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☐ Original Article ☐

Clinicopathologic Characteristics of Mucinous Gastric Adenocarcinoma

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Abstract

There has been considerable controversy over the prognosis of mucinous gastric adenocarcinoma (MGC). In this study we analyzed the clinicopathologic differences between MGC and non-mucinous gastric carcinoma (NMGC). In addition, the relationship between mucin content and other clinicopathologic variables, including prognosis in MGC, was also investigated. We reviewed 2118 patients with pathologically-confirmed gastric cancer who underwent gastrectomy at the Department of Surgery, Yonsei University College of Medicine, during the period between Jan. 1987 and Dec. 1993. Among them, 130 patients had gastric carcinoma with extracellular mucin (MGC) and 1988 patients had gastric carcinoma without extracellular mucin (NMGC). We placed the MGC patients into two groups according to mucin content: mucin content involving over 50% of the tumor (dominant type, n=94) and mucin content involving less than 50% of the tumor area (partial type, n=36). The results were as follows: MGC was more common in males than NMGC. The size of the tumor in MGC (mean 5.3 cm) was larger than that of NMGC (mean 4.4 cm). The patients with MGC had a higher incidence of Borrmann type IV (MGC : 16.1%, NMGC : 9.9%), more frequent serosal invasion (MGC : 75.4%, NMGC : 48.6%), lymph-node metastasis (MGC : 75.4%, NMGC : 50.7%), and peritoneal metastasis (MGC : 10.0%, NMGC : 3.5%) than patients with NMGC. The patients with MGC were more advanced in stage at the time of diagnosis and had a worse overall 10-year survival rate (44.9%) than patients with NMGC (54.7%). However, the 10-year survival rate according to the stage of MGC was similar to that of NMGC. There were no significant differences between the mucin content and other pathologic variables, including prognosis, i.e. similar biologic behavior between dominant type MGC and partial type MGC. In conclusion, we suggest that MGC was more frequently diagnosed in advanced stage than NMGC with a poorer prognosis and that it is reasonable to consider the carcinoma with mucin content involving more than 30% of the tumor area as MGC.

Key Words: Mucinous gastric adenocarcinoma, mucin content, clinicopathologic characteristics

INTRODUCTION

Mucinous adenocarcinoma can be found in the gastrointestinal tract, urogenital system, breast and other organs, and yet it differs in clinicopathologic characteristics and prognosis according to its primary site of occurrence. Mucinous adenocarcinomas of the ovary comprise 20% of primary ovarian malignancies but have no significant difference in prognosis from other types.[1] Mucinous adenocarcinoma of the prostate, though fairly rare, is diagnosed in an advanced stage and has a poor prognosis.[2,3] Mucinous carcinoma of the breast, comprising only 1−2% of all breast cancers, infrequently involves axillary lymph nodes and has a better prognosis than other types.[4] Mucinous adenocarcinoma in the colorectum makes up 10−20% of all colorectal cancers and is generally reported to have a worse prognosis than other types, though this is controversial.[5,6]

It has been reported that mucinous gastric adenocarcinomas (MGC) comprise about 5% of all gastric cancers.[7-9] The clinicopathologic characteristics and prognosis of MGC are still controversial and there have been few studies on the relationship between the extent of mucin content and other pathologic variables, including prognosis.

The purpose of this study was to clarify the biologic behavior of MGC, comparing the clinicopathologic characteristics including prognosis with non-mucinous adenocarcinoma (NMGC) and the relationship between mucin content and other pathologic variables in MGC.

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MATERIALS AND METHODS

A total of 2118 patients who underwent gastrectomy with pathologically-confirmed gastric cancer at the Department of Surgery, Yonsei University College of Medicine during the period from Jan. 1987 to Dec. 1993 were reviewed retrospectively. With the last follow-up of Oct. 1998, the median duration of follow-up was 53 months (range from 1 to 140 months) and the follow-up rate was 97.3%. 1988 patients with no mucin content were classified as NMGC and 130 patients with mucin content were classified as MGC. Ninety-four patients with a mucin content of more than 50% were grouped as dominant type (Fig. 1) and 36 patients with that less than 50% but more than 30% as partial type (Fig. 2).

