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Original article

Clinical study to identify specific characteristics of cancer newly developed in the remnant stomach

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Abstract

Background. **Cancer newly developed in the remnant stomach (CRS) after partial gastrectomy is worthy of attention not only because it is a typical model of carcinogenesis but also from the aspect of cancer diagnosis.**

Methods. **We treated 47 patients with CRS in the 20 years from 1979 to 1998. Clinicopathological variables, as well as long-term survival results after the second surgery, were reviewed to clarify whether there were any differences in the characteristics of this disease entity compared with the usual primary gastric cancer.**

Results. **The mean time interval between the initial surgery and surgery for CRS was 25.8 years for patients with CRS with previous benign gastric lesions, and 10.6 years for those with previous gastric cancer. CRS was frequently detected at an early stage in the patients with previous cancer, and in the patients who had undergone reconstruction by the Billroth I method (regardless of the primary nature of the disease). Cancers with a differentiated histology developed more frequently in the patients who had undergone the initial surgery for cancer disease. Long-term survival results after the second surgery clearly demonstrated that surgical treatment for CRS was as effective as that for primary cancer in the upper stomach (PUC). In addition, it was confirmed that new lymphatic drainage into the lower mediastinum or the jejunal mesentery had developed after the initial gastric surgery.**

Conclusion. **The findings suggested that patients with CRS and those with PUC should be treated similarly, although the findings of a high incidence of lymph node metastasis to the lower mediastinum and/or to the jejunal mesentery in the CRS patients should be taken into consideration.**

Key words Remnant stomach · Primary upper gastric cancer · Time interval · Initial surgery · Second surgery · Lymph drainage · Jejunal mesenterial nodes · Lower mediastinal nodes

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Introduction

Cancer in the remnant stomach is classified into three categories: (1) cancer newly developed in the remnant stomach (CRS), (2) cancer remaining in the remnant stomach at the initial gastric surgery, and (3) recurrent cancer in the remnant stomach [1]. CRS is the focus of much attention, not only as a typical model of carcinogenesis but also from the aspect of cancer diagnosis. In addition, lymph drainage from CRS frequently shows a unique pattern, probably as a result of lymph node and/or lymphatic ablation performed at the initial surgery.

We have treated 47 patients with CRS in the 20-year period from 1979 to 1998. In this study, we reviewed clinicopathological variables, as well as the long-term survival results after the second surgery, to clarify whether any characteristics of this disease entity were comparable with those of the usual primary gastric cancer.

Patients and methods

CRS was classified as either of the following two types; (1) cancer in the remnant stomach detected 10 years or more after the initial gastric surgery, regardless of the benign or malignant nature of the primary lesion, and (2) cancer in the remnant stomach that could be identified as a new development not related to the primary lesions [2,3]. In the 20-year period from 1979 to 1998, we performed gastric cancer surgery for 2561 patients, of whom 59 had type (1) CRS and 47 had type (2) CRS. Each of these cancers had developed in the proximal stomach after distal gastrectomy; no cancer was detected in the distal stomach after proximal gastrectomy. The 47 patients with the type 2 CRS were the CRS group investigated in this study. Of these 47 patients with the type (2) CRS, 20 patients (18 men and 2 women) had undergone the initial surgery for benign

Table 1. Stratification of 47 patients with cancer newly developed in the remnant stomach (CRS)

Previous disease	Mode of reconstruction
Benign gastric lesion ($n = 20$; male, 18; female, 2)	Billroth I ($n = 7$); Billroth II ($n = 13$)
Gastric cancer ($n = 27$; male, 23; female, 4)	Billroth I ($n = 18$); Billroth II ($n = 9$)

Table 2. Clinico-pathological variables in the 47 patients with CRS

Age (mean, years)	67.5
Sex	41 Male; 6 female
Disease stage	I: 18 II: 5 III: 8 IV: 16
Histology[a]	pap, 3; tub1, 8; tub2, 14; por, 12; sig, 7; muc, 1; adenosq, 2
Extent of lymph node dissection	D0, 7; D1, 9; D2, 27; D3, 3; D4, 1

