Current controversies in treating remnant gastric cancer: Are minimally invasive approaches feasible?

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Abstract

The incidence of remnant gastric cancer (RGC) is still increasing. Minimally invasive approaches including endoscopic resection, laparoscopic and robotic approaches, and function-preserving gastrectomy have been utilized as curative treatment methods for primary gastric cancer. However, adhesions and anatomical alterations due to previous gastrectomy make the use of minimally invasive approaches complicated and difficult for RGC. Application of these approaches for the treatment of RGC is still controversial. Endoscopic submucosal dissection is a favorable alternative therapy for the resection of early gastric cancer that occurs in the remnant stomach and can prevent unnecessary complications. The majority of retrospective studies have shown that endoscopic submucosal dissection is an effective and oncologically safe treatment modality for RGC. Subtotal gastrectomy could serve as a function-preserving gastrectomy for patients with early RGC and improve postoperative late-phase function. However, there are only two studies that demonstrate the feasibility and oncological efficacy of subtotal gastrectomy for RGC. The non-randomized controlled trials showed that compared to open gastrectomy, laparoscopic gastrectomy for RGC led to better short-term outcomes and similar oncologic results. Because of the rarity of RGC, future multicenter studies are required to determine the indications of minimally invasive treatment for RGC.

Key words: Remnant gastric cancer; Minimally invasive approaches; Endoscopic submucosal dissection; Subtotal gastrectomy; Laparoscopic gastrectomy

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Core tip: The incidence of remnant gastric cancer (RGC) is increasing. Minimally invasive
invasive approaches including endoscopic resection, laparoscopic and robotic approaches, and function-preserving gastrectomy have been utilized as curative treatment methods for RGC. The majority of recent studies have shown that endoscopic submucosal dissection is an effective and oncologically safe treatment modality for RGC. Subtotal gastrectomy could serve as a function-preserving gastrectomy for patients with early RGC and improve postoperative late-phase function. The non-randomized controlled trials demonstrated that compared to open gastrectomy, laparoscopic gastrectomy for RGC led to better short-term outcomes and similar oncologic results.

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INTRODUCTION

Gastric cancer is the fourth most common cancer worldwide and the second leading cause of cancer-related death[1,2]. Remnant gastric cancer (RGC) comprises nearly 1%–8% of all gastric neoplasms[3-5]. The incidence of RGC, however, is increasing due to advances in surgical techniques and treatment options, which have prolonged survival of patients with GC following gastrectomy[6,7]. In the past, RGC was commonly detected at an advanced stage, which resulted in low rates of curative resection and consequently poor prognoses[8,9]. Recently, an increasing number of cases have been diagnosed at an early stage after gastrectomy due to the advances in diagnostic techniques and routine periodic endoscopic surveillance[10-12].

Minimally invasive approaches including endoscopic mucosal resection or endoscopic submucosal dissection (ESD), laparoscopic and robotic approaches, sentinel lymph node biopsy, and function-preserving gastrectomy have been utilized as curative treatment methods for primary early GC with benefits such as improved pain, reduced blood loss, and reduced length of hospital stay[13-15]. However, adhesions and anatomical alterations due to previous gastrectomy make the use of minimally invasive approaches complicated and difficult. In addition, the literature in this area is sparse, and only a few small case series have described ESD or laparoscopic gastrectomy (LG) for RGC. The aim of this review is to provide an overview, based on the recent literature, of the current knowledge related to minimally invasive treatment for RGC.

DIVERSITY OF INITIAL DISEASE AND PREVIOUS RECONSTRUCTION METHODS

The use of gastrectomy for peptic ulcer disease has drastically declined in recent decades[14]. Although Balfour’s definition of RGC was the carcinoma arising in the remnant stomach after surgery for benign disease[17], later studies included carcinoma which was detected more than 5 years after the initial gastrectomy for GC[18]. Since the number of patients with long-term survival after gastrectomy has increased as a result of early detection and early treatment of GC, the number of patients who develop RGC following GC resection may increase[19,20]. Recently, RGC was defined by the Japanese Classifications and Treatment Guideline for Gastric Cancer (14th edition) as all carcinomas arising in the remnant stomach following gastrectomy, irrespective of the primary disease, risk of recurrence, extent of resection or reconstruction type[21]. Based on the Japanese classification definition of gastric carcinoma, the initial disease and surgery type are expanded.

