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EDITORIAL – GASTROINTESTINAL ONCOLOGY

Gastric Remnant Cancer: Is it different From Primary Gastric Cancer? Insights Into a Unique Clinical Entity

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Balfour first described gastric remnant cancer (GRC) in 1922 as cancer arising in the setting of previous gastric surgery for peptic ulcer disease (PUD).[1,2] More recently, GRC has been described as any cancer occurring in the setting of previous partial gastrectomy for benign or malignant conditions.[1,3]

GRC can be seen in approximately 10% of patients with previous gastric surgery.[3,4] Patients who undergo surgery for benign disease, especially PUD, usually have a long latency period of 15 to 60 years before GRC develops.[4–6] However, it can arise more rapidly ($\geq$ 1 years after resection) in patients with a history of malignancy because the remainder of the gastric mucosa already may have been exposed to carcinogenic risk factors.

Because PUD surgery was routine in the 1970s and 1980s, physicians may continue to encounter GRC given its long latency periods. Additionally, as the survival of primary gastric cancer (PGC) patients is improving, we might even see an increase in the number of GRC cases after malignant gastric resections. Therefore, it is essential for physicians to be familiar with the epidemiology, management, and prognosis of patients with GRC.

GRC has been reported more commonly in men.[1] In the setting of a previous benign resection, GRC usually occurs after a Billroth 2 (BII) reconstruction, and it has been hypothesized that BII leads to increased reflux of duodenal contents into the stomach, thus leading to chronic injury and carcinogenesis.[1,7] Untreated *Helicobacter pylori* infection is another common culprit.[1] Additionally, denervation during ulcer surgery can cause achlorhydria, which leads to impaired mucosal defense mechanisms, thus promoting chronic injury and carcinogenesis.[5] The risk factors for GRC in the setting of previous surgery for malignancy usually are the same as those for PGC, and these are most likely metachronous lesions.[5]

The risk factors have implications for the location of cancer in the remnant stomach. After benign gastric surgery, GRC usually occurs at the site of anastomosis as reflux, and mucosal injury is most prominent in this location.[1,5] However, skip lesions have been described. After resection for primary gastric cancer (PGC), GRC can occur anywhere within the remnant, but occurs most commonly along the lesser curvature and posterior wall, where most of the proximal PGCs arise.[8,9] Therefore, GRC, whether occurring after previous surgery for benign or malignant disease, usually requires a completion gastrectomy.

The management of GRC remains challenging as many patients are diagnosed at an advanced stage, given the lack of any screening protocol for GRC. Staging tools such as diagnostic laparoscopy are not always feasible due to adhesions. Additionally, given proximity and adhesions, there may be a direct extension to surrounding organs such as the colon.[1] Similarly, modes of lymphatic spread, as seen with PGCs, may not be applicable to GRC. GRCs arising around BII reconstruction may also involve the jejunal mesenteric lymph nodes, and jejunal mesentery should also be resected in such cases.[1] Additionally, the previous disruption of lymphatic channels may lead to unusual patterns of lymph node metastases. There is an increased propensity of spread toward the splenic hilum and potentially toward the lower mediastinal lymph nodes.[1]

The need for multi-visceral resections is more common for patients with GRC. It could be argued whether such extensive surgery is appropriate for such an aggressive disease. The accompanying manuscript by Galata et al.[6]

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highlights many of these issues. Galata et al.[6] retrospectively analyzed 95 patients (6.6%) with GRC in a cohort of 1440 consecutive patients who underwent gastrectomy from October 1972 to February 2014. The authors included GRC after previous benign or malignant resections. This cohort of GRCs is one of the largest reported in the literature. As in other studies, the authors noted that the majority of patients with GRC compared with PGC, were men (86.3% vs 54.8%). Most of the patients with GRC (95.7%) had undergone BII reconstruction in the past. The median time to the development of GRC after benign resections was 30 years (interquartile range [IQR], 20–36 years), compared with a median of 3 years (IQR, 2–9 years) after resection for malignant disease. The majority of these patients (92.6%) required a total gastrectomy. The authors reported that the GRC patients required more multivisceral resections than the PGC patients (71.6% vs 46%) but were noted to have a lower incidence of lymph node involvement (N0: 58.9% vs 43.7%), and a lower stage of disease (stage 1: 50.5% vs 40.8%) than the PGC patients (all $p < 0.05$). Additionally, the GRC patients exhibited a trend toward a lower incidence of metastases and signet-cell features than the PGC patients (M1: 2.1% vs 7.5%, $p = 0.06$; SC: 17.9% vs 27.1%, $p = 0.054$, respectively). However, the percentage of patients who had R0 resection was similar between the GRC and PGC groups (86.3% vs 90.4%; $p = 0.211$). Given the need for extensive surgery to achieve R0 resection, the incidence of major postoperative complications was higher (overall complications: 37.9% vs 27.1%, $p = 0.032$; major complications: 19% vs 11.5%, $p = 0.021$), as was the incidence of perioperative mortality (30-day mortality: 12.6% vs 4.7%; in-hospital mortality: 13.7% vs 6%, respectively) than for the PGC patients.

