

## Clinical and Histopathological Features of Remnant Gastric Cancers, After Gastrectomy for Synchronous Multiple Gastric Cancers

TAKEO FUJITA, MD, PhD,\* NAOTO GOTOHDA, MD, SHINICHIRO TAKAHASHI, MD, TOSHIO NAKAGOHRI, MD, MASARU KONISHI, MD, AND TAIRA KINOSHITA, MD  
Division of Digestive Surgery, National Cancer Center Hospital East, Kashiwa, Chiba, Japan

**Background:** Remnant gastric cancers have been extensively investigated; however, little has been unveiled the features of remnant gastric cancers with regard to the existence of synchronous multiple lesions. We evaluated the clinicopathological features of remnant gastric cancers, after initial gastrectomy for both single and multiple gastric cancers.

**Methods:** We retrospectively analyzed 3,042 patients diagnosed with gastric cancers who underwent gastrectomy. Of these, total gastrectomy cases were excluded, and remaining 2,120 cases were investigated.

**Results:** Among the 2,120 patients, 1,967 patients were histopathologically diagnosed with solitary lesion and 153 patients with multiple lesions. The incidence of remnant gastric cancers was higher in patients with multiple lesions at initial surgery than those with solitary lesion ( $P < 0.05$ ). Moreover, remnant cancers developed within shorter duration of follow-up after treatment of synchronous multiple lesions compared to those that developed after treatment of solitary lesions ( $P = 0.05$ ). Among the patients treated for synchronous multiple lesions, distance from the oral margin was a potential risk factor for the development of secondary cancers in the remnant stomach.

**Conclusions:** Patients with synchronous multiple gastric cancers are more susceptible to the development of secondary cancers in their remnant stomach. These patients need careful follow-up after initial gastrectomy.

*J. Surg. Oncol.* 2009;100:466–471. © 2009 Wiley-Liss, Inc.

**KEY WORDS:** remnant gastric cancer; multiple gastric cancer; gastrectomy

### INTRODUCTION

In the 1950s, Moertel et al. [1] reported that the incidence of synchronous multiple gastric cancers ranged from 0% to 3.4% in surgically resected specimens, thereafter, due to the advance in diagnostic strategy, series of reports demonstrated that multiple gastric cancers were found in ~4–7% of surgically resected cases [2]. In 1990, Kosaka [3] reported that synchronous multiple gastric cancers were observed in 5.8% of cases, and evaluation using serial sections of the whole stomach revealed that synchronous multiple gastric cancers were noticed in 13.2% of cases, thus, suggesting a higher incidence of latent lesions. Indeed, consistent with this report, Esaki [4] demonstrated the histological evaluation using serial sections of the whole stomach, and found that multiple gastric cancers were present in the resected stomach in 14.6% of cases. These observations suggested that although the incidence of multiple gastric cancers on macroscopic examination of the specimens was <10%, this figure would rise to ~14% if they were also studied using serial sections of the whole stomach.

Remnant gastric cancers are reported to be caused by multiple factors, and their incidence, pathological features, and potential mechanisms have been extensively investigated [5–7]. However, there have been few reports demonstrating the clinical and histopathological features of remnant gastric cancers with regard to the existence of synchronous multiple lesions.

In this study, we examined the clinical and pathological features of remnant gastric cancers after initial gastrectomy for synchronous multiple gastric lesions, and we discussed the potential optimal clinical approaches to the disease.

### PATIENTS AND METHODS

#### Patients

Patients who underwent surgery for gastric cancers were analyzed retrospectively from the database of the Division of the Clinical

Pathology in the National Cancer Center Hospital East, from October 1993 to July 2008, after approval from The Investigational Review Board in National Cancer Center. Preoperative diagnosis was based on preoperative imaging studies, including with upper gastrointestinal studies, endoscopy, and conventional cross-sectional imaging studies (computed tomography). Histological evaluation of endoscope-guided biopsy specimens was performed in all cases. Synchronous multiple gastric cancers were defined according to the criteria reported by Moertel et al. [1], which are as follows: (1) each lesion is histologically malignant, (2) each lesion is separated from another by the normal gastric tissue, and (3) each lesion is not the result of a local extension or metastasis of another lesion. If the depth of cancer infiltrations is the same in two or more lesions, the one extending over the greatest area is regarded as the main lesion, and the other lesions are regarded as accessory lesions. In this study, remnant gastric cancers were defined as either of the following two types: (1) cancer in the remnant stomach detected 10 years or more after the initial gastric surgery, and (2) cancer in the remnant stomach that could be identified as a new development not related to the primary lesions [8,9].