Clinicopathologic variables such as age, sex, location and size of the primary tumor, type of operation, Borrmann type, depth of invasion, number of lymph-node metastases, regional lymph-node metastasis, ratio of metastatic lymph nodes to dissected lymph nodes, presence of peritoneal metastasis, TNM stage based on UICC classification,[10] curability of gastric resection and overall survival rate as well as survival rate according to TNM stage were compared between MGC and NMGC, and also between dominant and partial type of MGC. The potentially-curative resections were defined by the following criteria: 1. The absence of distant metastasis; 2. Histologically-confirmed proximal and distal margin that is greater than 0.5 cm. Any other resections failing to meet these two criteria were regarded as non-curative resections.

Between-group comparisons of clinicopathologic variables were performed using the chi-square test. The Kaplan-Meier method was used for calculating the overall survival rate and the difference between the curves was assessed using the Log rank test. Multivariate analysis using Cox proprotional hazard model was performed to evaluate the independent prognostic value of each covariate. A p value <0.05 was considered statistically significant.

RESULTS

The comparison between MGC and NMGC

The mean (range) age of MGC was 55.2 years (22－82 years) while the mean (range) age of NMGC was 54.1 years (17－85 years). The male to female ratio for MGC was 1.2 : 1 and 2 : 1 for NMGC, with males showing a significantly higher incidence of

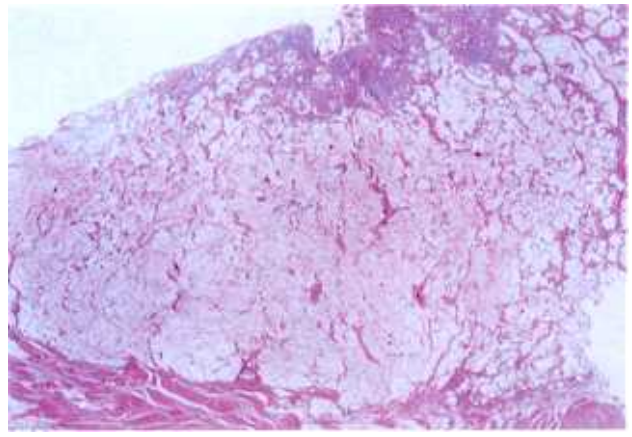

Fig. 1. Dominant type mucinous adenocarcinoma. The figure shows more than 50% of extracellular mucin content of the tumor area.

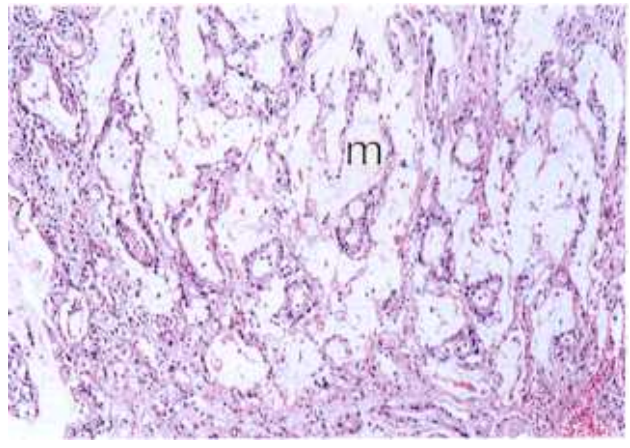

Fig. 2. Partial type mucinous adenocarcinoma. The figure shows less than 50% of extracellular mucin content of the tumor area. m, Extracellular mucin pools.

NMGC (Table 1).

The majority of primary tumors for both types were located in the lower one-third of the stomach and Borrmann type IV was seen in 16.1% of MGC and 9.9% of NMGC with a significant difference. A tumor size greater than 4cm in maximal diameter was found in 71.5% of MGC and 53.6% of NMGC. The mean tumor size was also greater in MGC than in NMGC, being 5.3 cm to 4.4 cm (Table 1).

A depth of invasion greater than T3 was more frequently found in MGC than in NMGC, being 75.4% to 48.6%. Positive regional lymph node metastasis was 75.4% in MGC and 50.7% in NMGC. Also, the number of lymph node metastases and the ratio of metastatic lymph node to dissected lymph node were higher in MGC. Peritoneal metastasis was more frequently observed in MGC (10.5%) than in

