that the Epstein–Barr virus (EBV) was also associated with de novo and metachronous RGC [45]. EBV infection, along with longstanding inflammation, which causes primary gastric cancer, may facilitate the development of de novo RGC. Therefore, the authors concluded that close follow-up of patients treated with distal gastrectomy for EBV-associated gastric carcinoma is necessary to detect metachronous RGC. This close association between EBV and RGC was confirmed by Chen et al. [46], who found EBV genome polymorphisms of EBV-associated gastric carcinoma in patients with RGC in a Chinese population. The proportion of EBV associated with RGC was apparently higher than that associated with primary gastric cancer in the intact stomach.

Aya et al. found that high-level microsatellite instability frequency of gastric RGC was significantly higher than that of sporadic gastric carcinoma [47]. Moreover, high-level microsatellite instability was significantly more frequent in RGC after Billroth II anastomosis than after Billroth I anastomosis. Sitarz et al. reported that the IL-1B-31T > C promoter polymorphism is associated with RGC but not with early-onset or primary gastric cancer [48]. A statistically significant difference in the presence of the C allele compared with the control group was found in patients with RGC, with the T allele conferring protection against gastric stump cancer.

Is the incidence of lymph node metastases for remnant gastric cancer greater than that for primary gastric cancer?

Many authors have pointed out the altered lymphatic pathway for RGC resulting from the initial surgery. The incidence of lymph node metastases for RGC is not higher than that for primary gastric cancer from studies comparing the two groups [3, 17, 22, 23, 26, 27], and some results suggest a rather higher incidence of lymph node metastases in primary gastric cancer [13, 29] (Table 2). The ratio of node-positive patients may be affected by the stage distribution of the patients. In the study by Tokunaga et al., 43.1 % (72/167) of the RGC group comprised tumor penetration of serosa (SE) or tumor invasion of adjacent structure (SI) patients; in contrast, only 18.9 % (143/755) of the primary gastric cancer group was constituted of these patients [29]. Although the ratio of node-positive patients was higher in the RGC group than in the primary gastric cancer group (49.1 % vs. 38.7 %), these ratios were not comparable. Eight studies suggested that the incidence of lymph node metastases in RGC is not always higher than that in primary gastric cancer (Table 2). The type of reconstruction (Billroth I vs. Billroth II) and disease (malignant/benign) of the initial surgery may not affect the incidence of lymph node metastases [49]. The initial surgery for benign disease did not include lymph node dissection, so the lymphatic pathway along the left gastric artery and left gastroepiploic artery is maintained at the time of surgery for RGC, with some alterations caused by the initial gastric resection and reconstruction. The obvious difference in the incidence of lymph node metastases may not be assumed between RGC and primary gastric cancer. The most recent report on this topic [50] suggested a lower incidence of lymph node metastases after complete dissection during the initial oncological surgery (Table 3). If

Table 2 Incidence of lymph node metastases for remnant gastric cancer [with data compared between remnant gastric cancer (RGC) and proximal gastric cancer (PGC)]

Reference no.	Author, year	Cases	<mp %	<se %	*N*+ %
[17]	Chen, 1996	25 (B)	100.0 (25/25)	80.0 (20/25)	60.0 (15/25)
	PGC	143	96.5 (138/143)	75.5 (108/143)	60.1 (86/143)
[3]	Thorban, 2000	47 (B)	70.2 (33/47)	40.4 (19/47)	53.2 (25/47)
	PGC	498	89.6 (446/498)	41.1 (205/498)	73.2 (365/498)
[13]	Kunisaki, 2002	33 (M/B:0.9)	72.7 (34/33)	51.5 (17/33)	48.5 (16/33)
	PGC	44	54.5 (24/44)	13.6 (6/44)	34.1 (15/44)
[22]	Inomata, 2003	15 (M/B:0.3)		40.0 (6/15)	46.7 (7/15)
	PGC	139		28.8 (40/139)	46.0 (64/139)
[23]	An, 2007	38 (M/B:0.5)	84.2 (32/38)	34.2 (13/38)	41.7 (15/36)
	PGC	770	73.2 (564/770)	31.7 (244/770)	49.9 (396/793)
[26]	Komatsu, 2012	33 (M/B:0.7)	69.7 (23/33)	39.4 (13/33)	39.4 (13/33)
	PGC	138	66.7 (138/207)	30.4 (63/207)	43.0 (89/207)
[29]	Tokunaga, 2013	167 (M/B:0.9)		43.1 (72/167)	49.1 (82/167)
	PGC	755		18.9 (143/755)	38.7 (292/755)
[27]	Costa-Pinho, 2013	47 (B)	93.5 (43/46)	82.6 (38/46)	63.8 (30/47)
	PGC	245	80.4 (197/245)	72.2 (177/245)	64.3 (148/230)
	All RGC			49.0 (198/404)	50.4 (203/403)
	All PGC			35.2 (986/2801)	51.8 (1455/2809)

