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The Prognosis of Mucinous Gastric Carcinoma

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점액성 위암의 예후

임상우 · 류성엽 · 김형록 · 김동의 · 김영진

Purpose: Mucinous gastric carcinoma (MGC) is a histopathologic subtype of gastric adenocarcinoma with a poor prognosis. It comprises about 3 10% of gastric carcinomas. The purpose of this study was to compare the disease course of MGC with non-MGC (NMGC) and study the clinicopathologic features that influence the prognosis of MGC patients.
Methods: We reviewed the records of 2,383 patients with a confirmed histologic diagnosis of gastric carcinoma who underwent surgery at the Department of Surgery, Chonnam National University Hospital. There were 157 patients with MGC compared to 2,226 with NMGC. Patients were evaluated on the basis of gender, age, tumor size, tumor location, depth of invasion, region and number of lymph nodes with metastasis, hepatic or peritoneal metastasis, stage at presentation, estimate of surgical curability, and TNM stage based on the UICC classification. Multivariate analysis was performed to test the hypothesis that the histologic mucin contents themselves in MGC are an independent prognostic factor.
Results: There was no gender or age-at-diagnosis distinction between these two groups. The mean tumor size of MGC was larger than that of NMGC, but the difference was not statistically significant. Most carcinomas of both types were located in the antrum with no statistical difference in location between MGC and NMGC. However, a depth of invasion greater than T3 was more frequently found in MGC than in NMGC, not to a statistically significant degree. The mean number of lymph node with metastases was 2.78 in MGC and 2.28 in NMGC ($P < 0.001$). There were more MGC patients with TNM stages II through IV(UICC classification). The overall survival rate was lower for the MGC group (46.5%) than for the NMGC group (64.0%). Depth of invasion, lymph node metastasis, and stage at diagnosis were significant factors affecting the outcome. Mucinous histologic type itself was not an independent predictive factor in survival.
Conclusion: The factors that influence the poorer prognosis (lower 5-year survival rate) of MGC are advanced stage at the time of diagnosis, lymph node metastases, and a higher TNM status. The histologic subtype itself was not an independent prognostic factor. **(J Korean Surg Soc 2002;63: 41-45)**

Key Words: Mucinous gastric carcinoma, Multivariate analysis, prognostic factor
중심 단어: 점액성 위암, 다변이 분석, 예후인자

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INTRODUCTION

Mucinous gastric carcinoma (MGC) is a pathological subtype of gastric adenocarcinoma with a poor prognosis. It comprises about 3 10% of all gastric carcinomas. (*1*) Its clinicopathologic characteristics are still controversial. (*1*) Some studies have supported a worse prognosis of a mucin-producing histologic subtype of adenocarcinoma, (*5*) but others have reported an indolent course. (*1,2*)

The purpose of this study was to compare the prognosis of mucinous gastric carcinomas with that of non-mucinous gastric carcinoma (NMGC). We also examined the clinicopathologic features that influence the prognosis of MGC patients.

MATERIALS AND METHODS

We reviewed the records of 2,383 patients who had a diagnosis of gastric carcinoma and were operated on from July 1979 through December 1999 in the Department of Surgery, Chonnam National University Hospital. One hundred and

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fifty-seven (6.6%) patients had a histologic diagnosis of MGC. We classified MGC as an adenocarcinoma characterized by a sustantial number of mucous lakes due to mucin pooling in the tumor stroma, using the definition of Japanese Research Society for Gastric Cancer. (*3*)

The remaining 2,226 patients with a diagnosis of NMGC were compared with the MGC group. Patients were evaluated on the basis of gender, age, tumor size, tumor location, depth of invasion, number of lymph node with metastases, presence of hepatic or peritoneal metastasis, the region of lymph-node metastasis, tumor stage at presentation, estimate of surgical curability, and TNM stage based on the UICC classification. (*4*)

Data were statistically analyzed using the chi-square test. Analysis of survival was performed by the Kaplan-Meier method, and differences between the curves were tested using the two-tailed log rank test. Multivariate analysis was performed using the Cox proportional hazards model in the program SPSS 9.0 program to test hypothesis that the histologic mucin contents itself in MGC is an independent prognostic variable. A P-value$<$0.05 was considered statistically significant.