Additional Supporting Information may be found in the online version of this article.

There are no financial supports or relationships that may pose a conflict of interest.

\*Correspondence to: Takeo Fujita MD, PhD, Division of Digestive Surgery, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan. Fax: 81-04-7131-9960.

E-mail: takfujit@east.ncc.go.jp

Received 20 January 2009; Accepted 3 June 2009

DOI 10.1002/jso.21352

Published online 3 August 2009 in Wiley InterScience (www.interscience.wiley.com).

The patients' medical records were reviewed for the preclinical stage of the disease, surgical procedures, histopathological findings of the lesions, incidence of remnant gastric cancers, and the outcome.

### Histopathological and Immunohistochemical Analysis

The resected stomachs were processed in the usual manner. Briefly, resected stomachs were opened along the greater curvature, placed on a wooden board with the mucosa facing up, and fixed with a 10% formalin solution for at least 24 hr. Several portions, including the distal and proximal stump as well as both main and sub-lesions, were sliced to a thickness of 5 mm and histologically examined. For exploration of multiple lesions, resected specimens were macroscopically evaluated before and after fixation, along with preoperative evaluation, using endoscopy and upper gastrointestinal studies. Furthermore, these examination methods were performed to identify suspected sub-lesions. For the histopathological evaluation, at least two specialized pathologists evaluated all stained slides of the lesions.

The gastric cancers were evaluated according to the General Rules for the Gastric Cancer Study of the Japanese Research Society for Gastric Cancer [10]. A macroscopic pattern of early gastric cancers was classified, according to the Japanese Society for Gastroenterology Endoscopic Criteria, as type I (protruded), type IIa (elevated), type IIb (flat), type IIc (depressed), and type III (excavated). In this study, the histological pattern of gastric cancers were classified into two types; well and moderately differentiated carcinoma were recorded as differentiated type, whereas poorly differentiated or undifferentiated carcinoma were recorded as undifferentiated type [11].

### Statistical Analysis

Statistical differences between the two groups were analyzed using the Chi-square test and the Mann-Whitney *U*-test. Univariate and multivariate analyses were performed to evaluate the significance of the clinical and histopathological parameters. A value of  $P < 0.05$  was considered statistically significant.

## RESULTS

### Incidence and Clinicopathological Features of Multifocal Gastric Cancers

From October 1993 to June 2008, 3,042 patients with gastric cancers underwent gastrectomy at the National Cancer Center Hospital East. Of these, 2,776 patients (91.3%) were histologically diagnosed with a solitary lesion, whereas the remaining 266 patients (8.7%) were diagnosed with synchronous multiple gastric cancers in which more than two gastric cancer lesions were found in the resected stomach. Among the 2,776 patients who were histologically diagnosed with a solitary lesion, 809 patients (29.1%) underwent total gastrectomy. On the other hand, among 266 patients who were histologically diagnosed with synchronous multiple cancers, 113 patients (42.4%) underwent total gastrectomy. For the evaluation of the remnant gastric cancers in this study, we excluded the patients who underwent total gastrectomy, and focused on the remaining 1,967 patients with a solitary lesion and 153 patients with multiple lesions. Clinical and histopathological features of the 153 patients with synchronous multiple cancers are shown in Table I. In patients with multiple gastric cancers, the mean age at diagnosis of initial lesions was 63.2 years and significantly older than those with solitary lesion (57.6 years); 109 patients were men and 44 patients were women. The mean number of lesions was 2.23 per patient. The histological types of main lesions were consistent with those of the sub-lesions in 109 patients (71.2%). Of these, the differentiated type was present in 91 patients (59.4%), and the undifferentiated type was present in 18 patients (11.6%), and

TABLE I. Patients' Characteristics of the Initial Lesions in Patients With Gastric Cancers

	Solitary (n = 1,967)	Multiple (n = 153)	P-value
Age (mean, years)	57.6	63.2	<0.05
Gender (M:F)	2.1:1	2.5:1	n.s.
Mean no. of lesions	—	2.23/case	—
Consistency with histological type of the main lesion (total)	—	71.2%	—
Histological type			<0.01
Differentiated-type	43.7%	59.4%	
Undifferentiated-type	51.3%	11.6%	
Average distance between the lesions	—	28.5 mm	—
Location of main lesion			n.s.
The upper third of the stomach	13.5%	6.5%	
The middle third of the stomach	42.5%	51.0%	
The lower third of the stomach	38.6%	42.5%	

Differentiated-type, well- or moderately-differentiated adenocarcinoma; undifferentiated-type, poorly differentiated adenocarcinoma, undifferentiated carcinoma.

