

WJG 20th Anniversary Special Issues (8): Gastric cancer**Gastric cancer arising from the remnant stomach after distal gastrectomy: A review**

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Abstract

Gastric stump carcinoma was initially reported by Balfour in 1922, and many reports of this disease have since been published. We herein review previous reports of gastric stump carcinoma with respect to epidemiology, carcinogenesis, *Helicobacter pylori* (*H. pylori*) infection, Epstein-Barr virus infection, clinicopathologic characteristics and endoscopic treatment. In particular, it is noteworthy that no prognostic differences are observed between gastric stump carcinoma and primary upper third gastric cancer. In addition, endoscopic submucosal dissection has recently been used to treat gastric stump carcinoma in the early stage. In contrast, many issues concerning gastric stump carcinoma remain to be clarified, including molecular biological char-

acteristics and the carcinogenesis of *H. pylori* infection. We herein review the previous pertinent literature and summarize the characteristics of gastric stump carcinoma reported to date.

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Key words: Remnant gastric cancer; Distal gastrectomy; Carcinogenesis; *Helicobacter pylori*; Endoscopic submucosal dissection

Core tip: Recent studies concerning gastric stump carcinoma were reviewed. Its carcinogenesis took more than 300 mo after distal gastrectomy for benign disease, in contrast to 100 mo for primary gastric cancer. Higher carcinogenetic risk was reported by molecular biological analysis in patients treated with Billroth II reconstruction than with Billroth I. Eradication of *Helicobacter pylori* in the remnant stomach improved the degree of inflammation and the pH level, and might prevent the development of carcinogenesis. Endoscopic treatment for gastric stump carcinoma has been recently reported, therefore, endoscopic surveillance should be repeated after distal gastrectomy.

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INTRODUCTION

Gastric cancer is the second leading cause of cancer-related death in Asia and the fourth most common malignan-

Table 1 Interval between primary gastric cancer and gastric stump carcinoma

| Ref. | Previous disease | Interval (mo) | Interval (mo) |
|--|---------------------|---------------|---------------------|
| | (benign/malignancy) | (all cases) | (benign/malignancy) |
| Kaneko <i>et al</i> ^[12] , 1998 | 21/22 | 180 | 288/118 |
| Take no <i>et al</i> ^[16] , 2006 | 11/21 | | 360/63 |
| Ohashi <i>et al</i> ^[17] , 2007 | | 90 | |
| Ahn <i>et al</i> ^[18] , 2008 | 13/45 | 150 | 384/83 |
| Tanigawa <i>et al</i> ^[19] , 2010 | 578/309 | 252 | |
| Ojima <i>et al</i> ^[20] , 2010 | 17/21 | 180 | 264/108 |
| Komatsu <i>et al</i> ^[21] , 2012 | 19/14 | 240 | 360/144 |
| Li <i>et al</i> ^[22] , 2013 | 88/24 | | 384/204 |

Table 2 Interval and location of gastric stump carcinoma by reconstruction

| Ref. | Primary reconstruction | Interval (mo) | Location |
|--|------------------------|-----------------|---|
| | Billroth I / II | Billroth I / II | B- I ana/B- I non/ B- II ana/B- II non |
| | | | |
| Take no <i>et al</i> ^[16] , 2006 | 21/11 | 84/276 | 4/17/6/5 |
| Ohashi <i>et al</i> ^[17] , 2007 | 71/28 | | 7/64/5/23 |
| Ahn <i>et al</i> ^[18] , 2008 | 26/25 | | 11/15/16/9 |
| Tanigawa <i>et al</i> ^[19] , 2010 | 368/519 | 252/372 | 81/176/289/114 |
| Komatsu <i>et al</i> ^[21] , 2012 | 16/16 | 144/384 | 2/5/9/2 |
| Li <i>et al</i> ^[22] , 2013 | 42/70 | | 19/23/45/25 |

B- I : Billroth I ; B- II : Billroth II ; ana: Anastomosis site; non: Non-anastomosis site.

cy worldwide^[1,2]. The five-year survival of patients with gastric cancer is estimated to be approximately 20%, and it has been reported that only surgery, including lymphadenectomy, can provide curative effects^[3-5]. However, recent advances in early detection and the development of anticancer drugs have prolonged the prognosis^[6,7].

