

2016 Gastric Cancer: Global view

Current status in remnant gastric cancer after distal gastrectomy

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Abstract

Remnant gastric cancer (RGC) and gastric stump cancer after distal gastrectomy (DG) are recognized as the same clinical entity. In this review, the current knowledges as well as the non-settled issues of RGC are presented. Duodenogastric reflux and denervation of the gastric mucosa are considered as the two main factors responsible for the development of RGC after benign disease. On the other hand, some precancerous circumstances which already have existed at the time of initial surgery, such as atrophic gastritis and intestinal metaplasia, are the main factors associated with RGC after gastric cancer. Although eradication of *Helicobacter pylori* (*H. pylori*) in remnant stomach is promising, it is still uncertain whether it can reduce the risk of carcinogenesis. Periodic endoscopic surveillance after DG was reported useful in detecting RGC at an early stage, which offers a chance to undergo minimally invasive endoscopic treatment or laparoscopic surgery and leads to an improved prognosis in RGC patients. Future challenges may be expected to elucidate the benefit of eradication of *H. pylori* in the remnant stomach if it could reduce the risk for RGC, to build an optimal endoscopic surveillance strategy after DG by stratifying the risk for development of RGC, and to develop a specific staging system for RGC for the standardization of the treatment by prospecting the prognosis.

Key words: Remnant gastric cancer; *Helicobacter pylori*; Endoscopic treatment; Surveillance; Laparoscopic surgery

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Core tip: There seemed two different categories of remnant gastric cancer. One develops at the stomal area

following distal gastrectomy for benign disease after a long latency period, caused by the duodenogastric reflux. The other develops in the remnant stomach following gastric cancer surgery during the follow-up period, correlated with *Helicobacter pylori*. Early detection and aggressive surgical approach are essential to improve the prognosis. A specific staging system should be necessary to predict the prognosis. Minimally invasive treatments, such as endoscopic or laparoscopic surgery, have been applied recently.

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INTRODUCTION

Gastric cancer is the fourth most common malignancy. Although the prognosis of gastric cancer has improved notably because of progress in diagnosis and treatment, it remains the second leading cause of cancer-related mortality worldwide^[1]. Remnant gastric cancer (RGC) after distal gastrectomy (DG) has been reported to account for 1%-8% of all gastric cancers^[2,3]. RGC and gastric stump cancer are recognized as the same clinical entity, where gastric cancer develops in the stump or in the remnant stomach following a gastrectomy irrespective of the histology of the primary lesion (benign or malignant). Since Balfour first described RGC in 1922^[4], many studies of RGC have been reported by various researchers. As possible important factors for the pathogenesis for RGC, duodenogastric reflux and *Helicobacter pylori* (*H. pylori*) infection, both of them are associated with chronic gastritis, have been investigated.

In comparison with primary gastric cancer, RGC has commonly been diagnosed at an advanced stage, resulting in a low rate of curative resection and a poor prognosis^[5-7]. However, recently, the incidence and etiology of RGC have been changing, because of the decrease in the opportunity to undergo gastrectomy for benign disease, early detection and the stomach-preserved treatment of the initial gastric cancer, and improvement of the outcomes in patients with gastric cancer. Furthermore, recent advances in diagnostic and therapeutic techniques have contributed to early detection and the minimally invasive treatment of RGC.

The aim of this review is to provide an overview of the current knowledge and issues related to RGC based on the recent literature.

PATHOGENESIS OF REMNANT GASTRIC CANCER

From the clinical observations, cancer in the remnant

stomach could be classified into several categories: cancer newly developed in the remnant stomach (newly developed RGC); cancer remaining in the remnant stomach after the initial gastric surgery (remaining RGC); metachronously developed gastric cancer; and recurrent cancer in the remnant stomach^[8]. It is considered that the mechanism of carcinogenesis in RGC after DG differs between the cause of initial operation; benign disease or gastric cancer.

Initial disease

Experimental studies have demonstrated that the risk for gastric cancer is higher in the remnant stomach than in the normal gastric mucosa^[9-11], but epidemiological studies have not reported definitive conclusions. In prospective cohort studies, some reports from Western countries have shown that remnant stomach after DG for peptic ulcer disease had a higher risk for gastric cancer^[12-14], whereas reports from Japan have shown the opposite result^[15,16]. This discrepancy could result from the difference in the rate of incidence of primary gastric cancer in the general population; Japan has one of the highest incidences of primary gastric cancer in the world^[17].