Although the prevalence of GC is decreasing, the incidence of adenocarcinoma of esophagogastric junction is increasing[22]. The choice of surgical technique for treating adenocarcinoma of esophagogastric junction is controversial, but proximal gastrectomy remains an important surgical option. Proximal gastrectomy is also widely used as a function-preserving approach for early-stage proximal stomach cancer[23]. The incidence of RGC after proximal gastrectomy (PG) is increasing and thus, RGC following proximal gastrectomy may be increasingly encountered by...
surgeons in the coming years[21]. Morbid obesity has become a worldwide health problem, probably due to the changes in dietary habits and sedentary lifestyles[24]. Bariatric surgery has been growing in popularity because of its long-term effectiveness in weight loss and comorbid resolution[25]. Over the last 10 years, the number of reported RGC cases in the literature has significantly increased, probably because of the concomitant increase in Roux-en-Y gastric bypass procedures or because of previous underreporting[26]. Torinese et al[26] evaluated the reported incidence of RGC after Roux-en-Y gastric bypass; the real-world incidence is unknown. The incidence of RGC following Roux-en-Y gastric bypass may increase in the coming years.

**ENDOSCOPIC SUBMUCOSAL DISSECTION FOR GASTRIC STUMP CANCER**

ESD is widely accepted as a treatment for early GC with a low risk of lymph node metastasis[27,28]. Traditionally, resection of the gastric stump is the standard treatment for RGC, but this method is associated with high morbidity and mortality[29]. ESD is a favorable alternative therapy for the resection of EGC that occurs in the remnant stomach and can prevent unnecessary complications. Moreover, Fukui et al[30] have found that complete gastrectomy does not improve survival outcomes compared with ESD, and complete gastrectomy may even adversely affect the long-term outcomes of patients with early RGC. However, performing ESD in the remnant stomach is challenging due to the narrow workspace and the presence of severe fibrosis, adhesions and staples under the suture lines[31,32]. We reviewed all published English language literature to assess the efficacy and feasibility of ESD in treating early RGC.

The incidence of lymph node metastasis in early RGC is similar to that of lymph node metastasis in primary early GC[33,34]. Lymph node metastasis of RGC is affected by the current disease stage, not by the initial disease stage. Therefore, it would be possible to apply the indications of ESD for primary GC to RGC. However, the lymphatic drainage system in the remnant stomach might be different from primary GC, and the regional lymph nodes may have already been dissected. Therefore, the indications of ESD for RGC may be different. However, only one study determined the indication of ESD for RGC. The study found that 17 patients who met the indications of ESD for primary GC had no lymph node metastases after radical gastrectomy of remnant stomach[33].

Several retrospective studies[35,36-40] have reported that en bloc resection and curative resection could be achieved (Table 1). According to these studies, the en bloc resection rate, complete resection and curative resection rate for RGC were 88.9%-100%, 77-95% and 74.2%-93.9%, respectively. Chung et al[39] reported rates of en bloc resection, complete resection and curative resection of 88.9%, 90% and 88%, respectively, and Suzuki et al[37] reported rates of en bloc resection and curative resection of 99.2%, and 91.6%, respectively, in the normal stomach. Perforation and delayed bleeding are the major complications of ESD. Previous studies have reported that the bleeding and perforation rates are 0-17.6% and 0-18% in ESD for RGC, respectively. Chung et al[39] reported bleeding and perforation rates of 8.9% and 8%, respectively, and Suzuki et al[37] also reported rates of 4.4% and 2.3%, respectively, in the normal stomach.

Only four studies have considered the long-term outcomes after ESD for RGC. The Nonaka et al[32] reported that the 5-year overall survival rate was 87.3% and the 5-year cause-specific survival rate of 100% during a median follow-up period of 4.5 years for 128 patients who underwent ESD for early RGC. Yabuuchi et al[33] reported the 5-year overall survival rate of 88.4% and 97.6%, respectively, for the patients with normal stomachs and 96.2% for patients with RGC. According to the pathologic results, all patients who died after receiving ESD treatments had contraindications for submucosal invasive EGC. Takeshi Yamashina et al[34] reported that the 3- and 5-year overall survival rates in the ESD group were 85.7% and 81.8% and were 87.5% and 75% in the gastrectomy group, respectively (P = 0.602). The 3-year and 5-year cause-specific survival rates in the ESD group were 94.1% and 89.8%, whereas those in the gastrectomy group were 100% and 100%, respectively (P = 0.334).

Lesions that occur on the suture line or anastomosis site are also difficult to resect en bloc due to fibrosis, adhesions, and staples. There have been a few reports about ESD for RGC at the staple site. Yabuuchi et al[33] found that the en bloc resection rate and intraoperative perforation rate were almost equal between the non-anastomosis or suture line group and the suture line group, whereas the en bloc resection rate was...
ESD is a feasible and oncologically safe treatment for early RGC. However, few studies have reported the outcomes of ESD for RGC after other types of partial gastrectomy were performed. Nomura et al.14 reported the outcomes of ESD for RGC after distal gastrectomy. However, few studies have evaluated the safety and efficacy of ESD for lesions occurring in the remnant stomach and tubular stomach and did not find a significant difference in the en bloc, complete, and curative resection rates. No difference in bleeding rates existed; however, there was a statistically significant difference in perforation rates between the two groups.