Statistical significance between both groups was analyzed by Chi-square test and Mann-Whitney *U*-test.

distribution of the histological types was significantly different compared with the cases with solitary lesion. The average distance between the main lesion and sub-lesions was 28.5 mm. Main lesions were located in the upper third of the stomach in 10 cases (6.5%), in the middle third of the stomach in 78 cases (51.0%), and in the lower third of the stomach in 65 cases (42.5%).

Supplemental Table I shows the comparison of the histopathological features of the initial lesions (main lesion vs. sub-lesion) among the patients who underwent gastrectomy for multiple lesions. The average tumor size of the main lesion and the sub-lesion was 37.9 and 13.8 mm, respectively ( $P < 0.05$ ). Moreover, 30.7% of the main lesions were histologically diagnosed as undifferentiated carcinoma (poorly differentiated adenocarcinoma or undifferentiated carcinoma), whereas 19.1% of sub-lesions were undifferentiated carcinoma ( $P = 0.13$ ). Furthermore, 73.4% of main lesions were histopathologically found to be mucosal or sub-mucosal lesions, whereas 96.7% of sub-lesions were mucosal or sub-mucosal lesions ( $P < 0.05$ ). Finally, histological examination revealed that 23.7% of main lesions and 4.1% of sub-lesions showed lymph infiltrations ( $P < 0.05$ ), 33.5% of main lesions and 6.9% of sub-lesions showed vascular invasion ( $P < 0.05$ ), and 18.8% of main lesions and 1.3% of sub-lesions showed perineural invasions ( $P < 0.05$ ).

### Incidence and Histopathological Features of Remnant Gastric Cancers

Among 153 patients with synchronous multiple gastric cancers, 7 patients (4.5%) developed a secondary lesion in their remnant stomach, whereas 9 out of 1,967 patients (0.45%) developed a secondary lesion in their remnant stomach after initial gastrectomy for a solitary lesion. At initial gastrectomy, the incidence of remnant gastric cancers was significantly higher in patients with multiple cancers compared with those with solitary cancer at initial gastrectomy ( $P < 0.05$ ; Fig. 1A).

As shown in Figure 1B, the average duration of follow-up for the detection of the remnant gastric cancers was 2.12 years in patients with multiple lesions and 3.93 years in patients with a solitary lesion ( $P = 0.051$ ). Clinical and histopathological features of the initial lesions in patients who developed remnant gastric cancers during follow-up are shown in Table II. There were no significant differences between the solitary lesions and multiple lesions in terms of mean age