Gastric stump carcinoma was originally defined as gastric cancer arising from the remnant stomach more than five years after distal gastrectomy for benign disease^[8-10]. The incidence of gastric stump carcinoma is estimated to be 1%-2%, according to the current literature^[11,12]. However, most cases of gastric cancer arising from the remnant stomach after distal gastrectomy involve a second primary gastric cancer, as the rate of gastrectomy against peptic ulcers has decreased for the last three decades due to the development of gastric acid inhibitor drugs and improvements in the prognosis of patients with gastric cancer, as described above^[6,7,13]. In addition, the development of endoscopic technology and periodical endoscopic surveillance has enabled clinicians to detect gastric cancer of the remnant stomach in the early stage, which may improve the unfavorable prognosis of patients with gastric stump carcinoma^[12].

The characteristics of remnant gastric cancer may have changed from those previously reported in the literature. Therefore, we reviewed recent articles and attempted to clarify the modern characteristics, carcinogenesis, diagnosis and optimal treatment of remnant gastric cancer.

EPIDEMIOLOGY

In 1922, Balfore first reported that, with respect to gastric cancer arising from the remnant stomach after surgery, the most important factor affecting life expectancy after surgery for gastric ulcers is the occurrence of gastric cancer, which accounts for approximately 40% of the total number of deaths in this patient population^[14]. That series included gastric cancer as well as benign ulcers as the primary lesions and reported the incidence of remnant gastric cancer to be 3% after resection of ulcerous lesions.

A population-based study of patients who underwent distal gastrectomy for benign disease was recently

reported from Sweden. In that study, the incidence of remnant gastric cancer was 0.74%, which is similar to the findings of previous reports^[11,12,15]. In addition, it is of interest that the incidence of gastric stump carcinoma is not higher than expected and increases only after more than 30 years after surgery for benign disease^[15]. Several reports have found that it takes more than 300 mo for gastric stump carcinoma to arise from the remnant stomach after distal gastrectomy for benign disease, in contrast to the approximately 100 mo observed following gastrectomy for primary gastric cancer (Tables 1 and 2)^[12,16-22].

EFFECTS OF RECONSTRUCTION DURING DISTAL GASTRECTOMY ON CARCINOGENESIS IN THE REMNANT STOMACH

It has been reported that a reduction in the level of serum gastrin and gastroduodenal reflux are factors for carcinogenesis in the remnant stomach after distal gastrectomy. This finding has also been experimentally evaluated by Miwa *et al*^[23]. Billroth II reconstruction is more frequently associated with atrophic changes and an increased S phase cell count in the proliferative zone compared to that observed following treatment with Billroth I in the Wister rat model. In addition, it has been reported that intestinal metaplasia is rare. However, to the best of our knowledge, no clinical studies have compared the incidence of atrophic changes and intestinal metaplasia between patients treated with the Billroth I and II methods. The interval between primary distal gastrectomy and the diagnosis of stump carcinoma is significantly longer in patients treated with Billroth I reconstruction than in those treated with Billroth II reconstruction, according to a review of previous clinical retrospective studies^[16-19,21,22].

In addition, there is a consensus that gastric stump carcinoma tends to arise from sites of anastomosis in patients treated with Billroth II reconstruction, in contrast to non-anastomotic sites in patients treated with

Table 3 *Helicobacter pylori* infection in the patients underwent distal gastrectomy

| Ref. | Total infection rate | Billroth I | Billroth II | Roux-en-Y |
|---|----------------------|------------|-------------|-----------|
| Onoda <i>et al</i> ^[31] , 2001 | 65.10% | 67.10% | 58.30% | |
| Matsukura <i>et al</i> ^[32] , 2003 | 68.20% | 72.20% | 58.80% | |
| Abe <i>et al</i> ^[33] , 2005 | 56.30% | 55.60% | 58.30% | |
| Chan <i>et al</i> ^[34] , 2007 | 50.00% | 58.60% | 66.70% | 26.30% |

Billroth I reconstruction, and that the incidence of gastric stump carcinoma is correlated with that of gastroduodenal reflux, similar to that observed in experimental rat models^[16-19,21,22].