CRS, cancer newly developed in the remnant stomach
[a] pap, Papillary adenocarcinoma; tub1, well-differentiated adenocarcinoma; tub2, moderately differentiated adenocarcinoma; por, poorly differentiated adenocarcinoma; sig, signet-ring cell carcinoma; muc, mucinous adenocarcinoma; adenosq, adenosquamous carcinoma
[b] D0, No lymph node dissection; D1, dissection of group 1 nodes; D2, dissection of group 1 and 2 nodes; D3, dissection of group 1, 2, and 3 nodes; D4, dissection of group 1, 2, 3, and 4 nodes

gastric lesions (benign group) and 27 had undergone the initial surgery for cancerous disease (cancerous group). In the 20 patients with previous benign gastric lesions, the initial surgery had involved reconstruction of the gastrointestinal tract by the Billroth I method in 7 patients and by the Billroth II method in 13 patients. Of the 27 patients (23 men and 4 women) with previous cancerous lesions, 18 had undergone gastrointestinal tract reconstruction by the Billroth I method and 9 patients, by the Billroth II method. Although Billroth I reconstruction was more frequently performed in the cancerous group, and Billroth II reconstruction was more frequent in the benign group, there were no significant differences between the two groups (Table 1).

The time interval between the initial and the second surgeries was 25.8 ± 9.7 years for the 20 patients in the benign group and 10.6 ± 6.8 years for the 27 patients in the cancerous group ($P < 0.0001$). The clinicopathological variables in the 47 patients with CRS are listed in Table 2. Each variable was defined according to the first English edition of the Japanese classification of gastric cancer [4].

Three hundred and ten patients with primary upper gastric cancer (PUC) who underwent curative surgery during the same period were also included in this analysis to determine whether there was any difference in postoperative survival as well as lymph node metastatic patterns, between CRS and PUC. The clinicopathological variables for the 32 patients with CRS and 310 with PUC who underwent curative surgery are listed in Table 3.

Statistical analysis of differences between the two groups (CRS and PUC) was checked by the χ^2 test. The survival curves were plotted according to the Kaplan-Meier method and checked by the long-rank test. A value of $P < 0.05$ was considered statistically significant.

Results

Clinicopathological variables in CRS

Location of CRS. Sites of CRS were classified into the following four groups, according to findings in previous reports [4]: Ggroup 1, anastomotic line; group 2, gastric stump; group 3, non-stump area; and group 4, tumor location cannot be specified because of diffuse spread in the total remnant stomach. In the 20 CRS patients with previous benign lesions, 8 (40%) were group 1; 3 (15%) were group 2, 5 (25%) were group 3, and 4 (20%) were group 4, while in the 27 CRS patients with previous cancer, 3 (11%) were group 1, 7 (26%) were group 2, 14 (52%) were group 3, and 3 (11%) were group 4. In contrast, in the 25 patients who had undergone Billroth I reconstruction at the initial surgery (7 with previous benign lesions and 18 with previous cancer) 1 (4%) patient was group 1, 6 (24%) were group 2, 14 (56%) were group 3, and 4 (16%) were group 4, while in the 22 patients who had undergone Billroth II reconstruction (13 with previous benign lesions and 9 with previous cancer) 9 (41%) were group 1, 4 (18%) were group 2, 6 (27%) were group 3, and 3 (14%) were group 4. Taken together, patients with previous benign lesions and/or those who had undergone Billroth II reconstruction at the initial surgery tended to have cancer development at stump sites, including the anastomotic line, while those with previous cancer and/or those who had undergone Billroth I reconstruction at the initial surgery tended to have cancer development at non-stump sites, although the difference was not significant.

Gross pattern of CRS. The elevated type of cancer, i.e., type I or II early cancer, or Borrmann type 1, was found in one patient (5%) with previous benign lesions, eight patients (30%) with previous cancer, seven patients (28%) who had undergone Billroth I reconstruction, and 2 patients (9%) who had undergone Billroth II reconstruction at the initial surgery. Namely, the elevated type of cancer tended to develop more frequently in patients with previous cancer or those with

Table 3. Clinicopathological variables in 32 patients with CRS and 310 patients with PUC who underwent curative surgery

	Patients with CRS ($n = 32$)	Patients with PUC ($n = 310$)
Age (mean, years)	69.4	60.3
Sex	29 Male; 3 female	232 Male; 78 female
Disease stage	I: 17 II: 3 III: 8 IV: 4	I: 154 II: 42 III: 86 IV: 28
Histology[a]	pap, 3; tub1, 7; tub2, 10; por, 6; sig, 4; muc, 1; adenosq, 1	pap, 34; tub1, 50; tub2, 79; por, 121; sig, 16; muc, 4; adenosq, 3; carcinoid, 3
Extent of lymph node dissection[b]	D0, 3; D1, 7; D2, 21; D3, 1; D4, 0	D0, 12; D1, 44; D2, 111; D3, 113; D4, 30

CRS, Cancer newly developed in the remnant stomach; PUC, primary upper gastric cancer

Billroth I reconstruction, although the difference was not significant.

