Original article

Study of clinicopathological factors associated with the occurrence of synchronous multiple gastric carcinomas

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Abstract

Background. Multiple gastric carcinomas often arise in gastric mucosa with chronic gastritis, particularly severe intestinal metaplasia. In regard to such characteristics, several clinicopathological risk factors for multiple carcinomas have been reported, but no clinically useful criteria are available at present for assessing the onset of multiple gastric carcinomas. If the risk for multiple gastric carcinomas could be accurately assessed, efficient and accurate surveillance could be performed following minimally invasive therapies.

Methods. In the present study, we investigated clinicopathological differences between 94 cases of multiple early gastric carcinomas and 285 cases of solitary early gastric carcinoma. We tested 379 specimens of gastric carcinomas that had been surgically resected at the Department of General and Gastroenterological Surgery of Osaka Medical College, Japan, from April 1999 to December 2006.

Results. Univariate analysis of clinicopathological factors in the present study showed that multiple gastric carcinomas were significantly correlated to old age (≥ 65 years), well- and moderately differentiated histological type, mucin phenotype (intestinal type), distribution of atrophic mucosa in the stomach (severe), degree of intestinal metaplasia in the surrounding mucosa (severe), and heterotopic glandular cysts. Multivariate analysis using the stepwise method identified age (≥ 65 years) and degree of intestinal metaplasia in the surrounding mucosa (severe) as significant independent risk factors for multiple gastric carcinomas.

Conclusion. While other studies have shown risk factors for multiple gastric carcinomas, the present study is unique in showing risk assessment criteria based on a combination of risk factors for multiple gastric carcinomas.

Key words Multiple gastric carcinoma · Minimum invasive surgery · Mucin phenotypes · Intestinal metaplasia

Introduction

In recent years, minimally invasive therapies, such as laparoscopic surgery and endoscopic resection, including endoscopic submucosal dissection (ESD), have been actively performed for early gastric carcinomas. Such minimally invasive therapies conserve function, but after such resections, a large quantity of the gastric mucosa remains from which the carcinomas arose, and concurrent multiple carcinomas and the development of post-therapeutic asynchronous multiple carcinomas represent serious problems. The early detection and treatment of multiple carcinomas associated with minimally invasive therapies requires strict post-therapeutic surveillance.

Studies of excised stomachs have shown an incidence of concurrent multiple gastric carcinomas of 4.8%–23.8% [1–3]. The incidence of asynchronous multiple gastric carcinomas after endoscopic resection is reportedly 1.0%–5.6% [4, 5]. Epidemiologically, multiple gastric carcinomas often occur in the elderly and in men, and histologically, multiple gastric carcinomas often arise in gastric mucosa with chronic gastritis, particularly severe intestinal metaplasia [6–10]. In regard to such characteristics, several clinicopathological risk factors for multiple carcinomas have been reported, but no clinically useful criteria are available at present for assessing the onset of multiple gastric carcinomas. If the risk for multiple gastric carcinomas could be accurately assessed, efficient and accurate surveillance could be performed following minimally invasive therapies.

The purpose of this study was to establish criteria for predicting the possible onset of multiple gastric carcinomas by comparing clinicopathological factors in solitary and multiple early gastric carcinomas.

Materials and methods

We examined 379 specimens of early gastric carcinomas that had been surgically resected at the Department of General and Gastroenterological Surgery of Osaka Medical College, Japan, from April 1999 to December 2006.

All of the resected materials (stomach including gastric carcinoma) were histologically confirmed as early-stage gastric carcinomas.

Early gastric carcinomas were investigated through the clinicopathological assessment of 94 cases of multiple early gastric carcinomas and 285 cases of solitary early gastric carcinomas.

The diagnosis of carcinoma was based on the criteria published in the *General rules for the gastric cancer study* of the Japanese Research Society for Gastric Cancer [11] and the TNM classification of malignant tumors [12]. The diagnosis of multiple carcinomas was made according to the criteria outlined by Moertel et al. [13], as follows: (1) each lesion must be of pathologically proved malignancy, (2) all lesions must be clearly separated by intervals of microscopically normal gastric wall, and (3) the possibility that one of the lesions represents a local extension or metastatic tumor must be ruled out beyond any reasonable doubt. The diagnosis of carcinoma was also made according to the criteria outlined by the Vienna consensus classification (category classification, 2000) [14].