Some authors have investigated RGC after DG for benign disease in order to elucidate the development of newly developed RGC. It has been reported that the two main factors responsible for environmental changes affecting remnant gastric mucosa after gastrectomy are chronic damage attributed to duodenogastric reflux and denervation of the gastric mucosa^[9-11,18]. Miwa *et al.*^[19] showed that duodenogastric reflux had potent carcinogenic activities in the rat. Kaminishi *et al.*^[10] demonstrated that denervation of the gastric mucosa promoted carcinogenesis in the remnant stomach using a rat model.

Because of the improvement of drug therapy for duodenal and gastric ulcers, gastrectomy for benign disease has decreased over the last 2 decades. Still, this type of RGC has not decreased due to the long latency period required for carcinogenesis after initial surgery. In contrast, RGC after DG for gastric cancer has become more common. Hosokawa *et al.*^[20] reported that the cumulative risk of developing RGC in patients who underwent DG after early gastric cancer was 2.4% at 5 years and 6.1% at 10 years. Similarly, Morgagni *et al.*^[21] reported that the cumulative risk of RGC in patients who underwent DG after early gastric cancer was 2.6% at 10 years, 3.2% at 15 years, and 4% at 20 years.

Several studies have demonstrated the clinico-pathological differences between RGC after benign disease and that after gastric cancer^[3,8,22-31] (Table 1). In these studies, compared with Billroth-I (B-I) reconstruction, RGC was observed more frequently at the anastomotic site in Billroth-II (B-II) reconstruction. The probable reason for this difference is that the anastomotic site is continuously bathed with

Table 1 Initial reconstruction, interval, and location of remnant gastric cancer based on primary disease

Ref.	Primary disease	No. of patients	Initial reconstruction (B- I /B- II /R-Y)	Interval (yr)	Location (Stomal/non-stomal)
Tanigawa <i>et al</i> ^[8] 2002	Benign	20	7/13	25.8	8/12
	Cancer	27	18/9	10.6	3/24
An <i>et al</i> ^[22] 2007	Benign	25	-	28.6	16/9
	Cancer	13	-	18.8	7/6
Ohashi <i>et al</i> ^[23] 2007	Cancer	108	71/28 ¹	7.5	14/94
Schaefer <i>et al</i> ^[24] 2007	Benign	19	1/18	34.0	11/8
Ahn <i>et al</i> ^[25] 2008	Benign	13	0/13	32.4	12/1
	Cancer	45	6/38 ¹	6.8	23/21
Firat <i>et al</i> ^[26] 2009	Benign	26	0/26	32.0	16/10
Ojima <i>et al</i> ^[27] 2010	Benign	17	12/5	22.0	8/9
	Cancer	21	16/5	9.0	2/19
Mezhir <i>et al</i> ^[3] 2011	Benign	105	B- II : 97	32.0	72/33
Komatsu <i>et al</i> ^[28] 2012	Benign	19	4/15	30.0	9/10
	Cancer	14	12/1 ¹	12.0	2/12
Li <i>et al</i> ^[29] 2013	Benign	88	28/60	32.1	55/33
	Cancer	24	14/10	16.8	9/15
Tokunaga <i>et al</i> ^[30] 2013	Benign	89	23/66	31.0	46/43
	Cancer	78	59/17 ¹	9.4	13/65
Leo <i>et al</i> ^[31] 2014	Benign	176	10/167	34.6	71/105

¹Remining cases were reconstructed by Roux-en-Y. Stomal: Anastomotic site, non-stomal: non-anastomotic site. B-I: Billroth-I; B-II: Billroth-II; R-Y: Roux-en-Y.

duodenogastric reflux, resulting in mucosal inflammation and regeneration after B- II reconstruction. The average interval between initial DG and the second surgery for RGC is reported to be 22-34.6 years for benign disease and 6.8-18.8 years for gastric cancer. This long interval for the development of RGC in the benign group is thought to be attributed to the chronic stimulation by duodenogastric reflux. Successive activation of cellular proliferation in the anastomotic site has been demonstrated. The reason for the shorter interval for RGC after DG for gastric cancer is that patients already have some precancerous lesions, such as atrophic gastritis and intestinal metaplasia, and they are followed-up closely with endoscopic examination^[32].