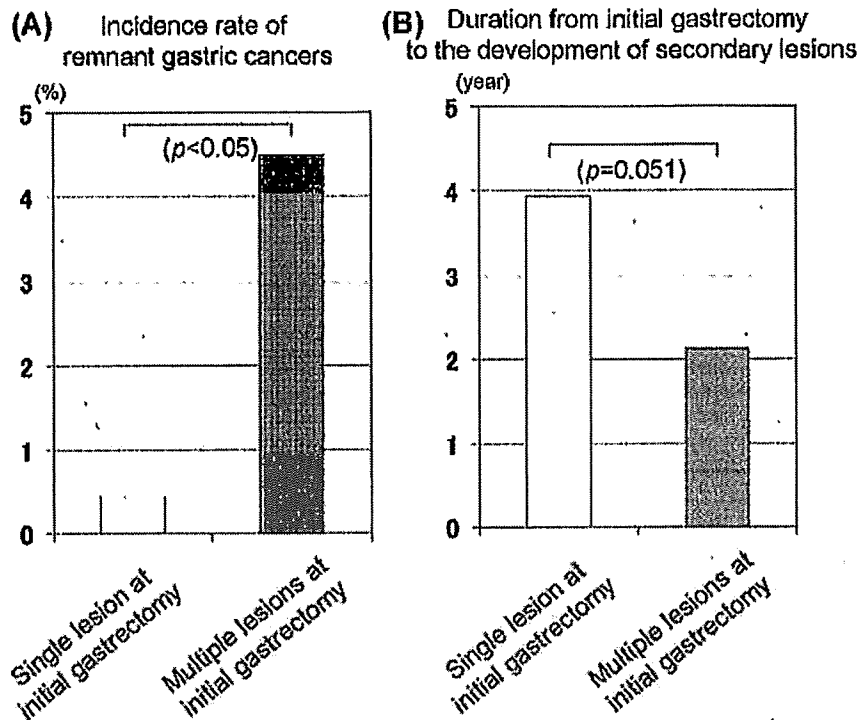


Fig. 1. Comparison of the incidence and interval of remnant gastric cancers after gastrectomy between patients with solitary and patients with synchronous multiple cancers as initial lesions. A: The incidence of remnant gastric cancers was significantly higher in patients with synchronous multiple gastric cancers compared to those with solitary lesions (Chi-square test). B: The average postoperative interval until detection of secondary cancers in the remnant stomach was shorter in patients with multiple gastric cancers (Chi-square test).

(61.8 years vs. 69.4 years;  $P=0.11$ ), gender (6:3 vs. 6:1;  $P=0.77$ ), population of the undifferentiated lesions (poorly differentiated carcinoma and undifferentiated carcinoma) (44.5% vs. 42.9%;  $P=0.78$ ), histological depth of the invasion (sub-mucosal layer) (55.5% vs. 85.7%;  $P=0.14$ ), mean tumor size (34.8 mm vs. 24.5 mm;  $P=0.24$ ), lymph infiltration (37.5% vs. 15.3%;  $P=0.32$ ), vascular invasion (44.5% vs. 15.3%;  $P=0.34$ ), perineural invasion (22.2% vs. 7.9%;  $P=0.53$ ), percentage of lymph node metastasis (11.1% vs. 0%;

$P=0.89$ ), and location of the main lesions at initial surgery (85.7% vs. 92.3%;  $P=0.68$ ). Table III shows the comparison of the histopathological features of secondary gastric cancer lesions in the remnant stomach. There were no significant differences between remnant gastric cancers that occurred after surgery for a solitary lesion and synchronous multiple lesions in terms of histological differentiation (55.6% vs. 14.3%;  $P=0.14$ ), depth of tumor invasion (sub-mucosal layer) (44.4% vs. 85.7%;  $P=0.14$ ), average size of the tumor (24.4 mm vs. 23.5 mm;  $P=0.82$ ), and percentage of lymph node metastasis (22.2% vs. 0%;  $P=0.56$ ). However, in patients who underwent initial gastrectomy for multiple lesions, a higher percentage of remnant gastric cancers were of the differentiated type and less deeply infiltrated the stomach wall, with no lymph node metastasis.

TABLE II. Comparison of the Clinicopathological Features of the Initial Lesions Which Developed Cancer in the Remnant Stomach During Follow-Up

Variables	Solitary lesion (n=9)	Multiple lesions (n=7)	P-value
Age (mean, years)	61.8	69.4	0.11
Gender (M:F)	6:3	6:1	0.77
Differentiation (undifferentiated-type)	44.5%	42.9%	0.78
Depth (m or sm)	55.5%	85.7%	0.14
Tumor size (mean)	34.8 mm	24.5 mm	0.24
Lymph infiltration	37.5%	15.3%	0.32
Vascular invasion	44.5%	15.3%	0.34
Perineural invasion	22.2%	7.69%	0.53
% of pN(+) case	11.1%	0%	0.89
Location (M, ML)	87.5%	92.3%	0.68

Undifferentiated-type, poorly differentiated adenocarcinoma, undifferentiated carcinoma; m or sm, mucosal or sub-mucosal layer of the stomach wall; M, the middle third of the stomach; ML, the lower two-thirds of the stomach; Statistical significance between both groups was analyzed by Chi-square test and Mann-Whitney U-test.

TABLE III. Comparison of the Histopathological Features of the Secondary Cancers on the Remnant Stomach During Follow-Up

Variables	Solitary lesion (n=9)	Multiple lesions (n=7)	P-value
Differentiation (differentiated-type)	55.6%	14.3%	0.14
Depth of invasion (m or sm)	44.4%	85.7%	0.14
Tumor size (mean)	24.4 mm	23.5 mm	0.82
% of pN(+) case	22.2%	0%	0.56

Differentiated-type, well- and moderately-differentiated adenocarcinoma; m or sm, mucosa or sub-mucosal layer of the stomach wall. Statistical significance between both groups was analyzed by Chi-square test and Mann-Whitney U-test.