Early gastric carcinomas were defined as mucosal carcinomas and submucosal invasive carcinomas of the stomach, and mucosal carcinomas were defined as greater than category 4, by the Vienna classification of gastrointestinal epithelial neoplasia [14], and which also showed Tis (carcinoma in situ: intraepithelial tumor without invasion of the lamina propria) and T1 (tumor invades lamina propria or submucosa) by the TNM clinical classification [12].

Differentiated adenocarcinoma was defined as tubular-forming adenocarcinoma and corresponded to “intestinal-type adenocarcinoma” according to Lauren [15] and Jarvi and Lauren [16]. A recent study of differences in the diagnostic criteria of gastric carcinoma between Japanese and Western pathologists [17] reports that, according to most Western pathologists, Japanese pathologists diagnosed definite carcinoma in 50% of cases with adenoma and/or low-grade dysplasia; diagnosed definite carcinoma in the majority of cases of adenoma and/or high-grade dysplasia; and diagnosed definite carcinoma in all cases of adenoma and/or high-grade dysplasia with suspicion of carcinoma. There were no major differences in the diagnoses of cases with clearly invasive carcinoma. The presence of invasion was the most important diagnostic criterion of gastric carcinoma for most Western pathologists, whereas for

the Japanese, the nuclear features and glandular structures were more important.

In the present study, the resected materials (stomach including gastric carcinoma) were fixed in formalin, embedded in paraffin, and stained with H & E. Sections (2- μ m-thick) of the maximum diameter of the tumor were evaluated for the following pathological factors. All cases were blindly reviewed twice by three of the authors (T.N., Y.E., and H.A.). If discrepancies arose, the cases were discussed to achieve consensus while being viewed under a multihead microscope.

Clinicopathological factors

We investigated the clinicopathological differences between multiple early gastric carcinomas and solitary early gastric carcinoma in terms of the following 12 factors:

1. Sex
2. Age
3. Histological type

Histologically, the carcinomas were classified into two types (well- and moderately differentiated type and poorly differentiated type) based on the criteria published in the *General rules for the gastric cancer study* [11] and the TNM classification [12]. We defined well- and moderately differentiated type (G1 and G2) if papillary adenocarcinoma, well-differentiated carcinoma, or moderately differentiated carcinoma was present. We defined the rest as poorly differentiated type (G3) if papillary adenocarcinoma, well-differentiated carcinoma, or moderately differentiated carcinoma was not present, and poorly differentiated carcinoma, signet ring cell carcinoma, or mucinous carcinoma was present.

4. Location

Location was classified into the upper (U), middle (M), and lower (L) thirds of the stomach based on the criteria published in the *General rules for the gastric cancer study* [11]. The upper (U) third shows the cardia or fundus; the middle (M) shows the corpus; and the lower (L) third shows the antrum and pylorus, according to the anatomical subsites of the TNM classification [12].

5. Size

The maximum tumor diameter in early gastric carcinoma was measured macroscopically.

6. Mucin phenotype

On the basis of mucin histochemistry, human gastric mucin (HGM; gastric mucin; Novocastra, Newcastle, UK) and MUC6 (Novocastra) were used as markers indicating gastric phenotype expression. MUC2 (Novocastra) and CD10 (Novocastra) were also used as

markers indicating intestinal phenotype expression. Both cytoplasmic and luminal membranous reactivity were judged as positive for HGM, while CD10 and cytoplasmic reactivity were judged as positive for MUC6 and MUC2 [18]. Differentiated adenocarcinoma that consisted of more than 90% of gastric-type cells was classified as carcinoma with gastric phenotype; that composed of more than 90% of intestinal-type cells was described as carcinoma with intestinal phenotype; and the remainder was assigned as carcinoma with mixed phenotype. In this study, gastric carcinoma was classified into gastric phenotype and intestinal phenotype, with the mixed phenotype being included in the intestinal phenotype.