Reconstruction method

B- II reconstruction is generally considered to have a higher risk of newly developed RGC than B- I reconstruction, because a significant association between B- II reconstruction and RGC after DG for benign disease has been demonstrated. However, Tanigawa *et al*^[33] and Leo *et al*^[31] noted that B- II reconstruction was performed more often in DG for peptic ulcer disease until the late 1980s in Japan and Italy. Although there have been some reports that showed a higher risk of newly developed RGC after DG for peptic ulcer disease in B- II reconstruction than in B- I reconstruction^[13,34], a meta-analysis^[35] and a recent large population-based study from Sweden^[36] demonstrated that type of reconstruction did not affect the risk of newly developed RGC. From these findings, whether B- II reconstruction results in a higher risk of newly developed RGC than B- I reconstruction remains uncertain.

H. pylori infection

In primary gastric cancer, it has been generally accepted that *H. pylori* infection is the definite carcinogen for gastric cancer^[37-39], and *H. pylori* eradication therapy can reduce the prevalence of gastric cancer^[40]. However, the significance of *H. pylori* infection in the development of RGC for patients after DG remains controversial.

The rate of *H. pylori* infection in the remnant stomach has been reported to have a broad range (17.4%-68.2%)^[41-49], which is lower than in the non-operated stomach. Although it has been reported that spontaneous regression of *H. pylori* is rare under normal circumstances, several researchers have demonstrated that spontaneous regression of *H. pylori* has been observed with time after operation, regardless of the initial disease for DG^[41,48,50]. We previously demonstrated that the prevalence of *H. pylori* infection was significantly lower in patients with severe duodenogastric reflux than in those without duodenogastric reflux^[41]. Although significant differences were not shown in any study, there seems to be a trend for a lower *H. pylori* prevalence in B- II reconstruction than in B- I reconstruction. Duodenogastric reflux is considered a possible factor that inhibits the growth of *H. pylori*. On the other hand, Nakagawara *et al*^[51] and Chan *et al*^[46] demonstrated that the prevalence of *H. pylori* was significantly lower in R-Y reconstruction than in B- II reconstruction, even though duodenogastric reflux was observed significantly less in R-Y reconstruction. These reports may indicate there are factors other than duodenogastric reflux that inhibit the growth of *H. pylori* in the remnant stomach.

Similar to patients with peptic ulcer disease, the

Table 2 The success rate of *Helicobacter pylori* eradication therapy in remnant stomach

Ref.	No. of patients	Regimen of eradication	Success rate, <i>n</i> (%)
Matsukura <i>et al</i> ^[42] 2003	20	Dual therapy Lansoprazole 60 mg, AMPC 1500 mg for 2 wk	14 (70.0)
	20	Triple therapy Lansoprazole 60 mg, AMPC 1500 mg, CAM 800 mg daily for 1 wk	18 (90.0)
Onoda <i>et al</i> ^[52] 2005	33	Triple therapy Rabeprazole 20 mg, AMPC 1500 mg, CAM 800 mg daily for 1 wk	30 (90.9)
Kim <i>et al</i> ^[53] 2008	61	Triple therapy Rabeprazole 20 mg, AMPC 2000 mg, CAM 1000 mg daily for 1 wk	53 (86.9)

AMPC: Amoxicillin; CAM: Clarithromycin.

success rate of *H. pylori* eradication using triple therapy in remnant stomach has been reported to be around 90%^[42,52,53] (Table 2). In a randomized, controlled trial, Kim *et al*^[53] demonstrated not only that the efficacy of preoperative and postoperative proton pump inhibitor-based eradication therapies was not significantly different in patients undergoing DG for gastric cancer, but also that neither the type of reconstruction method nor the presence of duodenogastric reflux in the remnant stomach affected its efficacy. There is evidence that *H. pylori* infection is a cause of chronic atrophic gastritis and intestinal metaplasia, which are considered possible precancerous conditions for gastric cancer^[38,54]. Several authors^[41,49,55] reported that chronic and active mucosal inflammation was closely associated with *H. pylori* infection in the remnant stomach. It was demonstrated that eradication of *H. pylori* infection in the remnant stomach improved the degree of chronic active gastritis^[42,52,56]. Given these reports, the eradication of *H. pylori* infection in the remnant stomach may prevent the development of RGC after DG. We have suggested that young patients with mild atrophic gastritis and without duodenogastric reflux may be the best candidates for *H. pylori* eradication therapy, because they had the highest probability of *H. pylori* colonization in the remnant stomach^[41,52]. However, it is still uncertain whether eradication of *H. pylori* in remnant stomach can reduce the risk of carcinogenesis. Further prospective, large studies are needed to elucidate the efficacy of *H. pylori* eradication therapy for the prevention of RGC in patients who undergo DG.