Tumor depth of CRS. Early-stage cancer (t1) was found in 2 patients (10%) with previous benign lesions, 12 (44%) with previous cancer, 12 (48%) who had undergone Billroth I reconstruction, and 2 (9%) who had undergone Billroth II reconstruction at the initial surgery. Namely, t1 cancer was more frequently observed in patients with previous cancer than in those with previous benign lesions ($P < 0.02$) and in those with Billroth I reconstruction than in those with Billroth II reconstruction ($P < 0.01$).

Tumor histology of CRS. Tumor histology was classified into two groups; differentiated type, which included papillary adenocarcinoma and, well or moderately differentiated adenocarcinoma; and undifferentiated type, which included poorly or undifferentiated adenocarcinoma, signet ring cell carcinoma, and mucinous carcinoma. Patients with previous benign lesions more frequently had CRS with an undifferentiated type (13/20, 65%), while patients with previous cancer more frequently had CRS with a differentiated type (17/27; 63%; $P < 0.05$). There was no significant difference in tumor histology between patients who had undergone Billroth I reconstruction and those who had undergone Billroth II reconstruction at the initial surgery (the percentage of patients with differentiated type was 52% (13/25) for those who had undergone Billroth I, and 50% (11/22) for those who had undergone Billroth II).

These analyses to investigate the relationship between various clinicopathological variables and CRS indicated significant differences in regard to the following features: (1) patients with previous cancer and those who had previously undergone Billroth I reconstruction tended to have an earlier stage of CRS than those with previous benign lesions and those with Billroth II reconstruction respectively, and (2) patients with previous benign lesions more frequently had undifferentiated tumor histologies, while those with previous cancer more frequently had differentiated histologies.

Surgery for CRS and survival analysis after the surgery

Surgical methods. Total gastrectomy was performed at a high frequency for patients with CRS, regardless of the nature of the previous lesions; namely, for 90% (18/20) of the patients with previous benign lesions and for 89%(24/27) of the patients with previous cancer. The percentages of patients with D2 or more lymph node dissection, those with combined resection of neighboring organs, and those in whom curative resection of curability A or B was achieved [4] were 80% (16/20), 70% (14/20), and 60% (12/20), respectively for the group with previous benign lesions, and 67% (18/27), 67% (18/27), and 74% (20/27) respectively, for the group with previous cancer. There were no significant differences in surgical procedures between these two patient groups.

Long-term survival rates of patients with CRS. In 12 patients with previous benign gastric lesions and 20 patients with previous cancer, curative surgery of curability A or B was achieved. Disease stages in these two groups were as follows: 5 stage I, 4 stage II, 3 stage III, and no stage IV disease for the group with previous benign lesions, and 13 stage I, 1 stage II, 3 stage III, and 3 stage IV disease, respectively, in the patients with previous gastric cancer. There were no significant differences in the disease stage distribution between the two groups. The 5-year cumulative survival of patients who

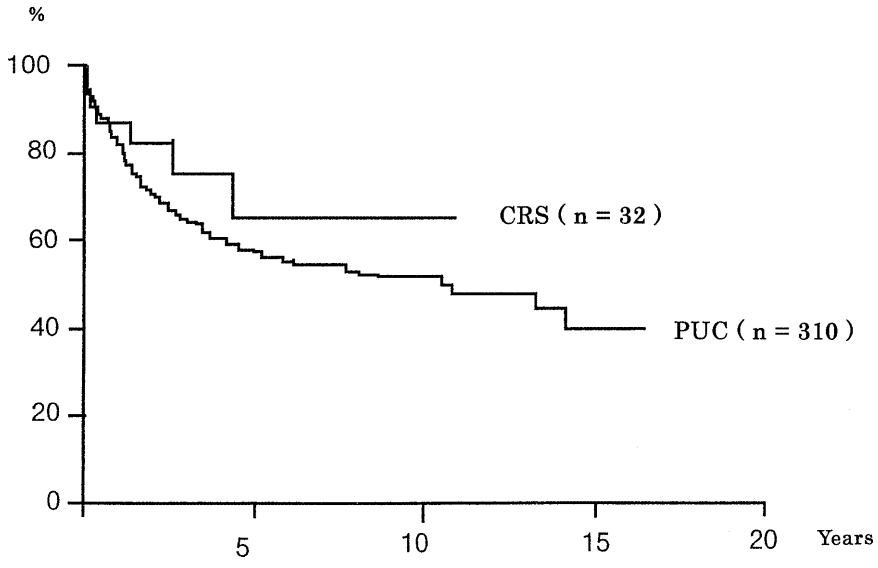

Fig. 1. Comparison of survival curves between patients with cancer newly developed in the remnant stomach (*CRS*) and those with primary upper third gastric cancer (*PUC*)