7. Distribution of atrophic mucosa in the stomach

Distribution of atrophic mucosa was classified into two categories (slight and severe) according to the criteria advocated by Nakamura et al. [19–21]. Atrophic mucosa surrounding carcinoma of the stomach was classified according to the following criteria: slight, with scattered atrophic mucosa; severe, with continuous atrophic mucosa beyond the angle of stomach.

8. Degree of atrophy in the mucosa surrounding the cancer lesion

The gastric mucosa was divided into three areas (fundic, pyloric, and intermediate) in terms of intestinal metaplasia, according to the criteria advocated by Nakamura et al. [19–21], where the F-line is a distal line with chief cells and parietal cells continuously appearing and the f-line is a distal line with parietal cells appearing separately or in the form of a nest; the area proximal to the F-line and f-line is called the intermediate zone area. In this study we checked the mucosa surrounding the cancer lesion and classified the three areas into two types; nonatrophic mucosa (fundic gland) and atrophic mucosa (intermediate zone + pyloric gland).

9. Degree of intestinal metaplasia in the surrounding mucosa

The degree of intestinal metaplasia in the surrounding mucosa was classified into two categories (slight and severe) according to the criteria advocated by Nakamura et al. [19–21]. Intestinal metaplasia in the surrounding mucosa within 1 cm from the cancer was classified as follows: slight, without intestinal metaplasia or with scattered intestinal metaplasia; severe, with continuous intestinal metaplasia or scattered nonmetaplastic glands in between.

10. Heterotopic glandular cysts

We checked whether heterotopic glandular cysts of the stomach were present (positive) or not (negative). Heterotopic glandular cysts are the translocation of pseu-

dopyloric cystic glands into the submucosal layer, cystic transformation, proliferation, and subsequent differentiation of the lining of the foveolar epithelium.

11. *Helicobacter pylori*

Microscopically, we investigated for the presence of a bacterial pathogen with spherical and spiral shapes, i.e., *H. pylori*, by H & E and Giemsa staining and we noted *H. pylori* positivity or negativity.

12. Lymphoid infiltration

The degree of lymphoid cell infiltration in the cancer nest was classified as either negative (no or little infiltration) or positive (infiltration with follicular structure or more lymphoid cells than the number of cancer cells).

Statistical method

The above pathological factors were compared between cases that were positive for multiple gastric carcinomas and those that were negative for multiple gastric carcinomas. Each pathological factor was assessed separately by univariate logistic regression analysis. Differences at $P < 0.10$ were considered significant. Factors were analyzed by stepwise multivariate logistic regression, and the odds ratio with 90% confidence interval was calculated for each factor. Statview version 5.0 [22] and SPSS II standard version [23] were used for all statistical calculations.

Results (Table 1)

1. Sex

In the group with solitary early gastric carcinoma, the male/female ratio was 195: 90. In the group with multiple early gastric carcinomas, the male/female ratio was 65: 27. The male/female ratio therefore showed no difference between the group with solitary early gastric carcinomas and the group with multiple early gastric carcinomas.

2. Age

The average age of the patients with solitary early gastric carcinoma was 62.4 years, and it was 66.1 years in those with multiple early gastric carcinomas. This difference was statistically significant ($P = 0.009$). In addition, the odds ratio was highest when subjects were divided into groups with a cutoff age of 65 years. The incidence of multiple early gastric carcinomas increased with age.

3. Histological type

In the group with solitary early gastric carcinoma, the ratio of well- and moderately differentiated type to

Table 1. Clinicopathological differences between multiple gastric carcinomas and solitary gastric carcinoma

	Solitary gastric carcinoma	Multiple gastric carcinomas	Total
Sex			
Male	195	65	260
Female	90	27	117
Age			
≥65	127	62	189
<65	158	32	190
	62.4 ^a	66.1 ^a	63.3 ^a]*
Location			
U	39	8	47
M	142	50	192
L	104	34	138
Histological type			
Well-differentiated	119	46	165
Poorly differentiated	166	46	212]*
Size			
mm	34.1	30.0	33.1
Mucin phenotype			
Gastric	167	36	203
Intestinal	98	56	154]*
Distribution of atrophic mucosa in the stomach			
Slight	127	31	158
Severe	113	56	169]*
Degree of atrophy in the mucosa surrounding cancer lesion			
Nonatrophic mucosa	45	10	55
Atrophic mucosa	234	82	316
Degree of intestinal metaplasia in the surrounding mucosa			
Slight	146	29	175
Severe	132	63	195]*
Heterotopic glandular cysts			
(–)	264	79	343
(+)	19	13	32]*
<i>Helicobacter pylori</i> infection			
(–)	49	21	70
(+)	92	26	118
Lymphoid infiltration			
(–)	274	87	361
(+)	11	5	16