In the multivariable analysis, similar to other studies of PGC, the major predictive variables for worse overall survival (OS) were higher tumor stage and occurrence of postoperative complications. The authors also performed a propensity-matched analysis of 166 patients using 1:1 matching, which resulted in a balanced cohort of GRC and predominantly proximal PGC (86.8%). In this matched cohort, the OS was comparable between the two groups (5-year estimated OS: GRC 36.4%, PGC 38.6%; $p = 0.772$). When a propensity-matched analysis was performed, the OS was similar for the GRC and PGC patients.

The study by Galata et al.[6] has all the limitations of a retrospective analysis. Additionally, the authors could not include important information such as the receipt, timing, or duration of chemotherapy or radiation data given the long duration of the study. Although the authors performed a D2 lymphadenectomy for PGC, the extent of lymphadenectomy for GRC could not be ascertained from the data. However, the authors suggest that given the need for multivisceral resections, it is unlikely that GRC was understaged.

Contrary to Galata et al.[6], Thorban et al.[10] reported that multi-visceral resections in GRC are not associated with increased perioperative morbidity (overall complications: GRC 40.4% vs PGC 35.5%, nonsignificant difference) or mortality (30-day mortality: GRC 2.1% vs PGC 2.2%, nonsignificant difference). Additionally, based on the study by Galata et al.,[6] it cannot be determined whether resection in the setting of previous benign versus malignant disease would have different morbidity or modes of lymphatic spread given the more extensive lymphadenectomy and dissection in patients with malignancy. Despite its limitations, the study by Galata et al.[6] highlights important points in the epidemiology, management, and prognosis of patients with GRC.

Several previous studies also have reported that for patients with similar stages of disease, the prognosis of GRC and PGC is comparable. Mezhir et al.[4] reported on 69 patients who underwent resection for GRC after previous surgery for benign disease. In their cohort, the stage-specific survival after R0 resection was similar to that for PGC. Additionally, the authors compared their findings with those of five other GRC series (2 from Germany,[10,11] 2 from China,[12,13] and 1 from Turkey[5]). The patients with GRC comprised 2.2% to 6% of all the gastric cancer cases. In these series, 60% to 100% of the patients had undergone previous BII. The resection rates varied from 61% to 100%, with R0 resection varying from 45% to 85%. The 5-year survival rate for the patients who underwent curative resection varied from 20% to 71%. Similarly, Ohashi et al.[8] reporting on 108 patients with GRC after previous gastric resection for malignancy in Japan estimated a 5-year OS of 53.1%. These data support the role of aggressive surgical management for well-selected patients with GRC.

Several areas of GRC still need further research. The current data raise the question whether GRC after previous PUD or malignancy behaves differently with regard to lymph nodal metastases or prognosis. Additionally, in this era of aggressive chemotherapy for gastric cancer, the sequencing of treatment for patients with GRC remains unclear. A diagnostic laparoscopy may not be feasible nor have a high yield given extensive adhesions, and peritoneal metastases may not be detected until operative exploration. Additionally, it remains unknown whether GRC has a geographic variation in prognosis similar to PGC. The data on MSI or molecular profiles of GRC also are lacking.[14] Because R0 resection improves survival, individual studies have recommended early detection of GRC through screening for anyone who had BII for PUD at least 5 years previously as long as the patient is fit for surgery.[4]

Similarly, screening has been recommended after distal gastrectomy for malignancy, starting 1 year after resection.[1,8] The cost-effectiveness of these recommendations remains unknown.

It is crucial for physicians to be aware of the epidemiology, management, and prognosis of patients with GRC. Although R0 resection improves survival, multi-visceral resections may be required. In this era of effective chemotherapy, such extensive resections for GRC should be undertaken in the context of multidisciplinary discussion because the sequencing of treatment remains unclear. Given the infrequent nature of this disease, it could be further studied by an international database or registry. Future studies are required for a better understanding of the molecular profiles, the role of screening, and the treatment sequencing in GRC.

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