Table 1. Comparative Data on MGC and NMGC

Clinicopathologic variables	MGC (%) (n=130)	NMGC (%) (n=1988)	p-value
Age range in years (mean)	22−82 (55.2)	17−85 (54.1)	0.794
Sex (Male/Female)	1.2 : 1	2.0 : 1	0.007
Location			0.628
Upper	12 (9.2)	250 (12.6)	
Middle	46 (35.4)	746 (37.5)	
Lower	66 (50.8)	992 (49.9)	
Operation			0.203
Total	28 (21.5)	529 (26.6)	
Subtotal	102 (78.5)	1459 (73.4)	
Borrmann type			0.002
I	13 (11.0)	70 (5.0)	
II	12 (10.2)	234 (16.9)	
III	74 (62.7)	944 (68.2)	
IV	19 (16.1)	137 (9.9)	
Size range (mean)	5.3	4.4	< 0.001
< 4cm	37 (28.5)	923 (46.4)	
4−7.9cm	74 (56.9)	823 (41.4)	
≥ 8cm	19 (14.6)	242 (12.2)	
Depth of invasion			< 0.001
T1	12 (9.2)	603 (30.3)	
T2	20 (15.4)	419 (21.1)	
T3	87 (66.9)	826 (41.6)	
T4	11 (8.5)	140 (7.0)	
LN metastasis			< 0.001
N0	32 (24.6)	979 (49.3)	
N1	51 (39.2)	492 (24.7)	
N2	36 (27.7)	365 (18.4)	
N3	11 (8.5)	152 (7.6)	
Number of positive LNs			< 0.001
0	30 (23.1)	979 (49.3)	
1−3	38 (29.2)	345 (17.3)	
4−9	32 (24.6)	330 (16.6)	
≥10	30 (23.1)	334 (16.8)	
Positive LNs/Dissected LNs			< 0.001
0%	31 (23.8)	979 (49.3)	
0−30%	74 (56.9)	720 (36.2)	
≥30%	25 (19.2)	289 (14.5)	
Peritoneal metastasis			< 0.001
Negative	117 (90.0)	1918 (96.5)	
Positive	13 (10.0)	70 (3.5)	
Stage			< 0.001
I	20 (15.4)	804 (40.4)	
II	20 (15.4)	348 (17.5)	
III	72 (55.4)	637 (32.1)	
IV	18 (13.8)	199 (10.0)	
Curability			0.067
Potentially Curative	109 (83.8)	1771 (89.1)	
Non-curative	21 (16.2)	217 (10.9)	

MGC, mucinous gastric adenocarcinoma; NMGC, nonmucinous gastric adenocarcinoma.

NMGC (3.5%), but the curability was not different between the two groups (Table 1).

The TNM staging according to UICC classification was 15.4% for stage I and 69.2% for stage III or IV in MGC and 40.4% for stage I and 42.1% for stage III or IV in NMGC (Table 1). The overall 10-year survival rate was significantly lower in MGC, 44.9% compared to 54.7% in NMGC (p=0.012)

Table 2. Survival Rates According to Stage in MGC and NMGC

Stage	MGC		NMGC		p-value
	5-year (%)	10-year (%)	5-year (%)	10-year (%)	
I	89.7	81.6	93.5	85.7	0.565
II	79.5	66.4	76.1	60.2	
III	51.9	43.2	45.1	35.6	
IV	17.1	6.8	12.4	8.6	

MGC, mucinous gastric adenocarcinoma; NMGC, nonmucinous gastric adenocarcinoma.

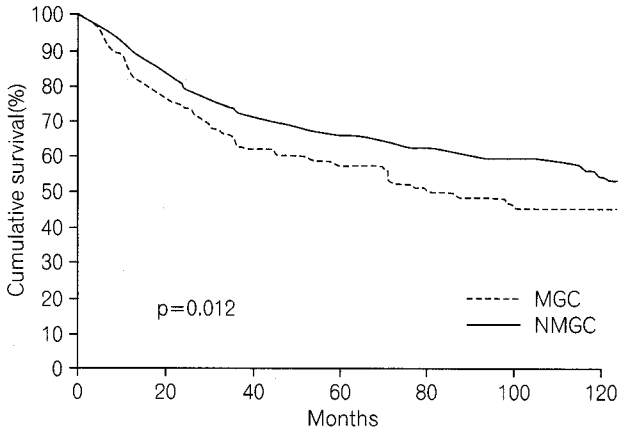

Fig. 3. Survival rate according to histologic type. MGC, mucinous gastric adenocarcinoma; NMGC, nonmucinous gastric adenocarcinoma.

(Fig. 3). However, the 5 and 10-year survival rates according to the stage of each type were not significantly different; stage I-89.7% and 81.6%, II-79.5% and 66.4%, III-51.9% and 43.2%, IV-17.1% and 6.8% for MGC and I-93.7 and 85.7%, II-76.1% and 66.4%, III-45.1% and 35.6%, IV-12.4% and 8.6% for NMGC (p=0.565) (Table 2). And in multivariate analysis histologic type was not an independent prognostic factor (p=0.195) (Table 3).