* $P < 0.10$ ^a Average age

poorly differentiated type was 119 (41.8%):166 (58.2%). In the group with multiple early gastric carcinomas, the ratio of well- and moderately differentiated type to poorly differentiated type was 46 (50.0%): 46 (50.0%). This difference was statistically significant ($P = 0.036$) and the well- and moderately differentiated type was present more often in the group with multiple early gastric carcinomas than in the group with solitary early gastric carcinomas.

4. Location

In the group with solitary early gastric carcinoma, the upper third of the stomach (cardia and fundus) had 39 cases (13.7%), the middle third (corpus) had 142 cases (49.8%), and the lower third (antrum and pylorus) had 104 cases (36.5%). In the group with multiple early gastric carcinomas, the upper third of the stomach

(cardia and fundus had 8 cases (8.7%), the middle third (corpus) had 50 cases (54.3%), and the lower third (antrum and pylorus) had 34 cases (37.0%). No difference was seen in the incidence of cases in the upper (U, cardia and fundus), middle (M, corpus), and lower (L, antrum and pylorus) thirds of the stomach between the groups with multiple early gastric carcinomas and solitary early gastric carcinoma.

5. Size

The median tumor diameter in the group with solitary early gastric carcinoma was 34.1 mm and the median tumor diameter in the group with multiple early gastric carcinomas was 30.0 mm. There was no statistically significant difference between the group with solitary early gastric carcinomas and the group with multiple early gastric carcinomas.

6. Mucin phenotype

In the group with solitary early gastric carcinoma, the ratio of gastric phenotype to intestinal phenotype was 167 (63.0%): 98 (37.0%). In the group with multiple early gastric carcinomas, the ratio of gastric phenotype to intestinal phenotype was 36 (39.1%): 56 (60.9%). The intestinal phenotype was present more often in the group with multiple early gastric carcinomas than in the group with solitary early gastric carcinomas. Statistically, the mucin phenotype (intestinal phenotype) was one of the most significant clinicopathological factors ($P = 0.0001$).

7. Distribution of atrophic mucosa in the stomach

In the group with solitary early gastric carcinoma, the ratio of slight type to severe type was 127 (52.9%): 113 (47.1%). In the group with multiple early gastric carcinomas, the ratio of slight type to severe type was 31 (35.6%): 56 (64.4%). This difference was statistically significant ($P = 0.0056$). “Severe” distribution of atrophic mucosa was present more often in the group with multiple early gastric carcinomas than in the group with solitary early gastric carcinomas.

8. Degree of atrophy in the mucosa surrounding the cancer lesion

In the group with solitary early gastric carcinoma, non-atrophic mucosa (fundic gland) was found in 45 (16.1%) and atrophic mucosa (intermediate zone + pyloric gland) in 234 (83.9%). In the group with multiple early gastric carcinomas, nonatrophic mucosa was found in 10 (10.9%) and atrophic mucosa in 82 (89.1%). There were no statistically significant differences in these factors between the two groups.

9. Degree of intestinal metaplasia in the surrounding mucosa

In the group with solitary early gastric carcinoma, the ratio of slight type to severe type was 146 (52.5%): 132 (47.5%). In the group with multiple early gastric carcinomas, the ratio of slight type to severe type was 29(31.5%): 63 (68.5%). Statistically, a “severe” degree of intestinal metaplasia in the surrounding mucosa was one of the most significant clinicopathological factors ($P = 0.0004$).