M malignancy, *B* benign, *PGC* proximal gastric cancer, *RGC* remnant gastric cancer, *mp* muscularis propria, *se* tumor penetration of serosa

Table 3 Incidence of lymph node metastases in remnant gastric cancer according to lymph node stations

Reference no.	Author	Cases	Nos. 1–4	Nos. 7–9	Nos. 10, 11	Nos. 12, 13	Jejunal	Mediastinal
[14]	Sasako, 1991	36	12–17	9–13	15–24		15	
	PGC	634	7.8–29.0	6.2–18.0	10.4			
[7]	Furukawa, 1991	43	7–36	0–14	10–21		7.0	
[15]	Ikeguchi, 1994	20	10.0–15.0	0–5.0	25.0		10.0	
	PGC	266	17.3–50.0	9.0–25.2	11.3–15.4		0.8	
[54]	Yonemura, 1994	87	17–30	14–21	23–27	2–8	31	25
	5 years		23–46	0–19	9–33	0	25	0
[56]	Kodera, 1996	26	15–44	8–25	8–25			
	5 years		0–50	0	0			
[55]	Isozaki, 1998	23	9–45	0–18	17–45			
	PGC		14–46	10–22	16–21			
[3]	Thorban, 2000	47					46.8	
[51]	Han, 2003	58	33–75	25–40	60–72	8.3–36	16.7	50
[26]	Komatsu, 2012	33			17		35	
	PGC	207			10		0	
[53]	Li, 2012	83	25–44.4	23.5–33.3	14.2–21.4	6.7–14.2	54.5	33.3
	PGC	300	30.6–52.5	15.8–23.9	16.7–36.4	5.9–11.1		13.0–13.6
[52]	Di Leo, 2014	176	4.2–25.3	8.3–19.6	7.1–10.0		46.4	
	M/SM		0–4.3	0–7.7	0		0	
	MP/SS		0–21	8.3–33.3	0		55.5	
[50]	Ohashi, 2015	50	35	31	26		0	1.4
	5 years		17	0	13			0

the initial surgery was for gastric cancer, only a few nodes are left at the time of surgery for RGC after the initial systematic lymph node dissection. The lower incidence of lymph node metastases can be supposed, but unexpected lymph node metastases may be possible.

What are the characteristics of lymph node metastases and optimal dissection for RGC?

Lymph node involvement in the jejunal mesentery is a phenomenon peculiar to the RGC after Billroth II reconstruction, with the reported incidence ranging from 7.0 % to 46.8 % [3, 6, 14, 15, 26, 51–56] (Table 4). Several authors have reported relatively high incidences of lymph node metastases at the splenic hilum in patients with RGC [15, 50, 51, 55]. The preceding lymph node dissection possibly increased the lymphatic flow from the remnant stomach to these nodes. However, the lymphatic flow and incidence of metastases after initial gastrectomy for peptic ulcers without dissection may be the same as for primary gastric cancer [13]. If the initial oncological surgery includes complete dissection on the lesser curvature side (Nos. 1, 3, and 7), RGC located at the lesser curve may easily develop lymph node metastases on the greater curvature side (Nos. 4sb, 4sa, and 10). This clinical question cannot be answered from these review series because there are few reports on RGC after initially malignant disease. Lymphatic spread to the mediastinal space was mentioned in a few reports [50, 51, 53, 54], but the precise ratio of mediastinal lymph node metastases is unknown because mediastinal dissection is not routinely performed for RGC in these previous series of patients. For similar reasons, there was little information on paraaortic lymph node metastases.