The comparison according to mucin content

The mean age of the dominant type (mucin content more than 50%) was 55.3 years ranging from 26−77 years and 54.9 years ranging from 22−82 years for the partial type (mucin content less than 50%). The dominant type showed a greater male to female ratio than the partial type, being 1.4 : 1 to 0.8 : 1 (Table 4).

The location of the primary tumor in partial type was located in the upper one-third of the stomach in 20.6% of cases, whereas only 4.5% of the dominant type was located in the upper one-third. Thus, partial

Table 3. Multivariate Analysis of the Prognostic Factors

Prognostic factors	Standard error	Relative risk	p-value
Distant metastasis	0.150	2.19	<0.001
Lymph node metastasis	0.103	2.65	<0.001
Depth of invasion	0.061	1.61	<0.001
Type of resection	0.102	1.56	<0.001
Borrmann type	0.046	1.15	0.003
Location	0.066	0.87	0.029
Size	0.057	1.14	0.022
Curability	0.114	1.91	<0.001
Histologic type	0.134	−	0.195

type required total gastrectomy in more cases (Table 4).

Borrmann type III or IV lesions were observed in over 70% of patients with both dominant and partial type. The size of the tumor was over 4 cm in maximal diameter in over 70% of both tumor types and the depth of invasion greater than T3 was found in 72.4% of dominant type and 83.3% of partial type. Metastasis to the regional lymph node was also fairly high in both tumor types, being 76.6% for dominant type and 72.2% for partial types, while over half the cases in both groups showed metastasis to more than 4 lymph nodes. The curability was not different between the two groups (Table 4).

The TNM staging according to the UICC classification in dominant cases was 15.9% in stage I and 60.2% in stage III and IV. The partial type was 14.7% in stage I and 70.6% in stage III and IV, thus both types showed a fairly advanced stage. The overall 10-year survival rates for both the dominant and partial types were 46.5% and 40.4% respectively, showing no statistical difference (Fig. 4). The predominant pathologic types of partial type carcinoma were 6 cases of well-differentiated adenocarcinoma, 5 cases of moderately- differentiated adenocarcinoma, 19

Table 4. Comparative Data on Dominant MGC and Partial MGC

Clinicopathologic variables	Dominant MGC (%) (n=94)	Partial MGC (%) (n=36)	p-value
Age range in years(mean)	26−77 (55.4)	22−82 (54.8)	0.242
Sex (Male/Female)	1.4 : 1	0.8 : 1	0.149
Location			0.019
Upper	5 (5.3)	7 (19.4)	
Middle	36 (38.3)	16 (44.4)	
Lower	53 (56.4)	13 (36.2)	
Operation			0.012
Total	15 (16.0)	13 (36.1)	
Subtotal	79 (84.0)	23 (63.9)	
Borrmann type			0.168
I	8 (9.5)	5 (14.7)	
II	7 (8.3)	5 (14.7)	
III	58 (69.0)	16 (47.1)	
IV	11 (13.1)	8 (23.5)	
Size range (mean)			0.621
< 4cm	29 (30.9)	8 (22.2)	
4−7.9cm	51 (54.2)	22 (61.1)	
≥ 8cm	14 (14.9)	6 (16.7)	
Depth of invasion			0.614
T1	10 (10.6)	2 (5.6)	
T2	16 (17.0)	4 (11.1)	
T3	60 (63.9)	27 (75.0)	
T4	8 (8.5)	3 (8.3)	
LN metastasis			0.997
N0	22 (23.4)	10 (27.8)	
N1	40 (42.6)	11 (30.6)	
N2	27 (28.7)	9 (25.0)	
N3	5 (5.3)	6 (16.7)	
Number of positive LNs			0.524
0	21 (22.3)	9 (25.0)	
1−3	30 (31.9)	8 (22.2)	
4−9	24 (25.5)	8 (22.2)	
≥ 10	19 (20.2)	11 (30.6)	
Peritoneal metastasis			0.360
negative	86 (91.5)	31 (86.1)	
positive	8 (8.5)	5 (13.9)	
Stage			0.223
I	15 (15.9)	5 (14.7)	
II	15 (15.9)	5 (14.7)	
III	55 (58.6)	17 (45.6)	
IV	9 (9.6)	9 (25.0)	
Curability			0.091
Potentially Curative	82 (87.2)	27 (75.0)	
Non-curative	12 (12.8)	9 (25.0)	

MGC, mucinous gastric adenocarcinoma.

cases of poorly-differentiated adenocarcinoma, and 6 cases of signet-ring-cell carcinoma.