10. Heterotopic glandular cysts

In the group with solitary early gastric carcinoma, 19 cases were positive for heterotopic glandular cysts (6.7%) and 264 cases were negative for heterotopic glandular cysts (93.3%). In the group with multiple early gastric carcinomas, 13 cases were positive for heterotopic glandular cysts (14.1%) and 79 cases were negative for heterotopic glandular cysts (85.9%). In

multiple early gastric carcinomas, coexistence with heterotopic glandular cysts was statistically significant ($P = 0.09$).

11. *Helicobacter pylori*

In the group with solitary early gastric carcinoma, 92 cases were *H. pylori*-positive (65.2%) and 49 cases were *H. pylori*-negative (34.8%). In the group with multiple early gastric carcinomas, 26 cases were *H. pylori*-positive (55.3%) and 21 cases were *H. pylori*-negative (44.7%). This difference was not statistically significant.

12. Lymphoid infiltration

In the group with solitary early gastric carcinoma, 11 cases were lymphoid infiltration-positive (3.9%) and 274 cases were lymphoid infiltration-negative (96.1%). In the group with multiple early gastric carcinomas, 5 cases were lymphoid infiltration-positive (5.4%) and 87 cases were lymphoid infiltration-negative (94.6%). This difference was not statistically significant.

Statistical analysis

Univariate logistic regression analysis showed that age (≥ 65 years), histological type (well and moderately differentiated type), mucin phenotype (intestinal type), distribution of atrophic mucosa in the stomach (severe), degree of intestinal metaplasia in the surrounding mucosa (severe), and heterotopic glandular cyst (positive) were statistically significant risk factors for multiple gastric carcinomas (Table 2). Multivariate logistic regression analysis by the stepwise method showed that the important risk factors for multiple gastric carcinomas were the degree of intestinal metaplasia in the surrounding mucosa (moderate or severe) and age (≥ 65 years; Table 2).

Predictive pathological risk algorithm for multiple gastric carcinomas

Univariate logistic regression analysis of clinicopathological factors in the present study showed that multiple gastric carcinomas were significantly correlated to old age (≥ 65 years), histological type (well- and moderately differentiated), mucin phenotype (intestinal type), distribution of atrophic mucosa in the stomach (severe), degree of intestinal metaplasia in the surrounding mucosa (severe), and heterotopic glandular cysts (positive). Furthermore, multivariate logistic regression analysis by the stepwise method identified the degree of intestinal metaplasia in the surrounding mucosa (severe) and age (≥ 65 years) as significant independent risk factors for multiple gastric carcinomas.

Table 2. Clinicopathological differences between multiple gastric carcinomas and solitary gastric carcinoma (logistic regression analysis; $P < 0.10$)

Pathological factors	Univariate analysis		Multivariate analysis	
	<i>P</i> value	Odds ratio	<i>P</i> value	Odds ratio
Sex	0.59			
Age	0.009	2.29	0.02	2.19
Location	0.98			
Histological type	0.036	1.89	0.87	
Size	0.17			
Mucin phenotype	0.0001	2.63	0.18	
Distribution of atrophic mucosa in the stomach	0.0056	2.06	0.82	
Degree of atrophy in the mucosa surrounding cancer lesion	0.15			
Degree of intestinal metaplasia in the surrounding mucosa	0.0004	2.49	0.004	2.75
Heterotopic glandular cysts	0.09	1.91	0.34	
<i>H. pylori</i> infection	0.24			
Lymphoid infiltration	0.82

Fig. 1. Risk chart for multiple gastric carcinomas

Based on these findings, the risk for multiple gastric carcinomas was classified as high, moderate, or low, as follows: when intestinal metaplasia in the surrounding mucosa (severe) or age (≥ 65 years) was found, the risk was classified as high; when the histological type was well- and moderately differentiated, mucin phenotype was the intestinal type, the distribution of atrophic mucosa in the stomach was severe, or heterotopic glandular cysts were positive, the risk for multiple gastric carcinomas was classified as moderate. The risk for mul-

tiple gastric carcinomas were classified as low when these risk factors were absent.

A risk chart, based on logistic regression analysis, for multiple gastric carcinoma was developed, as shown in Fig. 1. We calculated the sensitivity and the specificity for high risk and for high and intermediate risk for multiple gastric carcinomas. With this algorithm, sensitivity was 86.2% and specificity was 30.4% in the high-risk category, and sensitivity was 98.9% and specificity was 9.0% in the high-and-intermediate-risk category.