The therapeutic strategy for RGC involves complete resection of the tumor combined with safe surgical margins and sufficient lymph node dissection. Based on the reported results on lymph node metastases, dissection of the perigastric lymph nodes (Nos. 1–4) and the second-level lymph nodes (Nos. 7–9) are mandatory (Table 3). Dissection at the splenic hilum (No. 10) and along the splenic artery (No. 11) is also necessary for advanced RGC [50, 55]. As for splenectomy aiming for dissection of No. 10 and No. 11d (splenic hilum), the indication may be similar to primary gastric cancer in cases of RGC after benign diseases because of the similar lymphatic pathway. However, in cases of RGC after malignant disease, complete dissection at the lesser curvature side performed at the initial surgery may alter lymphatic flow and easily cause metastases at the splenic hilum. Sufficient evidence to support this

Table 4 Characteristics of 20 eligible studies for comparison of the survival rates for remnant gastric cancer (RGC) and proximal gastric cancer (PGC)

Reference no.	Author, date	Period	RGC[a] (5-year survival rate)	PGC[a] (5-year survival rate)	RGC vs. PGC
[14]	Sasako, 1991	1962–1988	39 %	45 %	NSD
[15]	Ikeguchi, 1994	1966–1991	52.5 %	62.1 %	NSD
[16]	Pointner, 1994	1984–1989	53.5 %	32.8 %	Better
[17]	Chen, 1996	1977–1993	25 %	46 %	NSD
[18]	Lo, 1997	1969–1994	43 %	55 %	NSD
[19]	Newman, 1997	1985–1994	63 %	37 %	NSD
[20]	Imada, 1998	1974–1996	93.3 %	83.5 %	NSD
[6]	Kaneko, 1998	1962–1995			NSD
[21]	Bruno, 2000	1986–1998	17.4 %	23.2 %	NSD
[3]	Thorban, 2000	1982–1998	–	–	NSD
[13]	Kunisaki, 2002	1980–1998	–	–	NSD
[22]	Inomata, 2003	1984–1998	69 %	81 %	NSD
[23]	An, 2007	1995–2004	53.7 %	62.9 %	NSD
[24]	Schaefer, 2007	1989–2005	29 %	29 %	NSD
[25]	Mezhir, 2011	1985–2010	53 %	50 %	NSD
[26]	Komatsu, 2012	1997–2008	54 %	61 %	NSD
[27]	Costa-Pinho, 2013	1980–2012	30.7 %	41.2 %	NSD
[28]	Li, 2013	1991–2008	13.6 %	10.7 %	NSD
[29]	Tokunaga, 2013	1980–2007	53.6 %	78.3 %	Worse
[30]	Wang, 2014	1995–2007	16.7 %	28.4 %	Worse