THE DIFFERENCE BETWEEN REMNANT GASTRIC CANCER AND PRIMARY PROXIMAL GASTRIC CANCER

In several studies, the clinicopathological features of RGC have been compared with those of primary proximal gastric cancer (PPGC) because of the similar anatomical location. It has been demonstrated that the male-to-female ratio was significantly higher for RGC than for PPGC^[8,22,57,58]. The reason for the male dominance is that male patients have a higher risk for

both gastroduodenal ulcer and gastric cancer^[30,31].

It has been reported that RGC has unique patterns of lymph node metastasis compared with PPGC. In PPGC, the main lymphatic flow drains to the lymph nodes along the celiac artery through the lymph nodes at the lesser curvature, the left gastric artery, and the right side of the cardia. In RGC, it has been considered that the characteristics of lymph node metastases are different from PPGC because abnormal lymphatic formation is induced as a result of cutting off these lymphatic pathways at the initial surgery^[31]. Furthermore, Tokunaga *et al*^[30] mentioned that altered lymphatic drainage after DG may affect the long-term survival of RGC patients with advanced stage disease. Previous studies have investigated the incidence of lymph node metastasis focusing on around the splenic artery, in the splenic hilum, at the lower mediastinum, and in the jejunal mesentery^[8,24,31,57,59-63] (Table 3). Some authors demonstrated a higher incidence of lymph node metastasis around the splenic artery, in the splenic hilum, and at the lower mediastinum in RGC; therefore, lymphadenectomy of these regions is recommended for curative surgery. In patients with previous B-II reconstruction, the rate of lymph node metastases in the jejunal mesentery has been reported to be 10.0%-67% (Table 3). Thorban *et al*^[57] reported that RGC patients with lymph node metastases in the jejunal mesentery had a poor prognosis, with a median survival time (MST) of 13.2 mo. Similarly, Leo *et al*^[31] reported that RGC patients with lymph node metastases in the jejunal mesentery had worse outcomes than those with metastases in other lymph node stations. Therefore, jejunal mesentery lymph node dissection including the origins of each involved jejunal artery is recommended for RGC patients with previous B-II reconstruction. However, the details of the spread of lymph node metastases in RGC patients are still uncertain, because the number of patients examined in these studies was too small.

Adhesions caused by prior surgery, especially for malignant disease because of lymph node dissection, lead to a higher rate of adjacent organ resections in comparison with primary gastric cancer to achieve curative resection^[3,8,24,57,63]. Prior studies reported the poor prognosis of patients with RGC^[5,6]. However,

Table 3 The incidence of lymph node metastases of remnant gastric cancer and primary proximal gastric cancer in the splenic hilar region, around the splenic artery, in the lower mediastinum, and in the jejunal mesentery