DISCUSSION

MGC is reported as infrequent in incidence, about 3−10% of all gastric carcinomas, and there has been much debate about its clinicopathologic characteristics and prognosis.[7-9] We found that MGC comprised 5.9% of the total cases of gastrectomies performed, and 4.3% according to WHO classification. However, this data only included MGC found after gastrectomy, thus there may be some difference in the over-

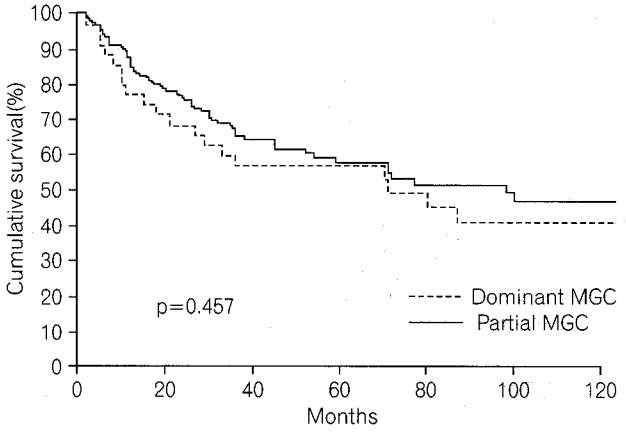

Fig. 4. Survival rate according to mucin content. MGC, mucinous gastric adenocarcinoma.

all incidence of MGC among all gastric carcinoma from this study.

The definition of mucinous adenocarcinoma differs in mucin content and the site of occurrence. Prostatic mucinous adenocarcinoma is defined as when at least 25% of the resected tumor contains lakes of extracellular mucin,[2,3] whereas breast and ovarian mucinous adenocarcinomas are not defined quantitatively but rather as when a substantial amount of extracellular mucin exists.[1,4] Colorectal mucinous adenocarcinoma is defined as when mucin content exceeds 60%.[5,6] The definition of MGC by the WHO international histological classification is "an adenocarcinoma in which a substantial amount of extracellular mucin (more than 50% of the tumor) is retained within the tumor".[11] And the Japanese Research Society for Gastric Cancer defines MGC as "an adenocarcinoma characterized by a substantial amount of mucous lakes due to mucin pooling in the tumor stroma."[12]

The factors affecting the prognosis of gastric cancer are depth of invasion, lymph-node metastasis, distant metastasis, age, location of the primary tumor, gross appearance (Borrmann type) of advanced cancer, and size. The histologic type as a prognostic factor is still controversial.[13-15]

Kim suggested that histology is not a prognostic factor.[14] Borchard also concluded that the WHO histological classification of gastric cancer is not related to its prognosis and that the prognosis of MGC is also unrelated to its biologic and histologic type.[16] And Hoerr et al. found that there is no difference in prognosis between MGC and NMGC when there is no regional lymph-node metastasis.[9] However, Brander et al. suggested that MGC had a more favorable prognosis than other histologic types of gastric adenocarcinoma.[8] Kinosita et al. found no difference in survival rate between histologic types, but also reported that other types of gastric adenocarcinoma showed an improved 5-year survival rate as the years progress, whereas MGC showed little change; 1960's-43.6%, 1970's-47.5%, 1980'-38.2% of 5-year survival rates, respectively.[17] Martin et al. reported that MGC falls 10−30% more in the 5-year survival rate than any other type of gastric adenocarcinoma.[18] Adachi et al. concluded that apart from the fact that MGC showed higher invasion rates than the lymphatics, there was no difference in clinicopathologic characteristics and prognosis.[7]

We found that MGC is different than NMGC in gender, Borrmann type, size, depth of invasion, lymph node metastasis, peritoneal metastasis, TNM stage, and overall survival. MGC showed a greater metastasis rate to the peritoneum and lymph-node, more serosal invasion, and was larger in size with more frequency of Borrmann type III and IV. Therefore, MGC was more frequently diagnosed in advanced stage than NMGC with a poorer survival rate. However, there was no difference in survival rate between the two types of the same stage. And the multivariate analysis also showed that the histologic difference was not an independent prognostic factor. Therefore, rather than the histologic type, the depth of invasion, lymph node and distant metastasis, Borrmann type, location, size and type of resection contribute more to the overall survival. We found that though MGC is more aggressive in biologic behavior than NMGC, the results of surgery are equal. If MGC was considered clinically more malignant, it may be because, rather than the biologic nature of the tumor itself, the lack of early diagnosis leads to a poorer prognosis of MGC.