NSD no statistically significant difference

[a] These numbers were based on numbers reported in the original article

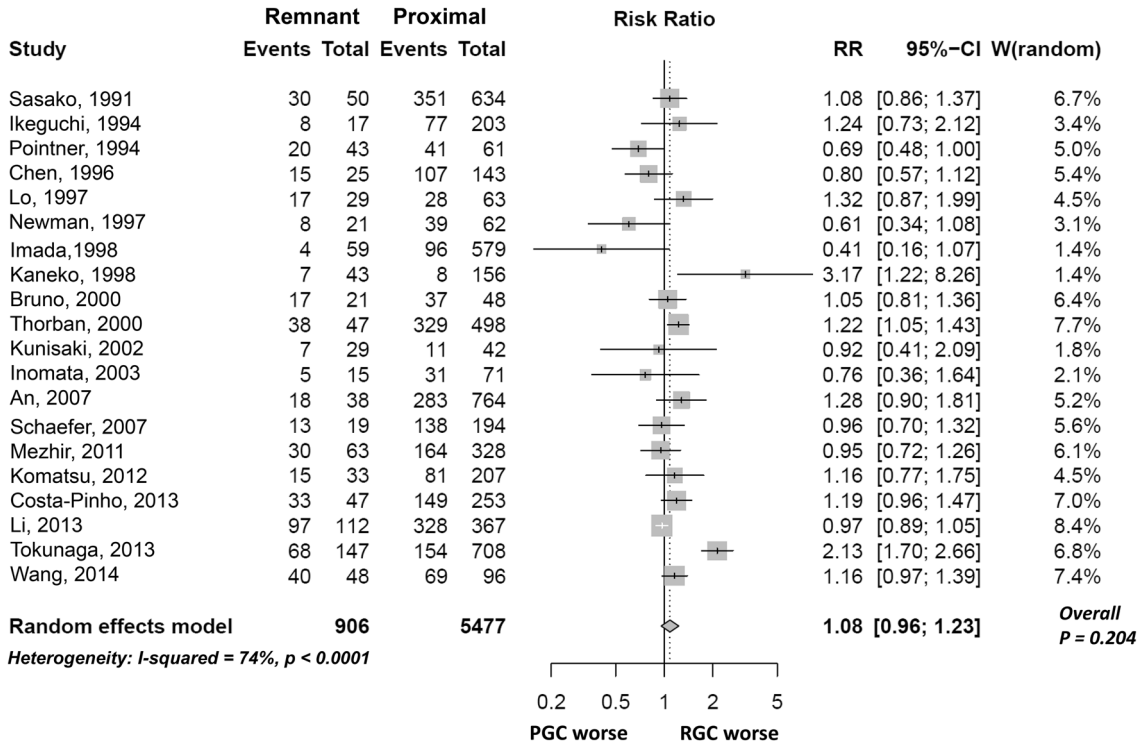

Fig. 1 Meta-analysis comparing the 5-year survival rates between remnant gastric cancer and proximal primary gastric cancer. *PGC* proximal gastric cancer, *RGC* remnant gastric cancer, *RR* risk ratio, *W* weight

speculation cannot be drawn from the current review. Jejunal mesentery nodes should be dissected for RGC previously reconstructed by Billroth II for initial surgery (Supplement 2), particularly for patients with a gastric stump tumor. However, the efficacy of this dissection is still controversial because of the poor prognosis of the patients with metastases at this site. Almost all the reviewed data in the present systematic review contained various heterogeneous factors regarding preceding surgery, including benign or malignant disease, Billroth I or Billroth II reconstruction, and the initial tumor stages. Preceding surgery for malignant disease is becoming more common than that for benign disease. Therefore, prospective cohort studies on cases of RGC treated by initial gastrectomy for malignant disease are important to determine the optimal range of lymph node dissection.

Is the prognosis of RGC different from that of primary PGC?

The characteristics of 20 eligible studies are shown in Table 4 and Fig. 1. In total, 6383 patients (906 RGC and 5477 PGC) were included in this meta-analysis. The crude 5-year mortality of RGC was 1.08 times higher than that of PGC, but this difference was not statistically significant (risk ratio = 1.08; 95 % confidence interval, 0.96–1.23; Fig. 1). Because there appeared to be strong heterogeneity among the studies ($I^2 = 74$ %; p for heterogeneity < 0.0001), it was difficult to analyze these studies together. Next, we conducted a subgroup analysis based on the tumor stage (Fig. 2). In the stage I or II subgroup, the 5-year mortality was not significantly different between RGC and PGC, and there was still strong heterogeneity among the studies ($I^2 = 77$ %; p for heterogeneity < 0.0001). On the other hand, there was a statistically significant difference in the 5-year mortality between RGC and PGC in the stage III or IV subgroup (risk ratio = 1.14; 95 % confidence interval, 1.06–1.22; overall $p = 0.0001$), without statistical heterogeneity among the studies. RGC showed 14 % worse prognosis compared with PGC in the stage III or IV subgroup.

Many studies have reported no significant difference in the prognosis between RGC and PGC (Table 4). However, the difference in the reported survival rates caused by the various backgrounds of patients in different studies and the small sample sizes may confound the findings. Some reports suggest worse survival of patients with advanced RGC [6, 30], in contrast with the good prognosis of patients with early-stage RGC. Current statistical analysis shows a worse prognosis of RGC than that of PGC in the advanced stage. Definitive answers cannot be drawn from this review, so a large-scale cohort is necessary to elucidate this problem.