### Evaluation of Potential Risk Factors for the Development of Remnant Gastric Cancers After Gastrectomy for Multiple Lesions

Results of our study suggested that patients with multiple gastric cancers are more susceptible to the development of secondary gastric cancers in the remnant stomach (Fig. 1). Thus, to address the potential risk factors for the development of secondary lesions, we examined the differences in the clinical and histopathological features (differentiation of cancer, depth of invasion, size of the lesion, lymph infiltration, vascular invasion, perineural invasion, number of lymph nodes dissected, percentage of the cases with lymph node metastasis, macroscopic type, distance from the margin, location of tumors) of the primary lesions in patients with multiple gastric cancers at initial gastrectomy who developed remnant cancers and those who did not. As shown in Table IV, results of the univariate analysis revealed that there were no statistically significant differences in the percentage of poorly differentiated cancers, histopathological invasion of the lesion, size of the main lesion, percentage of lymph infiltration, percentage of vascular invasion, percentage of perineural invasion, and lymph node metastasis, between patients with and without development of secondary lesions. However, the margin to the oral side of stomach was significantly shorter in patients who developed secondary lesions (40.9 mm vs. 17.9 mm,  $P=0.03$ ). Furthermore, in patients who developed remnant gastric cancers, a higher percentage of lesions were located in the middle third of the stomach, and the location of the initial lesions (including main and sub-lesions) were significantly different compared to cases with no remnant gastric cancers ( $P=0.048$ ; Table IV, Fig. 2).

Multivariate analysis revealed that the margin to the oral side of the stomach at initial gastrectomy is a possible indicator for predicting the development of remnant gastric cancers after gastrectomy for synchronous multiple lesions ( $P=0.049$ , 95% confidence interval (CI); 0.26–0.97).

### DISCUSSION

The incidence of synchronous multiple gastric cancers is reported to be about 4–8%, using standard histopathological analysis of surgically resected specimens [3,12,13]. Several reports have indicated that the incidence of multiple gastric cancers has been increasing in recent years. In particular, studies that involved histopathological exploration of serial sections of the whole stomach showed a higher detection rate of multiple gastric cancers [3,4], which suggests a high

frequency of coexistent latent lesions in surgically resected specimens. Detection of multiple gastric cancers could be influenced by several factors, including the method of histopathological analysis. Improvement in diagnostic devices is another important factor contributing to the current higher incidence in detection of multiple lesions.

Clinical and histopathological features of synchronous multiple gastric cancers have been reported sporadically [3,13,14], and it has been demonstrated that multiple gastric cancers are more frequently observed in elderly, predominantly male, patients [12,14]. Consistent with these observations, we found that patients with multiple gastric cancers were relatively old men compared to patients with a solitary lesion. Furthermore, in the present study, most of the lesions in patients with multiple gastric cancers were histopathologically confined to the mucosa or sub-mucosa, and did not infiltrate beyond the sub-mucosal layer of the stomach. These clinicopathological characters of multiple gastric cancers can be understood in several ways. Previous studies of histopathological examinations demonstrated possible associations for the initiation of multiple gastric cancers with intestinal metaplasia of the gastric mucosa [15]. Mai and Takagi [16] investigated the patterns of intestinal metaplasia and the histological type of stomach cancers, and demonstrated that synchronous multiple gastric cancers were frequently found as differentiated adenocarcinomas and were associated with the condition of a diffuse extensive type of intestinal metaplasia. Since a high incidence of intestinal metaplasia is usually observed in the stomach of elderly males [17–19], it is reasonable to assume that patients with multiple gastric cancers are most commonly found among this sub-group. The present study revealed that 71.2% of main lesions in synchronous multiple gastric cancers were consistent with the histological type of sub-lesions, which is compatible with previous observations [20]. This result shows that about 30% of sub-lesions have different histological type from that of main lesions, suggesting that several other factors are involved in the formation of sub-lesions although intestinal metaplasia may be important in the initiation of multiple cancers.