Discussion

In the elderly, the incidence of gastric carcinomas reportedly tends to be high, and the frequency of multiple cancers is also high. Old age has therefore been recognized as a risk factor for multiple gastric carcinomas [24]. In the present study, old age was significantly correlated to multiple gastric carcinomas, and multivariate analysis showed old age as a significant independent risk factor. Logistic regression analysis was performed by dividing subjects into two age groups, elderly and young, and odds ratios were highest when subjects were divided into groups with a cutoff age of 65 years. Based on this finding, the assumption that elderly individuals aged 65 years or more are at greater risk for multiple gastric carcinomas appears valid. Studies have not fully clarified the age at which the risk for multiple gastric carcinomas increases, and using age as a risk factor in clinical settings has been difficult. The current finding of a concrete value of 65 years is thus clinically significant.

Meanwhile, studies have shown that chronic atrophic gastritis and intestinal metaplasia are carcinogenic factors and represent important risk factors for multiple cancers [25, 26]. In the present study, chronic gastritis was investigated in terms of the following four factors: distribution of atrophic mucosa in the stomach, degree of atrophy in the mucosa surrounding the cancer, degree of intestinal metaplasia in the surrounding mucosa, and *H. pylori* infection. The results showed that multiple gastric carcinomas were correlated significantly to the distribution of atrophic mucosa in the stomach and the degree of intestinal metaplasia in the surrounding mucosa, and multivariate analysis confirmed the latter as a significant independent factor. Recent studies have shown that *H. pylori* not only causes peptic ulcer and gastritis but also exhibits a strong correlation to gastric carcinomas [27–29]. The WHO/International Agency for Research on Cancer (IARC) recognized *H. pylori* as a definite carcinogen in 1994 [30]. Many prospective epidemiological studies have shown that the incidence of gastric carcinomas in persons infected with *H. pylori* is significantly higher when compared to that in uninfected persons, and *H. pylori* also appears to represent a risk factor for multiple carcinomas. However, in the present study, the incidence of *H. pylori* infection tended to be higher for solitary carcinomas than for multiple carcinomas, but no significant differences were identified and *H. pylori* infection was not shown as a risk factor for multiple carcinomas.

Heterotopic glandular cysts is a condition in which a non-neoplastic proper gastric gland proliferates ectopically in the submucosal layer, with an acquired ectopic gland developing during the regeneration process of erosion and ulcer. Yasuda et al. [31] reported that the

incidence of gastric carcinomas, particularly multiple gastric carcinomas, was high in stomachs with multiple heterotopic glandular cysts. In the present study, univariate analysis showed heterotopic glandular cysts as a significant risk factor for multiple gastric carcinomas, but multivariate analysis did not identify heterotopic glandular cysts as an independent risk factor.

Lymphocyte-infiltrating carcinomas are seen in various organs and, in the gastrointestinal tract, the number of such reports is highest for gastric carcinoma. Lymphocyte-infiltrating gastric carcinoma is a cancer with better prognosis and lower incidence of lymph node metastasis, and Epstein-Barr virus (EBV) infection in the gastric mucosa is seen in more than 90% of cases. EBV infection in the gastric mucosa has been examined as a risk factor for gastric carcinoma [32–34]. The risk factors for gastric carcinoma are the same risk factors as those for multiple gastric carcinomas, and the incidence of multiple gastric cancers in lymphocyte-infiltrating gastric carcinoma is considered high. In the present study, the incidence of lymphocyte-infiltrating gastric carcinoma in multiple carcinomas tended to be higher than that in solitary carcinomas, but no significant difference existed, and lymphocyte-infiltrating carcinoma was not a risk factor for multiple carcinomas.

It is known that multiple gastric carcinomas more often accompany well- and moderately differentiated carcinoma than poorly differentiated carcinoma. In the present study, univariate analysis showed well- and moderately differentiated carcinoma as a significant risk factor, but multivariate analysis did not reveal well- and moderately differentiated carcinoma as an independent risk factor.