The condition of the remnant stomach mucosa after distal gastrectomy has been biologically examined at the molecular level. Tanigawa reported that the apoptotic index, p53 labeling index and Ki-67 labeling index are significantly higher in patients treated with Billroth II reconstruction than in those treated with Billroth I reconstruction^[24]. In addition, Nakachi *et al*^[25] and Aya *et al*^[26] demonstrated a higher frequency of microsatellite instability in patients with gastric stump carcinoma (88.9%, 43%) than in those with primary upper third gastric carcinoma (20%, 6%). Furthermore, Aya reported a significantly higher level of microsatellite instability, as well as a higher frequency of both hMLH1 and hMSH2 inactivation, in patients treated with Billroth II reconstruction than in those treated with Billroth I reconstruction^[26].

Taking both clinicopathological and molecular biological changes into consideration, the Billroth I procedure is thus considered to be preferable to the Billroth II method, at least with respect to preventing the development of gastric stump carcinoma.

Roux-en-Y reconstruction has recently been adopted for reconstruction after distal gastrectomy to prevent gastroduodenal reflux. The time for which the remnant gastric mucosa is exposed to bile reflux is shorter and the degree of remnant gastritis is more mild in patients treated with Roux-en-Y reconstruction than in those treated with Billroth I reconstruction^[27]. Both the latest multi-institutional randomized controlled study and a meta-analysis support this finding, and it appears that a consensus has been reached on this issue^[28-30]. No reports have thus far suggested that the incidence of gastric stump carcinoma is lower in patients treated with Roux-en-Y reconstruction than in those treated with Billroth I reconstruction. However, Roux-en-Y reconstruction is preferred from the viewpoint of reducing the incidence of gastroduodenal reflux and remnant gastric mucosal injury related to gastric carcinogenesis.

HELICOBACTER PYLORI INFECTION

Helicobacter pylori (*H. pylori*) infection is a well-known ma-

Table 4 Epstein-Barr infection in the patients with gastric stump carcinoma

| Ref. | Total infection rate | Billroth I | Billroth II |
|---|----------------------|------------|-------------|
| Tanigawa <i>et al</i> ^[19] , 2000 | 22.2% | 5.9% | 32.1% |
| Nishikawa <i>et al</i> ^[36] , 2002 | 41.2% | 0.0% | 58.3% |
| Kaizaki <i>et al</i> ^[37] , 2005 | 23.1% | 12.5% | 30.4% |

ajor causative factor of carcinogenesis in the stomach. Nagahata reported that the rate of infection following gastrectomy gradually decreases over time. Recent studies have also examined the frequency of *H. pylori* infection in the remnant stomach after distal gastrectomy. The rate of infection ranges from 50% to 68.2% among all patients treated with distal gastrectomy, 55.6% to 72.2% among patients treated with Billroth I reconstruction and 58.3% to 66.7% among patients treated with Billroth II reconstruction (Table 3)^[31-34]. Only one series has suggested the rate of infection to be lower in patients treated with the Roux-en-Y method, and further studies are thus required to clarify this issue^[34]. It therefore appears that there are no significant differences between Billroth I and II reconstruction. Matsukura *et al*^[32] reported that eradication with dual and triple therapy is successful in 70% and 90% of *H. pylori* patients who undergo distal gastrectomy, respectively, and that the therapeutic efficacy is the same in patients treated with and without distal gastrectomy. It has also been demonstrated that the degree of inflammation improves and the pH level normalizes following eradication of *H. pylori* in the remnant stomach^[35]. Therefore, treatment with eradication of *H. pylori* in the remnant stomach is recommended to prevent the development of gastric stump carcinoma, although no significant correlations have been reported between *H. pylori* infection and carcinogenesis in the remnant stomach.

EPSTEIN-BARR VIRUS INFECTION IN THE REMNANT STOMACH

Infection with the Epstein-Barr (EB) virus has been reported to be associated with various cancers, including stomach cancer. A few series have examined EB virus infection in patients with gastric stump carcinoma. According to these studies, the rate of infection ranges from 22.2% to 41.2% among all patients treated with distal gastrectomy, 0% to 12.5% among patients treated with Billroth I reconstruction and 30.4% to 58.3% among patients treated with Billroth II reconstruction (Table 4)^[19,36,37]. Therefore, a higher rate of infection with the EB virus has been demonstrated in patients treated with Billroth II reconstruction.