Cancer in the remnant stomach is the focus of much attention not only as a typical model of carcinogenesis, but also from the diagnostic aspect of the lesion. As a result of improvements in outcomes for gastric cancers, more attention to the possibility of formation of remnant gastric cancers is needed during follow-up after initial gastrectomy. Notably, together with advances in diagnostic modalities, the incidence of remnant gastric cancers is reported to be increasing, and the current incidence is ~0.5–1.7% [21–23]. On the other hand, few reports have demonstrated the occurrence rate or clinicopathological characters of remnant gastric cancers that developed after gastrectomy for multiple gastric cancers. Of these, the largest series

TABLE IV. Comparison of the Clinicopathological Features of the Initial Lesions Between the Cases With Or Without Remnant Gastric Cancers Among the Patients With Synchronous Multiple Lesions

Variables	Remnant cancer (-)	Remnant cancer (+)	P-value (univariate)	P-value (multivariate)
Undifferentiated-type	35.3%	53.8%	n.s.	—
Depth (m or sm)	85.8%	84.6%	n.s.	—
Size of the lesion	24.3 mm	24.6 mm	n.s.	—
Lymph infiltration	12.6%	15.4%	n.s.	—
Vascular invasion	18.8%	23.1%	n.s.	—
Perineural invasion	8.3%	7.7%	n.s.	—
No. dissected LNs	36.7	39.5	n.s.	—
% of pN(+) case	11.1	0.0	n.s.	—
Macroscopic type (type 0-IIc)	68.6%	76.9%	n.s.	—
Distance from margin (mean)	40.4 mm	17.9 mm	0.03	0.049 (0.26–0.97)
Location of the lesion on the middle two-thirds of stomach	37.6%	85.7%	0.048	n.s. (0.38–1.39)

Undifferentiated type, poorly differentiated adenocarcinoma, undifferentiated carcinoma; m or sm, mucosal or sub-mucosal layer of the stomach wall; type 0-IIc, early gastric cancer with depressed type of endoscopic finding. Statistical significance between both groups was analyzed by Chi-square test and Mann-Whitney U-test.

Comparison of location of the initial lesions  
between the cases with or without remnant gastric cancers  
among the patients that underwent gastrectomy for multiple lesions

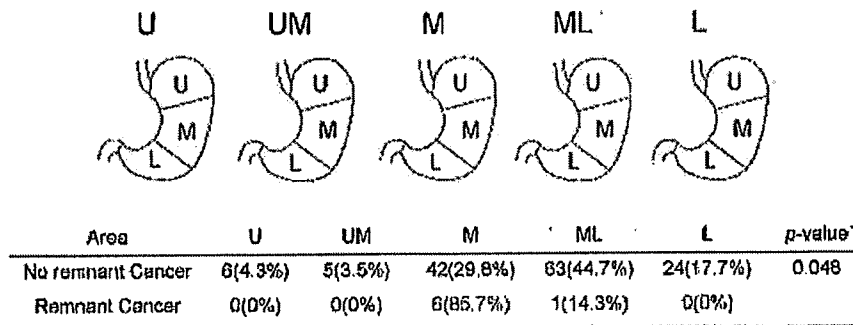


Fig. 2. Comparison of the location of initial lesions between patients with and without remnant gastric cancers, among the patients who underwent gastrectomy for multiple lesions. The distribution of initial lesions was significantly different in patients with and without remnant lesions (Chi-square test).

from a Japanese group showed that the incidence of remnant gastric cancers after gastrectomy for solitary gastric cancers was 1.7%, whereas that after surgery for synchronous multiple lesions was 4.7% [20]. Results of our study are consistent with this report; our results add to the previous literature because we demonstrated that the proximal surgical margin is a potential indicator to predict the formation of remnant gastric cancers after gastrectomy for multiple lesions. Furthermore, the present study found that in patients with remnant gastric cancers, the distribution of initial lesions was different from that of the initial lesions in patients without remnant cancers. More than 80% of the lesions in patients with remnant cancers were located in the middle third of the stomach, whereas 60% of lesions in patients without remnant cancers were found in the lower two-thirds of stomach. These results suggest that although no lesions were found in the upper third of the stomach, a higher percentage of multiple cancers tended to be present in the oral side of the stomach in patients with subsequent remnant lesions. This speculation, based on our results which showed a possible association between the oral margin and the potential risk of remnant gastric cancers, seems to be compatible with evidence from previous investigations into the clinical and histopathological aspects of remnant gastric cancers.