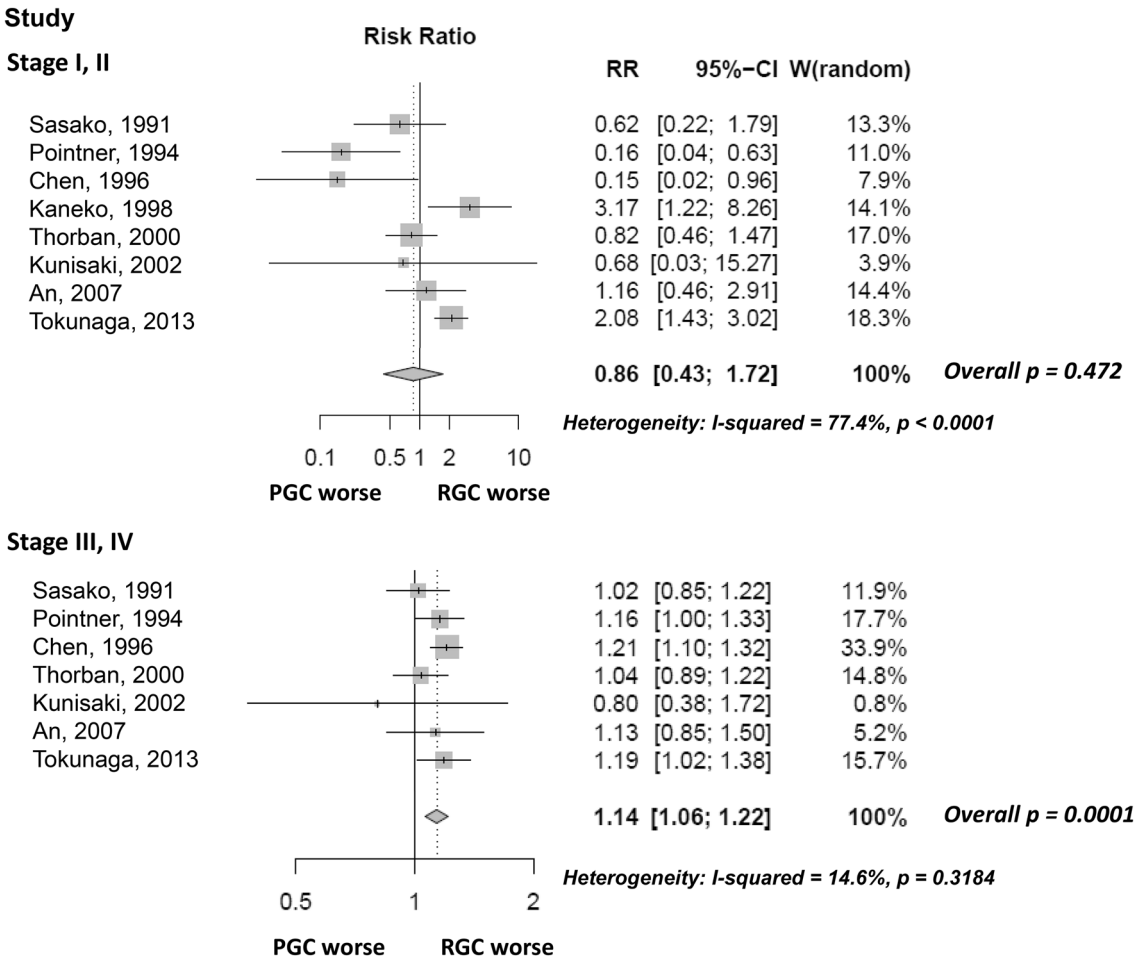

Fig. 2 Meta-analysis comparing the 5-year survival rates between remnant gastric cancer and proximal primary gastric cancer according to TNM stage. *PGC* proximal gastric cancer, *RGC* remnant gastric cancer, *RR* risk ratio, *W* weight

Table 5 Five-year postoperative survival rates in remnant gastric cancer between initial surgery for benign disease and initial surgery for malignant disease