Table 4. Comparison of the incidence of regional lymph node metastases in CRS and PUC patients

Lymph node station	Incidence (percentage) in CRS	Incidence (percentage) in PUC
No.1	18 (5/28)[a]	33 (103/310)[a]
No.2	15 (4/27)	23 (66/290)
No.3	25 (7/28)	39 (121/307)
No.4sa	11 (3/27)	15 (41/275)
No.7	14 (2/14)	19 (56/293)
No.8a	0 (0/25)	10 (28/267)
No.9	5 (1/22)	10 (25/253)
No.10	8 (2/24)	17 (44/264)
No.11	9 (2/22)	22 (56/258)
No.12a	0 (0/10)	3 (5/183)
No.14v	0 (0/6)	6 (9/139)
No.111	50 (2/4)	7 (1/15)
No.16	18 (2/11)	22 (33/148)
Jejunal mesentery	60 (6/10)	

CRS, Cancer newly developed in the remnant stomach; PUC, primary upper gastric cancer
[a] Fractions in parentheses denote the number of patients positive for metastasis/total number of patients who underwent the corresponding node dissection

underwent curative surgery was 58% for the group with benign lesions and 55% for the group with previous gastric cancer, with no significant difference between the groups. Were compared the 5-year cumulative survival rates in these 32 patients with CRS and the 310 patients with primary upper gastric cancer (PUC) in whom curative surgery was achieved. As shown in Table 3, there were no significant differences in the stage distribution between the 32 CRS patients and the 310 PUC patients. The 5-year cumulative survival rate was 56% (18/32) for the patients with CRS and 53% for those with PUC, suggesting that CRS may not differ significantly from PUC in terms of postoperative survival (Fig. 1).

Characteristic patterns of lymph drainage from CRS. The incidence of regional lymph node metastasis was studied in the patients with CRS and those with PUC. The patients with PUC tended to have a higher incidence of perigastric lymph node metastasis than those with CRS, who, in contrast, had a higher incidence of metastases to either the jejunal mesenterial or lower mediastinal lymph nodes, suggesting that marked changes in lymph drainage had developed in the patients with CRS (Table 4). We then compared the pattern of regional node metastases in the CRS patients with previous benign lesions and the CRS patients with previous cancer. A high incidence of perigastric node metastasis was observed in the group with previous be-

Table 5. Comparison of the incidence of regional lymph node metastases in two groups with CRS stratified by mode of reconstruction at the initial surgery

Lymph node station	Incidence (percentage) in Billroth I	Incidence (percentage) in Billroth II
No.1	0 (0/13)[a]	33 (5/15)[a]
No.2	0 (0/13)	29 (4/14)
No.3	8 (1/12)	38 (6/16)
No.4sa	8 (1/13)	14 (2/14)
No.7	0 (0/7)	29 (2/7)
No.8a	0 (0/12)	0 (0/13)
No.9	0 (0/9)	8 (1/13)
No.10	8 (1/12)	8 (1/12)
No.11	0 (0/10)	17 (2/12)
No.12a	0 (0/4)	0 (0/6)
No.14v	0 (0/4)	0 (0/5)
No.111	33 (1/3)	100 (1/1)
No.16	20 (1/5)	17 (1/6)
Jejunal mesentery		60 (6/10)

CRS, Cancer newly developed in the remnant stomach
[a] Fractions in parentheses denote the number of patients positive for metastasis/total number of patients who underwent the corresponding node dissection

nign lesions, while the incidence of metastases to lymph nodes around the stomach wall, and the left gastric, celiac, and splenic arteries was very low in the group with previous cancer, probably because these nodes had been removed at the initial surgery. This idea seemed to be supported by the following findings. Namely, 18 of the 25 patients with CRS who had undergone Billroth I reconstruction had received regional lymph node dissection at the initial surgery (72%), and this Billroth I group rarely had perigastric node involvement, while 9 of the 22 patients who had undergone Billroth II reconstruction had received node dissection at the initial surgery (41%) and this Billroth II group had an incidence of regional lymph node involvement of 20%–30%. In addition, as indicated in Table 5, a high incidence of lymph node involvement in the jejunal mesentery was found in the patients who had previously undergone Billroth II reconstruction, compared with those with Billroth I, regardless of the nature of the primary gastric disease. There was also a high incidence of metastases to the lower mediastinal nodes in the CRS patients with previous cancer regardless of whether reconstruction was performed by either the Billroth I or the Billroth II method.