We did not examine the area of intestinal metaplasia, nor did we investigate the correlation between the fields of intestinal metaplasia. However, it is reasonable to assume that if the metaplastic area was diffusely extended in the oral direction of the stomach, the mucosa would be more susceptible to the development of a secondary lesion in the proximal area of the stomach. Therefore, there is a high possibility that these lesions would be close to the proximal margin of the stomach. Indeed, to support these speculations, several Japanese investigators have demonstrated that the diffuse type of intestinal metaplasia was found in about 80% of patients with synchronous multiple gastric cancers compared to 40–50% of patients with solitary cancers [15,16,18]. Since the concept of "field cancerization" has been postulated to explain the formation of multifocal gastric cancers [24–26], we should be more cautious in our approach to patients with synchronous multiple gastric cancers, particularly elderly males with diffuse type of intestinal metaplasia. The present study further indicated that although there were no significant differences, a higher percentage of remnant gastric cancers, in patients who underwent gastrectomy for multiple lesions, were of the differentiated type and less deeply infiltrated the stomach wall, with no lymph node metastasis. Thus, postoperative follow-up should be adequately

planned to fully examine the remnant stomach, and endoscopic treatment should be considered as a useful option to resect secondary lesions in patients undergoing initial gastrectomy for multiple lesions.

Our study had several limitations. Some patients may have been excluded from analysis because of the lack of complete information about the postoperative findings of endoscopic examination. Endoscopy is the indispensable examination for the follow-up and occasionally the removal of secondary lesions in the remnant stomach; therefore, excluded information could have biased our observations. Moreover, we excluded the cases of total gastrectomy in this study. By excluding all patients that underwent total gastrectomy, the pathological contributions to the development of remnant gastric cancer could have biased. Furthermore, our study covered an almost 15-year period, during which preoperative diagnostic accuracy and postoperative follow-up regimens were different. However, histopathological explorations were consistently performed in the study, which may even be considered a strong point of the study.

In conclusion, the results of our study indicate the following: (1) Patients with synchronous multiple gastric cancers are at potential risk of developing secondary lesions in their remnant stomach after initial surgery. Furthermore, since a series of observations demonstrated that 20–30% of synchronous sub-lesions were detected during histopathological evaluation, we need to be more careful in the preoperative evaluation of these patients. (2) Moreover, in patients with multiple cancers, the supposed risk of secondary lesions is estimated to be around 3–4% in the remnant stomach. Therefore, intense postoperative follow-up is important, and total gastrectomy may be the alternative option in the case with adequate surgical margin cannot be obtained. (3) Since endoscopic exploration is the most reliable examination to detect these remnant lesions [22], patients with synchronous multiple gastric cancers, who are more susceptible to developing secondary gastric lesions in their remnant stomach, should be regularly checked by this technique. In this study, because remnant gastric cancers were detected 2.12 (mean, Fig. 1) years after initial gastrectomy, postoperative follow-up with intense endoscopic examination is required at least first couple of years after initial gastrectomy. Furthermore, given that most remnant gastric cancers after gastrectomy for multiple lesions are differentiated-type and do not infiltrate deep into the sub-mucosal layer of the stomach (Table III), the importance of endoscopic examination is noteworthy not only for detection but also for the subsequent treatment of these lesions on the remnant stomach.

## ACKNOWLEDGMENTS

We thank the members of the Division of Digestive Surgery for their critical discussion of this study. We greatly appreciate Dr. Atsushi Ochiai and Dr. Satoshi Fujii for providing us with histopathological suggestions. We also appreciate the members of the Division of Gastrointestinal Medicine for providing us with information about the endoscopic examinations.