Ref.	No. of patients		Splenic hilar (No. 10)	Splenic artery (No. 11)	Lower mediastinum		Jejunal mesentery lymph node metastases
					No. 110	No. 111	
Sasako <i>et al</i> ^[59] 1991	RGC	52	15.2%	23.5%	-	-	15.2%
	PPGC	656	10.4%	10.4%	-	-	-
Ikeguchi <i>et al</i> ^[60] 1994	RGC	20	0%	25.0%	-	-	10.0%
	PPGC	266	11.3%	15.4%	-	-	-
Thorban <i>et al</i> ^[57] 2000	RGC	47	-	-	-	-	31.9%
	PPGC	498	-	-	-	-	-
Tanigawa <i>et al</i> ^[8] 2002	RGC	32	8.3%	9.1%	-	50.0%	60.0%
	PPGC	310	16.7%	21.7%	-	6.7%	-
Han <i>et al</i> ^[61] 2003	RGC	67	60.0%	72.3%	-	50.0%	16.7%
	PPGC	-	-	-	-	-	-
Schaefer <i>et al</i> ^[24] 2007	RGC	19	-	-	-	-	22.2%
	PPGC	194	-	-	-	-	-
Li <i>et al</i> ^[62] 2012	RGC	83	21.4%	14.2%	33.3%	33.3%	54.5%
	PPGC	300	36.4%	16.7%	13.6%	13.0%	-
Komatsu <i>et al</i> ^[63] 2012	RGC	33	12.1%	-	-	-	67.0%
	PPGC	207	6.8%	-	-	-	-
Leo <i>et al</i> ^[31] 2014	RGC	176	10.0%	7.1%	-	-	46.4%
	PPGC	-	-	-	-	-	-

RGC: Remnant gastric cancer; PPGC: Primary proximal gastric cancer.

Table 4 Comparison of operative outcomes between remnant gastric cancer and primary proximal gastric cancer

Ref.	No. of patients		RO resection rate (%)	Adjacent organ resection rate	Prognosis after curative resection
Thorban <i>et al</i> ^[57] 2000	RGC	50	85.1	Colon: 19.1%, pancreas: 6.4%, liver: 8.5%	MST: 30.9 mo
	PPGC	516	73.9	Colon: 0%, pancreas: 2.8%, liver: 4.9%	MST: 32.1 mo
Tanigawa <i>et al</i> ^[8] 2002	RGC	47	68.1	68.1%	5-yr OS: 56%
	PPGC	310	-	-	5-yr OS: 53%
An <i>et al</i> ^[22] 2007	RGC	38	92.1	-	5-yr OS: 54%
	PPGC	794	86.4	-	5-yr OS: 63%
Schaefer <i>et al</i> ^[24] 2007	RGC	19	-	Colon: 5.3%, pancreas: 10.5%, liver: 5.3%	5-yr OS: 71%
	PPGC	194	-	-	5-yr OS: 48%
Mezhir <i>et al</i> ^[3] 2011	RGC	105	60.0	Colon: 10.1%, pancreas or liver: 5.8%	5-yr OS: 53%
	PPGC	2099	-	-	Unknown
Komatsu <i>et al</i> ^[63] 2012	RGC	33	78.8	Colon: 6.1%, pancreas: 12.2%, liver: 6.1%	Unknown
	PPGC	207	-	Colon: 2.9%, pancreas: 4.3%, liver: 1.9%	Unknown
Tokunaga <i>et al</i> ^[30] 2013	RGC	167	88.0	-	5-yr OS: 54%
	PPGC	755	93.8	-	5-yr OS: 78%

RGC: Remnant gastric cancer; PPGC: Primary proximal gastric cancer; MST: Median survival time; OS: Overall survival.

as shown in Table 4, most recent studies, except the study by Tokunaga *et al*^[30], have reported that RGC had equivalent survival compared with PPGC, regardless of stage^[3,8,22,24,30,57,63].

ENDOSCOPIC SURVEILLANCE

Recent advances in endoscopic diagnostic techniques have led to more frequent detection of early RGC after DG. Early detection is essential not only to improve the prognosis of RGC, but also to offer a chance for endoscopic treatment. For early detection of RGC, some authors have reported the importance of periodic follow-up endoscopy after gastrectomy^[20,21,32,64]. Komatsu *et al*^[28] reported that the duration of follow-up was significantly associated with the stage of RGC progression. An *et al*^[22] reported that the prognosis of 7 patients with RGC diagnosed at annual

examination was excellent, with a 5-year survival of 100% without recurrence. Thus, early detection by periodic endoscopic examination may lead to a better prognosis.