Discussion

The present analysis demonstrated that, in patients CRS with previous cancer and/or in those who had undergone Billroth I reconstruction at the initial surgery, The CRS tended to be detected at an early stage, and to have a differentiated tumor histology. Other reports have indicated similar associations. Namely, Suzuki et al. [5] reported that an early stage of cancer was detected in the remnant stomach in 45% of the patients with previous cancer, a significantly higher incidence than that in the patients with previous benign lesions. In patients with multiple cancer development in the stomach, the cancers generally tended to have a well-differentiated histology. This finding, taken together with our analyses, seems to suggest that some CRS may reflect multiple cancer development in the remnant stomach. Furukawa et al. [6] postulated, similarly, that CRS with previous cancer tended to have a well-differentiated histology, while most CRS with previous benign lesions had an undifferentiated histology, in agreement with the present findings. In addition, the significantly shorter interval between the initial and the second surgeries in CRS patients with previous cancer that we found in our analysis seems relevant to the consideration of the possible emergence of metachronous multiple cancer, and indicates the need for careful check-up after the initial surgery.

The present study also indicated that patients with previous benign lesions and/or those who had undergone Billroth II reconstruction at the initial surgery tended to have cancer development at stump sites, including the anastomotic line, while those with previous cancer and/or those who had undergone Billroth I reconstruction tended to have cancer development at non-stump sites, although the difference was not significant. These tendencies are in line with the findings in some other reports [7,8]. Gastritis cystica polyposa, which is suspected to be of great relevance in regard to cancer development in the remnant stomach, was

detected more often on the anastomotic line, as well as being detected more often in patients with Billroth II reconstruction than in those with Billroth I [9]. These findings, together with various data from animal experiments [10,11], suggest that the reflux of duodenal juice into the stomach could be associated with the development of CRS. In addition, we found in the present study that the mean time interval for the emergence of CRS was 25.8 years for patients with previous benign lesions, longer than the time interval for those with previous gastric cancer (10.6 years). This finding appears to be in line with the speculation that carcinogenesis through bile reflux would take longer than the emergence of multiple cancers. However, there are several criticisms regarding the association between the risk of CRS development and Billroth I or II reconstruction [12]. Thus, there is no definite conclusion on this issue at present.

Curative resection, of curability A or B, was accomplished in 60% (12/20) of the patients with previous benign lesions, in 78% (21/27) of those with previous cancer, and in 70% (33/47) of the total of 47 patients with CRS. These figures were in line with other reports of curative resection rates of 50%–70% for CRS [13]. Total removal of the remnant stomach was the most frequently selected surgical procedure. In addition, in the current series, the rate for the resection of neighboring organs together with the remnant stomach was 72% (34/47); this was also compatible with the rates at other surgical centers which are recognized as specialized centers for gastric cancer treatment, i.e., the rate was 62% at the Department of Surgery, Center for Digestive Disease, Tokyo Womens Medical College [14], 64% at the Second Department of Surgery, Chiba University [15], and 69% at the Division of Surgery, Cancer Center Hospital Tokyo [16].

Of interest was the marked difference in the patterns of lymph drainage from lesions in the remnant stomach between patients with previous benign lesions and those with previous cancer. For instance, in most patients with previous cancer, lymph drainage from the remnant stomach was newly developed to the lower mediastinum, to the jejunal mesentery, or to the duodenal side through the anastomotic line made at the initial surgery; this was probably caused by the surgical ablation of preexisting lymphatics and lymph nodes in the perigastric areas at the initial cancer surgery [17]. In this context, our current analysis confirmed a higher incidence of metastasis to the lower mediastinal nodes in CRS patients with previous cancer and a higher incidence of metastasis to the jejunal mesenterial lymph nodes for CRS patients with previous Billroth II reconstruction.

In addition, our comparison of long-term survival after surgery for CRS and PUC demonstrated that surgery for CRS was as effective as that for PUC, as indicated by previous studies [13,14]. Accordingly, treatment for CRS should be conducted in a manner similar to that employed for primary gastric cancer, with the high incidence of lymph node metastasis to the lower mediastinum and/or the jejunal mesentery being taken into consideration.

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