## REFERENCES

1. Moertel CG, Bargen JA, Soule BH: Multiple gastric cancers: Review of the literature and study of 42 cases. *Gastroenterology* 1957;32:1095-1103.
2. Yamagiwa H, Yoshimura H, Matsuzaki O, et al.: Pathological study of multiple gastric carcinoma. *Acta Pathol Jpn* 1980;30:421-426.
3. Kosaka T, Miwa K, Yonemura Y, et al.: A clinicopathologic study on multiple gastric cancers with special reference to distal gastrectomy. *Cancer* 1990;65:2602-2605.
4. Esaki Y, Hirokawa K, Yamashiro M: Multiple gastric cancers in the aged with special reference to intramucosal cancers. *Cancer* 1987;59:560-565.
5. Kaminishi M, Shimizu N, Shiomoyama S, et al.: Etiology of gastric remnant cancer with special reference to the effects of denervation of the gastric mucosa. *Cancer* 1995;75:1490-1496.
6. Tersmette AC, Offerhaus GJ, Tersmette KW, et al.: Meta-analysis of the risk of gastric stump cancer: Detection of high risk patient subsets for stomach cancer after remote partial gastrectomy for benign conditions. *Cancer Res* 1990;50:6486-6489.
7. Ahn HS, Kim JW, Yoo MW, et al.: Clinicopathological features and surgical outcomes of patients with remnant gastric cancer after a distal gastrectomy. *Ann Surg Oncol* 2008;15:1632-1639.
8. Kaminishi M, Shimizu N, Shimoyama S, et al.: Denervation promotes the development of cancer-related lesions in the gastric remnant. *J Clin Gastroenterol* 1997;25:S129-S134.
9. Takeda J, Toyonaga A, Koufujii K, et al.: Early gastric cancer in the remnant stomach. *Hepatogastroenterology* 1998;45:1907-1911.
10. Japanese Gastric Cancer Association. Japanese Classification of Gastric Carcinoma—2nd English Edition. *Gastric Cancer* 1998;1:10-24.
11. Maehara Y, Orita H, Okuyama T, et al.: Predictors of lymph node metastasis in early gastric cancer. *Br J Surg* 1992;79:245-247.
12. Kim DY, Joo JK, Ryu SY, et al.: Clinicopathologic characteristics of gastric carcinoma in elderly patients: A comparison with young patients. *World J Gastroenterol* 2005;11:22-26.
13. Kodama M, Tur GE, Shiozawa N, et al.: Clinicopathological features of multiple primary gastric carcinoma. *J Surg Oncol* 1996;62:57-61.
14. Otsuji E, Kuriu Y, Ichikawa D, et al.: Clinicopathologic characteristics and prognosis of synchronous multifocal gastric carcinomas. *Am J Surg* 2005;189:116-119.
15. Honmyo U, Misumi A, Murakami A, et al.: Clinicopathological analysis of synchronous multiple gastric carcinoma. *Eur J Surg Oncol* 1989;15:316-321.
16. Mai M, Takagi S: New concepts on precancerous lesions of the stomach. *Gan To Kagaku Ryoho* 1995;22:2029-2037.
17. Fedeli G, Cannizzaro O, Gambassi G, et al.: Increased prevalence of intestinal metaplasia in the gastric mucosa of the elderly: Clinical implications. *Ann Ital Med Int* 1990;5:26-30.
18. Furukawa H, Iwanaga T, Imaoka S, et al.: Multifocal gastric cancer in patients younger than 50 years of age. *Eur Surg Res* 1989;21:313-318.
19. Pianzola HM, Ottino A, Pianzola MA, et al.: Systematic study of gastrectomy specimens for cancer, in search of synchronous carcinomas. *Acta Gastroenterol Latinoam* 1997;27:27-30.
20. Yanadori E, Oguma H, Sasagawa T, et al.: Clinicopathological study of multifocal gastric cancer. *Jpn J Gastroenterol Surg (Article in Japanese)* 2001;34:9-14.
21. An JY, Youn HG, Ha TK, et al.: Clinical significance of tumor location in remnant gastric cancers developed after partial gastrectomy for primary gastric cancer. *J Gastrointest Surg* 2008;12:689-694.
22. Takenaka R, Kawahara Y, Okada H, et al.: Endoscopic submucosal dissection for cancers of the remnant stomach after distal gastrectomy. *Gastrointest Endosc* 2008;67:359-363.
23. Tanigawa N, Nomura E, Niki M, et al.: Clinical study to identify specific characteristics of cancer newly developed in the remnant stomach. *Gastric Cancer* 2002;5:23-28.
24. Zaky AH, Watari J, Tanabe H, et al.: Clinicopathologic implications of genetic instability in intestinal-type gastric cancer and intestinal metaplasia as a precancerous lesion: Proof of field cancerization in the stomach. *Am J Clin Pathol* 2008;129:613-621.
25. McDonald SA, Greaves LC, Gutierrez-Gonzalez L, et al.: Mechanisms of field cancerization in the human stomach: The expansion and spread of mutated gastric stem cells. *Gastroenterology* 2008;134:500-510.
26. Kang GH, Kim CJ, Kim WH, et al.: Genetic evidence for the multicentric origin of synchronous multiple gastric carcinoma. *Lab Invest* 1997;76:407-417.