The optimal period and interval of endoscopic surveillance to detect RGC at an early stage have not been determined. In patients who undergo DG for gastric cancer, endoscopic surveillance is considered mainly to detect remaining and metachronous gastric cancer. Hosokawa *et al*^[20] noted that periodic endoscopic examinations to detect RGC at an early stage are recommended at intervals of 2-3 years, because, among 15 patients examined at an interval of no more than 2 years, RGC was detected at an early stage in 12 patients (80%). Ohashi *et al*^[23] and Ojima *et al*^[27] recommended annual endoscopic surveillance from 1 year after DG for gastric cancer to at least 10 years. On the other hand, because the risk of newly

Table 5 Clinical outcomes of endoscopic submucosal dissection for remnant gastric cancer *n* (%)

Ref.	No. of ESD lesions	No. of lesions located on the suture line	<i>En bloc</i> resection rate	Complete resection rate	Complications	
					Perforation	Bleeding
Takenaka <i>et al</i> ^[65] 2008	31	12 (38.7)	30 (96.8)	23 (74.2)	4 (12.9)	0
Hirasaki <i>et al</i> ^[66] 2008	17	-	17 (100)	14 (82.4)	0	3 (17.6)
Hoteya <i>et al</i> ^[67] 2010	40 ¹	-	-	38 (95.0)	1 (2.5)	2 (5.0)
Lee <i>et al</i> ^[68] 2010	13	6 (46.2)	13 (100)	11 (84.6)	0	0
Nishide <i>et al</i> ^[69] 2012	62 ²	29 (46.8)	59 (95.2)	53 (85.5)	11 (17.7)	5 (8.2)
Nonaka <i>et al</i> ^[70] 2013	94	-	86 (91.5)	77 (81.9)	2 (2.1)	2 (2.1)
Tanaka <i>et al</i> ^[71] 2014	33	11 (33.3)	33 (100)	31 (93.9)	3 (9.1)	1 (3.0)

¹Including 9 patients of gastric tube cancer after esophagectomy; ²Including 14 patients of gastric tube cancer after esophagectomy. ESD: Endoscopic submucosal dissection.

developed RGC after gastrectomy for benign disease is thought to be increased from more than 20 years, annual endoscopic screening is recommended to start at least 15-20 years after gastrectomy for benign disease and continue for as long as the patients can receive treatment for RGC^[24,57,64].

OPTIMAL TREATMENT

The mainstay of treatment for RGC patients is radical surgical resection. R0 resection is an important prognostic factor in RGC, as well as conventional gastric cancer^[3,25,29,57]. As some authors have recommended, although R0 resection with an aggressive surgical approach is technically difficult in RGC patients, it might contribute to improving the long-term outcome.

In most studies, the UICC classification was used to determine the N stage in RGC patients, regardless of the initial reconstruction method and the previous disease. However, the number of retrieved lymph nodes is expected to be insufficient to determine the N stage in some RGC patients, especially those with previous malignant disease, which may lead to uncertain staging. Indeed, some authors showed that the total number of retrieved lymph nodes and the perigastric lymph node metastasis rate were lower than for PPGC^[3,8,58,63]. Li *et al*^[62] and Costa-Pinho *et al*^[58] reported that the N stage of the 7th edition of the TNM staging system was not suitable for predicting the outcomes of RGC patients. Therefore, it may be one of the future challenges to create a specific staging system for RGC.

Endoscopic intervention

Endoscopic submucosal dissection (ESD) has been widely accepted as the standard treatment for early gastric cancer patients without potential risk of lymph node metastasis, because ESD is less invasive than surgery and provides better quality of life. Surgical resection for RGC has been reported to have a relatively high postoperative morbidity rate and a high adjacent organ resection rate, so ESD is an attractive treatment. However, it is considered challenging to perform ESD for early RGC, because performing ESD

is technically difficult due to the limited space within which to manipulate and the existence of staples or severe fibrosis around the anastomosis and suture line. Recently, several retrospective studies of ESD for RGC have been reported^[65-71] (Table 5). According to these studies, the en bloc resection rate and the complete resection rate were reported to be 91%-100% and 74%-94%, respectively. Lee *et al*^[68] demonstrated that there were no significant differences between RGC and upper-third gastric cancer in the complete resection rate of ESD, whereas Takenaka *et al*^[65] reported that, when the lesion was located on or not on the suture line, the complete resection rates were 58% and 84%, respectively. With regard to complications, the perforation and bleeding rates were reported to be 0%-17.7% and 0%-17.6%, respectively. The occurrence of perforation was reported to be significantly higher for RGC than for non-remnant gastric cancer^[65], and Tanaka *et al*^[71] demonstrated that the occurrence of perforation was significantly more frequent in anastomotic sites (27.3%) than in non-anastomotic sites (0%).