The majority of recent studies have shown that ESD is an effective and safe treatment modality for RGC after distal gastrectomy. However, few studies have evaluated the safety and efficacy of ESD for lesions occurring in the remnant stomach and tubular stomach and did not find a significant difference in the en bloc, complete, and curative resection rates. No difference in bleeding rates existed; however, there was a statistically significant difference in perforation rates between the two groups.

ESD is a feasible and oncologically safe treatment for early RGC based on the present studies. However, evidence is limited. Further multicenter studies are needed to confirm these findings.
required to precisely evaluate clinical outcomes of ESD in the remnant stomach.

### SUBTOTAL GASTRECTOMY FOR PATIENTS WITH REMNANT GASTRIC CANCER

Total gastrectomy (TG) combined with radical lymph node dissection has been accepted as a standard treatment for RGC. A survey in Japan revealed that TG was performed in approximately 90% of patients with resectable RGC. Instead of undergoing TG, some patients with early RGC underwent partial gastrectomy as a less invasive surgery, which is based solely on the assumption that early RGC might have a low incidence of lymph node involvement. Hosokawa et al. first investigated the surgical techniques, outcomes, and postoperative quality of life of patients who underwent subtotal gastrectomy (SG) \((n = 13)\) or TG \((n = 22)\) for early RGC. The authors found that the operating time, blood transfusion, and length of hospital stay were similar between the two groups. One year after surgery, the levels of hemoglobin and total protein in the SG group were higher than those in the TG group because of the preserved stomach. In terms of long-term outcomes, no recurrence was found in the SG group during a median follow-up period of 99.2 mo. Irino et al. also reported 24 patients treated with SG. There was no significant difference in the number of lymph nodes harvested between the two groups. The 5-year overall survival rate of the SG group (94.7%) was acceptable (Table 2).

For patients with RGC, SG could serve as a function-preserving gastrectomy which is known to improve postoperative late-phase function. Although there are only two studies that demonstrate the safety of SG for RGC, we believe that this procedure would benefit selected patients with early RGC. However, whether SG is feasible for RGC not limited to the early stage is unknown. Further studies with a larger number of patients are necessary to reach a more definitive conclusion.

### LAPAROSCOPIC GASTRECTOMY FOR REMNANT GASTRIC CANCER

Randomized controlled trials (RCTs) in Eastern countries have demonstrated the benefits of LG for patients with early-stage GC, including a fast recovery and improved quality of life. The fourth edition of the Japanese Gastric Cancer Association guideline considers laparoscopy-assisted distal gastrectomy as a treatment option for clinical stage I cancer. The RCTs have also demonstrated that laparoscopic distal gastrectomy with D2 lymph node dissection for locally advanced GC is safe and associated with a lower complication rate, faster recovery, and less pain than open surgery. However, LG has not generally been indicated in patients with RGC in the early era of laparoscopic surgery because of the adhesions to the adjacent organs, alterations of the anatomical structures and changes in the lymphatic flow caused by previous gastrectomy which make the laparoscopic surgery complicated and difficult. Yamada et al. reported the use of LG for RGC in a patient who had undergone a previous Billroth II reconstruction first in 2005. Since then, several other similar reports of using LG for RGC have been published sporadically. However, the number of cases reported remains small because RGC is rare. The safety and feasibility of using laparoscopic approaches to treat RGC are still unclear. The evidence for the oncologic safety of LG is currently limited. Therefore, we reviewed all published English language literature on LG for RGC to better characterize the technical aspects of the currently used procedures (Table 3). Recently, ten non-RCT studies with a small series of patients compared the perioperative results of LG for RGC with those of open gastrectomy (OG).

All studies comparing the operating time between OG and LG reported that LG required more time than OG, even though the difference was not statistically significant in five out of the ten studies. However, LG was associated with lower intraoperative blood loss than OG in six of the ten studies. The number of resected lymph nodes was reported in all non-RCTs and case studies. There were also no significant differences in the number of lymph nodes harvested between LG and OG in 9 out of the ten studies. Only one study found that the number of retrieved lymph nodes was significantly larger in the LG group than in the OG group (22 ± 13 vs 12 ± 9, respectively; \(P = 0.03\)). The number of harvested lymph nodes is occasionally used as an indicator of the quality of oncological gastrectomy. Compared to the open approach, LG harvested a similar number of lymph nodes at least, if not more. A laparoscopic approach provides a magnified view of the anatomy.
of the abdominal cavity, could illuminate landmarks for surgeons for optimal lymphadenectomy and potentially help reveal more lymph nodes and reduce intraoperative blood loss\[^{63}\].