Gastric carcinoma can now be immunohistologically classified into gastric type with mucinous transformation originating from the proper gland and intestinal type with mucinous transformation originating from intestinal metaplasia. Marked differences exist in the biological behaviors of these two types [35]. In the present study, intestinal transformation exhibited a significant correlation to multiple gastric carcinomas, and multivariate analysis also showed intestinal transformation as a significant independent risk factor for multiple gastric carcinomas.

Based on the present study, the risks for multiple gastric carcinomas were classified as high, moderate, and low. The specificity of these new multiple gastric carcinoma risk assessment criteria (where only the high-risk group was considered at risk for multiple gastric carcinomas) was high, and the sensitivity of the multiple gastric carcinoma risk assessment criteria (where moderate- and high-risk groups were considered at risk for multiple gastric carcinomas) was high. While other studies have shown risk factors for multiple gastric carcinomas, the present study is unique in showing risk

assessment criteria based on a combination of risk factors for multiple gastric carcinomas.

Conclusion

Clinicopathological risk factors for multiple gastric carcinomas were extracted to develop risk assessment criteria. Using these criteria, patients at high risk for multiple gastric carcinomas can be identified, and the criteria will be useful for developing surveillance plans following reductive therapy for gastric carcinomas.

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References

- Honmyo U, Misumi A, Murakami, Haga Y, Akai M. Clinicopathological analysis of synchronous multiple gastric carcinoma. *Eur J Surg Oncol* 1989;15:316–21.
- Noguchi Y, Ohta H, Takagi K, Ike H, Takahashi T, Ohashi I, et al. Synchronous multiple early gastric carcinoma. A study of 178 cases. *World J Surg* 1985;9:786–93.
- Mikami T, Takizawa T, Inokari T, Hishima T, Kawamura T, Tei S, et al. Multiple gastric cancer from the pathological viewpoint (in Japanese with English abstract). *I to Cho (Stomach and Intestine)* 1994;29:627–32.
- Tomimatsu H, Baba Y, Kaku S, Shimizu H, Takemoto N, Maruyama M, et al. Multiple early gastric cancer from the standpoint of endoscopic therapy-with analysis of surgically resected multiple early gastric cancer cases (in Japanese with English abstract). *I to Cho (Stomach and Intestine)* 1994;29:667–79.
- Yokoi C, Nakajima T, Gotoda T, Ikehara H, Nishimoto F, Matsuda N, et al. Metachronous gastric cancer after initial EMR/ESD (in Japanese with English abstract). *I to Cho (Stomach and Intestine)* 2005;40:1602–8.
- Nihei Z, Ichikawa W, Ito M, Yamashita T, Uetake H, Osanai T. Local excision for synchronous multiple gastric cancer (in Japanese with English abstract). *Nippon Shoukaki Geka Gakkai Zasshi (Jpn J Gastroenterol Surg)* 1997;30:2107–11.
- Esaki Y, Hirokawa K, Yamashiro M. Multiple gastric cancers in the aged with special reference to intramucosal cancers. *Cancer* 1987;59:560–5.
- Mitsudomi T, Watanabe A, Matsusaka T, Fujinaga Y, Fuchigami T, Iwashita A. A clinicopathological study of synchronous multiple gastric cancer. *Br J Surg.* 1989;76:237–40.
- Kosaka T, Miwa K, Yonemura Y, Urade M, Ishida T, Takegawa S, et al. A clinicopathological study of multiple gastric cancers with special reference to distal gastrectomy. *Cancer* 1990;65:2602–5.
- Isozaki H, Okajima K, Xiang H, Fujii K, Sako S. Multiple early gastric carcinomas. Clinicopathologic features and histogenesis. *Cancer* 1996;78:2078–86.
- Japanese Research Society for Gastric Cancer. The general rules for the gastric cancer study (in Japanese). Tokyo: Kanehara; 1993.