In addition, EB-virus infection has been suggested to be correlated with the incidence of gastritis cystic polypoid and may also facilitate the development of *de novo* gastric stump carcinoma^[37].

Table 5 Clinicopathologic characteristics of gastric stump carcinoma

| Ref. | Patients age | pT (1/2/3/4) | pN (positive/negative) | pM (positive/negative) | pStage | 5-yr survival |
|--|--------------|-----------------|------------------------|------------------------|-----------------|---------------|
| Takeo <i>et al</i> ^[16] , 2006 | 68.7 | 10/22 (1,2/3,4) | 12/20 | 4/28 | 21/11 (1,2/3,4) | |
| Ohashi <i>et al</i> ^[17] , 2007 | 67 | 67/16/8/17 | 13/84 | | 77/6/2/23 | 53.10% |
| Ahn <i>et al</i> ^[18] , 2008 | | 18/17/0/19 | 23/29 | 10/42 | | |
| Ahn <i>et al</i> ^[18] , 2008 | 58 | 15/31 (1/2,3,4) | 19/25 | 17/41 | 26/32 (1,2/3,4) | 63.4% (3-yr) |
| Tanigawa <i>et al</i> ^[19] , 2010 | 68 | 315/245/197/130 | 534/327 | 26/861 | | |
| Komatsu <i>et al</i> ^[21] , 2012 | 68 | 10/22 (1/2,3,4) | 14/13 | | 17/15 (1/2,3,4) | |
| Li <i>et al</i> ^[22] , 2013 | | 1/3/44/64 | 66/46 | 31/81 | 3/16/62/31 | 11% |

Table 6 Clinicopathological comparison between primary upper third gastric cancer and gastric stump carcinoma

| Clinicopathologic characteristics | Ikeguchi <i>et al</i> ^[39] , 1993 | P value | Chen <i>et al</i> ^[40] , 1996 | P value | Newman <i>et al</i> ^[41] , 1997 | P value | Komatsu <i>et al</i> ^[42] , 2012 | P value |
|-----------------------------------|--|---------|--|---------|--|---------|---|---------|
| pT (1/2/3/4) | | | | | | | | |
| PUTGC | 63/15/157/31 | NS | 5/30/88/20 | NS | 11/15/46/7 | NS | 69/75/54/9 | 0.07 |
| GSC | 4/3/7/6 | | 0/5/13/7 | | 7/6/11/1 | | 10/10/7/6 | |
| pN (negative/positive) | | | | | | | | |
| PUTGC | 99/167 | NS | 47/86 | NS | 24/54 | NS | 118/89 | 0.7 |
| GSC | 11/9 | | 10/15 | | 14/11 | | 20/13 | |
| M (negative/positive) | | | | | | | | |
| PUTGC | | | 127/16 | NS | Nov-68 | NS | | |
| GSC | | | 20/5 | | 22/3 | | | |
| 5-yr survival | | | | | | | | |
| PUTGC | 62.1% | NS | 25% | 0.31 | 37% | 0.1 | | 0.67 |
| GSC | 52.5% | | 46% | | 63% | | | |

PTUGC: Primary upper third gastric cancer; GSC: Gastric stump carcinoma; NS: Not significant.

CLINICOPATHOLOGICAL CHARACTERISTICS

The clinicopathological characteristics of gastric stump carcinoma have been analyzed in many reports, as summarized in Table 5^[16-19,21,22,38]. For example, it has been reported that the prognosis of gastric stump carcinoma is unfavorable compared to that of primary gastric cancer, which may result from the more advanced stage of disease observed at diagnosis. There is currently no consensus regarding this issue based on a Japanese nationwide report of gastric cancer, although unevenness in the disease stage at diagnosis has been observed in various studies^[19].

It has also been reported that there have been no remarkable changes in the number of gastric stump carcinoma patients with progressive tumor invasion. In contrast, the number of patients with progressive cancer invasion has been reported to gradually decrease in Japan since 1991, according to data for resected gastric cancer. Among patients with lymph node metastasis, there are no significant trends, as approximately half of all such patients were found to have node metastasis in a Japanese nationwide study and be negative for node metastasis in the previous literature regarding gastric stump carcinoma.