There are several hypotheses on why MGC is diagnosed at a later stage and they are as follows;

1) MGC is thought to arise initially as a typical adenocarcinoma which then becomes MGC as the tumor progresses. This progression can be regarded as a dedifferentiation process.

2) As the tumor invades the gastric wall, the intraluminal excretion of mucin decreases and an increasing deposition of mucin leads to the intramural accumulation.

3) MGC is located mainly in the submucosal or deeper layer, and this also may be explained by the intramural accumulation of mucin.[7,19,20]

There have been some reports on the rarity of early

MGC: Adachi et al. reported that of 42 cases of MGC, only 1 case was early gastric cancer.[7] Hirota et al. also reported that MGC accounts for only 0.7% of early gastric cancer.[19] We also found that only 1.9% of all early gastric cancer was MGC and that 9.2% of MGC was diagnosed as early gastric cancer.

In cases of colorectal carcinoma, there are differences in clinicopathologic characteristics and prognosis according to its mucin content. Umpleby et al. found that when the mucin content accounts for more than 80% of the tumor, the tumor is more advanced at diagnosis with a poorer prognosis than a tumor retaining 60−80% of mucin content.[6] The clinicopathologic characteristics and prognosis of MGC according to its mucin content is still controversial. It is understood that most gastric adenocarcinomas are composed of more than one histologic type of cancer cells, i.e. pluriform. And although its histologic type is classified according to the predominant histologic cell type, it is possible that its clinicopathologic characteristics may not be determined by the predominant histologic cell type. Those were the points that led us to classify a tumor which retains less than 50% but more than 30% extracellular mucin as MGC. So we compared between tumor types according to their mucin content and also compared dominant type MGC (over 50% of extracellular mucin) with partial type MGC (less than 50% of extracellular mucin).

Paile reported that as was the case with colorectal mucinous carcinomas, an increase in mucin content leads to a poorer prognosis, but he included signet ring cell carcinoma which has intracellular mucin content similar to MGC.[21] Adachi et al. found no difference in clinicopathologic characteristics between tumors with mucin content within 50-80% and those with over 80%.[7] Rather than the mucin content, it was the histologic subtype, whether well or poorly differentiated type of MGC, which contributed to the difference in biologic behavior. Martin et al. reported that the greater the mucin content, the poorer the prognosis and that the production of mucin, regardless of the histologic differentiation, contributed more to the overall survival.[18] However, the above case compared those tumors with over 50% mucin content. In this study, we compared the tumors with less than 50% but more than 30% of extracellular mucin content (partly mucinous adenocarcinoma in the other predominant histologic type, partial type) which could not be defined as MGC by the WHO classification or by the Japanese Research Society for Gastric Cancer with mucin content more than 50% (dominant type). We found a significant difference in location of the primary tumor and type of operation, but no difference in sex, Borrmann type, size, depth of invasion, lymph node metastasis or peritoneal metastasis. In both groups, we found greater size, more serosal invasion, more lymph nodes and peritoneal metastasis, and more Borrmann type III and IV lesions. So the clinicopathologic characteristics of the partial type were similar to MGC rather than NMGC.

Davessar et al. and Kinosita et al. reported that those tumors located in the upper part of the stomach showed a poorer prognosis.[13,17] In this study, we also found that the partial type was located more often in the upper part of the stomach and showed a lower 10-year survival rate (46.5%) than dominant type (40.4%), though statistically insignificant. As well, the prognosis of the partial type was significantly poorer than that of NMGC. Thus we suggest that it is reasonable to consider the carcinoma with mucin content involving less than 50% of tumor area as MGC. We excluded the tumors with less than 30% of extracellular mucin content, so that further study of those tumors is warranted.

In conclusion, 1) MGC was more frequently diagnosed in advanced stage than NMGC with a poorer 10-year survival rate. However, the 10-year survival rate according to the stage of MGC was similar to that of NMGC and histologic type was not an independent prognostic factor. 2) The similar biologic behavior and the prognosis between dominant MGC and partial MGC suggest that it is reasonable to consider the carcinoma with mucin content involving more than 30% of tumor area as MGC.

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