Reference no.	Author, year	Initially benign	Initially malignant	*p* value
[57]	Takeda, 1996	32.1 % ($n = 28$)	61.5 % ($n = 13$)	<0.05
[34]	Hu, 2009	38.1 % ($n = 47$)	10.4 % ($n = 47$)	<0.05
[36]	Namikawa, 2010	75.0 % ($n = 10$)	51.4 % ($n = 24$)	Not significant
[29]	Tokunaga, 2013	49.0 % ($n = 79$)	59.3 % ($n = 68$)	Not significant
[8]	Takeno, 2014	50 % ($n = 14$)	37 % ($n = 58$)	<0.05
	Total	45.2 % ($n = 180$)	41.7 % ($n = 210$)	Not significant

Prognosis of RGC between first operation for benign disease and that for malignant disease

Because gastric cancer resection usually accompanies extensive lymphadenectomy, the route for lymph node metastasis in the initial operation for malignant disease may differ from that in the initial operation for benign disease. Therefore, it remains controversial whether there is any difference in the prognosis between the malignant and benign groups. Previous studies have revealed contradictory results regarding the 5-year survival rates between initial surgery for benign disease and that for malignant disease (Table 5) [8, 29, 34, 36, 57]. No significant difference in the stage distribution was found between the two groups, except for one study; Takeda et al. reported that stage I (53.8 %) is more common in the malignant group than in the benign group (21.4 %) [57]. With these limitations, we combined the data, which

revealed no significant difference between the two groups (45.2 % vs. 41.7 %). Although no stage-stratified comparison was made, the 5-year survival rates seemed comparable between the two groups. A risk-adjusted comparison including tumor-related and physiological variables should be performed using a large database.

Postoperative morbidity and mortality rates for RGC resection in comparison with primary gastric cancer resection

Resection of RGC is associated with intraabdominal adhesion, especially in the initially malignant group. Surgeons sometimes encounter technical difficulties during resection, leading to prolonged surgical duration and/or excessive blood loss. Furthermore, intraoperative surgical complications, such as intestinal injury, may occur during the procedure. Therefore, it remains uncertain whether RGC resection has higher postoperative morbidity and mortality rates than conventional gastric cancer resection. Previous studies have reported that the postoperative morbidity rates following RGC resection range from 20 % to 42 % [3, 14, 35, 58–61], with postoperative mortality rates ranging from 0 % to 12.5 % [20, 30, 60–62]. Regarding the literature from East Asia, the postoperative mortality rates range from 0 % to 7.7 % [20, 30, 35, 56, 59]. There were only two retrospective reports comparing postoperative morbidity and/or mortality rates between the two types of resection [3, 20]. Imada et al. reported that mortality rates of each group were 3.4 % (2/59) in RGC resection and 2.1 % (12/579) in primary gastric cancer [20]. Thorban et al. also reported very similar results, with mortality rates of 2.1 % (1/47) in RGC resection and 2.2 % (11/498) in primary gastric cancer [3]. Moreover, they showed that morbidity rates of both group were equal (40 % in RGC and 36 % in primary gastric cancer) [3]. Neither study reported any significant difference between remnant cancer resection and conventional cancer resection. From these results, postoperative morbidity and mortality rates after RGC resection seem to be comparable to those in conventional cancer resection. Risk-adjusted comparison of the patient's physiological stability, tumor characteristics, and the surgical procedure is warranted for definitive conclusions to be reached.

As our overall conclusions of this review showed that prognosis and postoperative morbidity of RGC were comparable to conventional primary gastric cancer, the question raised is to ask whether exclusion of RGC from clinical trials for gastric cancer treatment is unnecessary. We would like to answer this question as follows. For clinical trials for surgical approaches, RGC should be excluded because of those different lymphatic structures from primary gastric cancer. Although RGC after distal gastrectomy for benign disease may preserve original lymphatic structures, reconstruction can be different from primary gastric cancer surgery. For clinical trials for chemotherapeutic approaches, RGC should also be excluded because of potential differences in molecular carcinogenesis from primary gastric cancer.

In conclusion, this systematic review evaluated a total of 106 papers selected from 1154 publications related to RGC. Although no prospective cohort study that evaluates the clinical significance of RGC has yet been completed, the results of the present literature review suggest that RGC itself does not have significant risk factors that adversely affect patient prognosis and the postoperative course.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

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