There have been several reports of prognostic analyses comparing gastric stump carcinoma and primary upper third gastric cancer^[39-42] (Table 6). All such studies have suggested that there are no significant differences in either the prognosis or rate of progression between

these two diseases. In contrast, it is of interest that gastric stump carcinoma exhibits a more favorable prognosis than primary upper third gastric cancer in patients with stage I or II disease and, inversely, a more unfavorable prognosis in patients with stage III or IV disease^[40]. Concerning this result, Chen *et al*^[40] reported that the left gastric artery is usually resected during distal gastrectomy, which may change the lymphatic flow and thereby influence the difference in prognosis observed in analyses of the cancer stage. Ikeguchi *et al*^[39] also reported the incidence of jejuna mesenteric lymph node metastasis to be increased in patients with gastric stump carcinoma; these results may correlate with those of Chen. Controversially, Newman *et al*^[41] reported that there are no prognostic differences between gastric stump carcinoma and upper third primary gastric cancer, even when the analysis is classified according to the cancer stage. Meta-analyses and/or multi-institutional randomized controlled studies with large series are therefore required to clarify these controversial results, although it may be difficult to conduct such studies due to the rarity of the disease.

ENDOSCOPIC TREATMENT

Previously, radical resection was the only curable treatment for gastric stump carcinoma, as observed in the setting of primary gastric cancer. However, advancements in endoscopic diagnosis and the popularization of periodic endoscopic screening after gastrectomy have enabled clinicians to detect gastric stump carcinoma at the early

Table 7 Endoscopic submucosal dissection for gastric stump carcinoma n (%)

| Ref. | No. of ESD cases | En bloc resection | Complete resection | Mortality | Delayed bleeding | Perforation |
|--|------------------|-------------------|--------------------|-----------|------------------|-------------|
| 1 Takenaka <i>et al</i> ^[44] , 2008 | 31 | 30 (97) | 23 (74) | 0 | 0 | 4 (13) |
| 2 Hirasaki <i>et al</i> ^[45] , 2008 | 17 | 17 (100) | 14 (82) | 0 | 3 (18) | 0 |
| 3 Lee <i>et al</i> ^[46] , 2010 | 13 | 13 (100) | 12 (92.3) | 0 | 0 | 0 |
| 4 Nonaka <i>et al</i> ^[47] , 2013 | 139 | 131 (94) | 118 (85) | 0 | 2 (1.4) | 2 (1.4) |
| 5 Tanaka <i>et al</i> ^[48] , 2013 | 33 | 33 (100) | 31 (94) | 0 | 1 (3) | 3 (9) |

ESD: Endoscopic submucosal dissection.

stage. Hosokawa reported that 15 patients with gastric stump carcinoma were detected among 509 patients who underwent distal gastrectomy over more than 10 years, 12 of whom were diagnosed at an early stage, and concluded that endoscopic surveillance should be repeated every two to three years after distal gastrectomy^[43].

Similarly, several studies including small series of endoscopic treatment for gastric stump carcinoma have recently been reported, as summarized in Table 7^[44-48]. En bloc resection and complete resection were performed in more than 90% of cases and 74%-94% of cases, respectively. Concerning complications after endoscopic treatment, there were no mortalities, and 0%-18% and 0%-13% of the patients exhibited delayed bleeding and perforation, respectively. However, morbidity, as well as the en bloc and complete resection rates, have been shown to have improved in the latest reports.

Only one study, by Nonaka *et al*^[47], has reported long-term outcomes after endoscopic treatment for gastric stump carcinoma. In that study, the overall and disease-specific survival was 87.3% and 100%, respectively. Further studies using large series should thus be conducted to confirm the oncological feasibility of providing endoscopic treatment in patients with gastric stump carcinoma.

CONCLUSION

Clarifying the differences in the characteristics of gastric stump carcinoma and primary gastric cancer may enable clinicians to make an early diagnosis and improve clinical outcomes in patients with gastric stump carcinoma. In addition, multi-institutional analyses using large series may positively contribute to clarifying these issues.

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