Although the indications for ESD for primary gastric cancer were similar to those of early RGC in previous studies^[65-71], there has been only one report assessing whether the same indication for ESD for primary gastric cancer can be applied to RGC. Choi *et al*^[72] reviewed 17 surgically resected patients who were possible candidates for ESD for RGC, and they demonstrated that they had no evidence of lymph node metastasis. There is only one study of long-term outcomes after ESD for RGC, in which Nonaka *et al*^[70] reported that the cause-specific survival rate was 100% during the median follow-up period of 4.5 years. Further studies are required to confirm the indications and oncological feasibility of ESD for RGC.

Laparoscopic surgery

Laparoscopic surgery for gastric cancer has been widely accepted because of several advantages, such as less postoperative pain, reduced blood loss, earlier recovery, fewer complications, and shorter hospitalization^[73-75]. However, because adhesions and anatomical alterations due to previous gastrectomy

Table 6 Clinical outcomes of laparoscopic surgery for remnant gastric cancer

Ref.	Type of procedure	No. of patients	Operation time (min)	Blood loss (mL)	Conversion to open surgery	No. of retrieved lymph nodes	Complication rate (%)	5-yr OS (%)
Kim <i>et al</i> ^[76] 2014	Lap	17 ¹	197	-	0%	12.9	23.5	-
	Open	50	149	-	-	-	30.0	-
Kwon <i>et al</i> ^[77] 2014	Lap	18 ²	266	182	5.6%	8	33.3	100.0
	Open	58	203	193	-	7	44.8	94.9
Nagai <i>et al</i> ^[78] 2014	Lap	12	362	69	0%	23.7	0.0	77.8
	Open	10	271	746	-	15.9	20.0	72.9
Tsunoda <i>et al</i> ^[79] 2014	Lap	10	325	55	0%	22	10.0	-
	Open	6	289	893	-	7	33.3	-
Son <i>et al</i> ^[80] 2015	Lap	17	234	228	47.1%	18.8	35.3	67.0
	Open	17	170	184	-	22.3	29.4	60.3

¹Including 10 cases of distal gastrectomy; ²Including 8 cases of robotic surgery. OS: Overall survival.

make laparoscopic surgery complicated and difficult, laparoscopic total gastrectomy has not generally been considered to be indicated in patients with RGC in the early era of laparoscopic surgery. Recently, five studies, including small series of laparoscopic total gastrectomy for RGC compared with open gastrectomy, have been reported^[76-80] (Table 6). All studies showed a longer operation time for laparoscopic surgery. On the other hand, four of five studies, except Son *et al*^[80], showed less blood loss, more retrieved lymph nodes, shorter time to first flatus, and a lower complication rate in laparoscopic surgery. In the study reported by Son *et al*^[80], there were 8 cases (47.1%) of open conversion, for which the most common reason was the presence of severe adhesions after gastrectomy for malignant disease. Although the follow-up time was short in each study, all three studies that assessed survival demonstrated that the 5-year survival rate was similar between laparoscopic surgery and open surgery^[77,78,80]. Because the size of each study was small, multicenter studies should be considered to confirm the advantages of laparoscopic gastrectomy for RGC.

CONCLUSION

In conclusion, there are two different diseases included in the category of RGC. One is RGC that develops at the stomal area of the remnant stomach following DG for benign disease. The lesion commonly develops after a long latency period, possibly influenced by the successive activation of cellular proliferation with the duodenogastric reflux. The other is RGC that develops in the atrophic mucosa of the remnant stomach following DG for gastric cancer. The lesion could be found during the follow-up period by periodic endoscopic examination and might be in line with the carcinogenic pathway of the initial gastric cancer correlated to *H. pylori*. There is no guideline to indicate the standardized stratification method or to suggest the possible optimal treatment strategy for RGC. Still, it is obvious that the prognosis of patients with gastric cancer depends on the stage, which is determined by the T and N categories, and that early detection

and an aggressive surgical approach to achieve R0 resection are essential to improve the prognosis of RGC patients. Recent advances in endoscopic interventions or laparoscopic surgery may provide patients with a better quality of life after minimally invasive treatments.

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