In terms of the postoperative complication rate, five of the ten studies reported a 6.5%-23.3% risk reduction with LG compared to that of OG\[^{60,62,64,65,68}\]. The remaining five studies showed unfavorable results from the laparoscopic approach in terms of the postoperative mortality rate, although the result was not statistically significant\[^{61,63,66,67,69}\]. LG was also associated with a significantly shorter postoperative hospital stay than OG, as shown in one of the non-RCTs.

In terms of oncological outcomes, long-term clinical outcomes were reported by five studies. All studies indicated comparable 5-year survival rates between the LG and OG groups. Son et al\[^{60}\] reported that the 5-year survival rate of the LG group was 66.6%, which was similar to the rate of 66.7% in the OG group. Nagai et al\[^{62}\] found that the overall 5-year survival rate was 77.8% in the LG group and 72.9% in the OG group. Kwon et al\[^{63}\] found that the 5-year survival rates of the LG group and OG group were also similar (94.9% vs 100%, respectively). Nakaji et al\[^{66}\] found that the 5-year overall survival (OS) of LG and OG were 81% and 60.6%, respectively. The 5-year OS of RGC was different among the stages of disease in each study. However, these results remain inconclusive due to the short follow-up time (21 to 39.1 mo). Therefore, further studies with longer follow-up periods are required to confirm the long-term oncologic outcomes of LG and to establish LG as a standard treatment option for RGC.

Some cases required an open conversion because of severe adhesions or bleeding. However, few reports have investigated the open conversion rate of LG for RGC. Three studies reported a 5.6%-47.1% conversion rate to OG. Liao et al\[^{65}\] found that Billroth I reconstruction, previous open surgery and surgeon experience were the factors significantly associated with conversion to open surgery. Booka et al\[^{66}\] reported that 2 out of the 8 patients who required an open conversion had previously undergone OG and Billroth I reconstruction, and the authors found that neither patient experienced any postoperative complications; the open conversion was safely performed in the presence of severe adhesions. The conversion to OG during LG is an unavoidable phenomenon in a number of patients. More data about the effects of conversion in comparison to those of open surgery are needed.

The evidence concerning locally advanced RGC is scarce. Luo et al\[^{60}\] reported 18 patients with locally advanced (T2-4N0-3M0, stage II-III) RGC who underwent hand-assisted laparoscopic (n = 9) or open surgery (n = 9) and found that hand-assisted LC had several advantages, including small incisions, mild intraoperative hemorrhage, fast postoperative recovery, and few postoperative complications. However, Sasako showed their results at 13\(^{th}\) International Gastric Cancer Congress and believed that LG did not benefit locally advanced RGC because of the lack of tactile sensation with LG, making it difficult to discriminate severe adhesions and to judge the depth of tumor invasion. The author believed that the left kidney needs to be mobilized from the retroperitoneum to obtain a good view.

The present non-RCT’s demonstrated that compared to OG, LG for RGC led to better short-term outcomes and similar oncologic results. Although LG for RGC is technically complex, this method is technically feasible, can be performed safely, and has the advantages of a minimally invasive technique. However, further studies are required to draw any conclusions about the significance of LG for RGC because the number of cases was too small.

## CONCLUSION

| Ref. | Type of procedure | No. of patients | Operating time (min) | Blood loss (mL) | Retrieved lymph node | Hospital stay (days) | Complications | Follow-up (mo) | Recurrence/5-yr OS |
|------|------------------|----------------|---------------------|----------------|----------------------|---------------------|---------------|---------------|------------------|
| Hosokawa et al\[^{53}\], 2014 | SG | 13 | 174 ± 53.0 | 381 ± 372 | NA | 17.8 ± 8.7 | 23.10% | 99.2 | 0 |
| | TG | 22 | 200 ± 59.8 | 597 ± 489 | NA | 18.6 ± 7.1 | 27.30% | 57.2 | 1 |
| Irino et al\[^{52}\], 2014 | SG | 24 | NA | NA | 18.5 (0-46) | NA | 29% | 36 | 94.10% |
| | TG | 42 | NA | NA | 16.5 (3-86) | NA | 14% | 32 | 67.30% |

NA: Not applicable; OS: Overall survival.
Because of the rarity of RGC, reports about minimally invasive approaches for RGC are sporadic. Based on those limited evidence, we could conclude ESD, SG and LG are feasible to treat early RGC. As for LG for locally advanced RGC, the evidence is scarce. Therefore, it is of most importance that the surveillance system to detect early diseases should be established. Future multicenter studies are required to determine the indications of minimally invasive treatment for RGC and provide concrete evidence.

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