- Sobin LH, Witteking Ch, editors. International Union Against Cancer TNM classification of malignant tumors. 6th ed. New York: Wiley-Liss; 2002.
- Moertel CG, Barga JA, Soul EH. Multiple gastric cancers. *Gastroenterology* 1957;32:1095–103.
- Schlemper R, Riddell R, Kato Y, Borchard F, Cooper H, Dawsey S, et al. The Vienna classification of gastrointestinal epithelial neoplasia. *Gut* 2000;47:251–5.
- Lauren P. Two histological main types of gastric carcinoma: diffuse and so-called intestinal types of carcinoma. *Acta Pathol Microbiol Scand* 1965;64:31–45.
- Jarvi O, Lauren P. On the role of heterotopias of the intestinal epithelium in the pathogenesis of gastric cancer. *Acta Pathol Microbiol Scand* 1951;29:26–43.
- Schlemper R, Itabashi M, Kato Y, Lewin K, Riddell R, Shimoda T, et al. Differences in the diagnostic criteria of gastric carcinoma between Japanese and Western pathologists. *Lancet* 1997;14:1725–9.
- Shiroshita H, Watanabe H, Ajioka Y, Watanabe G, Nishikura K, Kitano S. Re-evaluation of mucin phenotypes of gastric minute well-differentiated-type adenocarcinomas using a series of HGM, MUC5AC, MUC6, M-GGMC, MUC2, and CD10 stains. *Pathol Int* 2004;54:311–21.
- Nakamura K, Sugano H, Takagi K. Carcinoma of the stomach in incipient phase: its histogenesis and histological appearances. *Gann* 1968;59:251–8.
- Nakamura K, Sugano H, Takagi K. Histogenesis of gastric cancer (in Japanese). *Geka Chiryou (Surgical Therapy)* 1970;23:435–48.
- Nakamura K, Sugano H, Takagi K. Structure of the gastric cancer (in Japanese). Tokyo: Igaku-shoin; 1982. p. 236–43.
- Statview (computer program). Version 5.0. Berkeley, CA, USA: Abacus Concepts; 1998.
- SPSS II standard version (computer program). Windows Version; Chicago, IL: SPSS; 2008.
- Arai T, Esaki Y, Inoshita N, Sawabe M, Kasahara I, Kuroiwa K, et al. Pathologic characteristic of gastric cancer in elderly: retrospective study of 994 surgical patients. *Gastric Cancer* 2004;7:154–9.
- Stemmermann GN. Intestinal metaplasia of the stomach: a status report. *Cancer* 1994;74:556–64.
- Morsom BC. Intestinal metaplasia of the gastric mucosa. *Br J Cancer* 1955;9:365–76.
- Correa P. Human gastric carcinogenesis: multi-step and multifactorial process. *Cancer Res* 1992;52:6735–40.
- Kitahara F, Shimazaki R, Sato T, Kojima Y, Morozumi A, Fujino M. Severe atrophic gastritis with *Helicobacter pylori* infection and gastric cancer. *Gastric Cancer* 1998;1:118–24.
- Helicobacter and Cancer Collaborative Group. Gastric cancer and *Helicobacter pylori*: a combined analysis of 12 case control studies nested within prospective cohorts. *Gut* 2001;49:347–53.
- Schistosomes, liver flukes and *Helicobacter pylori*. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, 7–14 June 1994. *IARC Monogr Eval Carcinog Risks Hum* 1994;6:1–241.
- Yasuda T, Kashimura H, Ikegami M. Clinicopathological study of diffuse heterotopic submucosal cysts in the stomach — histogenesis and differentiation evaluated by a classification of mucin phenotype (in Japanese with English abstract). *Jikei Idaishi (Tokyo Jikeikai Medical Journal)* 2001;116:289–98.
- Watanabe H, Enjoji M, Imai T. Gastric carcinoma with lymphoid stroma. Its morphologic characteristics and prognostic correlations. *Cancer* 1976;38:232–43.
- Oda K, Tamaru J, Takenouchi T, Mikata A, Nunomura M, Saitoh N, et al. Association of Epstein-Barr with gastric carcinoma with lymphoid stroma. *Am J Pathol* 1993;143:1063–71.
- Chang M, Lee J, Kim J, Kim H, Lee H, Kim C, et al. Microsatellite instability and Epstein-Barr virus infection in gastric remnant cancers. *Pathol Int* 2000;50:486–92.
- Gum JR Jr. Human mucin glycoproteins: varied structures predict diverse properties and specific functions. *Biochem Soc Trans* 1995;23:795–9.