RESULTS

1. Age and gender

There was no statistical difference in the mean age of patients with MGC (56.2 years) compared to the NMGC group (56.0 years). Of the 157 patients with MGC, 104 (67.0%) were males and 53 (33.0%) were females. There were 1,488 (66.8%) males and 738 (33.1%) females in the group of 2,226 patients with NMGC. There were more males than females in each group, but the gender ratio was the same (Table 1).

2. Tumor size and location

The mean tumor size of MGC (5.4 cm) was lager than that of NMGC (4.5 cm), but the difference was not significant after standardization. Most gastric carcinomas were located in the antrum in both MGC (89 cases; 56.7%) and NMGC patients (1,327 cases; 59.6%), and differences in location were not significant (Table 1).

3. Clinicopathologic features

A depth of invasion greater than T3 was found in stomachs removed from patients with MGC (78.9%) more frequently than in those with NMGC (58.6%). Regional lymph node metastases were found in 65.6% of patients with MGC and in 50.6% with NMGC. The mean number of lymph nodes with metastases was higher in MGC (2.78) than in NMGC (2.28; P$<$0.001). Peritoneal metastases were present in 12.1% of MGC and 11.0% of NMGC cases. Hepatic metastases were found in 3.8% of MGC and 4.2% of NMGC patients.

The TNM staging according to the UICC classification was 14.1% for stage I, 24.2% for stage II, 34.4% for stage III, and

Table 1. Clinicopathologic features of MGC and NMGC

Variables	MGC (%) (n=157)	NMGC (%) (n=2226)	P value
Gender			
Male	104 (67.0)	1488 (66.8)	0.470
Female	53 (33.0)	738 (33.1)	
Age range (yrs)	33 83	31 85	
Mean age (yrs)	56.18	56.00	0.973
Tumor size (mean, cm)	5.37	4.50	0.073
Location			
Upper	205 (9.2)	13 (6.0)	
Middle	615 (27.6)	50 (7.5)	0.720
Lower	1327 (59.6)	89 (6.3)	
Whole	79 (3.5)	5 (6.0)	
Depth of invasion			
T1	10 (6.5)	577 (26.0)	
T2	23 (14.6)	343 (15.4)	$<$0.001
T3	101 (64.3)	1047 (47.0)	
T4	23 (14.6)	259 (11.6)	
LN metastasis			
Nx	5 (3.2)	112 (5.0)	
N0	54 (34.4)	1099 (49.4)	
N1	47 (29.9)	443 (19.9)	0.001
N2	30 (19.1)	378 (17.0)	
N3	21 (13.4)	194 (8.7)	
Stage			
I	22 (14.1)	768 (34.5)	
II	38 (24.2)	406 (18.2)	
IIIa	38 (24.2)	304 (13.7)	$<$0.001
IIIb	16 (10.2)	203 (9.2)	
IV	43 (27.3)	532 (23.9)	
Peritoneal metastasis			
Negative	138 (87.9)	1980 (88.9)	0.917
Positive	19 (12.1)	246 (11.1)	
Hepatic metastasis			
Negative	151 (96.2)	2132 (95.8)	0.618
Positive	6 (3.8)	94 (4.2)	
Curability			
Potentially curative	121 (77.0)	1784 (80.1)	0.049
Non-curative	36 (23.0)	442 (19.9)	

27.4% for stage IV in MGC and 34.5% for stage I, 18.2% for stage II, 22.8% for stage III, and 23.9% for stage IV in NMGC. Estimate of curability with operation for MGC and NMGC was 77.1% and 80.1% respectively - a statistically insignificant difference (Table 1).

4. Outcome

The overall survival rate was lower for the MGC group (46.5%) than for the NMGC group (64.0%) (Fig. 1). The Kaplan-Meier survival curves for the two types of tumors are shown in Fig. 2. The 5-year survival rate was significantly lower for MGC than for NMGC ($P<0.05$). To adjust these curves for the factors that may have influenced survival, we used the Cox proportional hazard model to analyze the following covariates; gender, age, tumor size, location, depth of invasion, lymph node involvement, stage at diagnosis, metastases to other organ and estimated resectability (Table 2). Depth of invasion, lymph node metastasis, and stage at diagnosis were significant factors affecting the outcome. Mucinous histologic type itself was not an independent predictive factor in survival (Fig. 3).

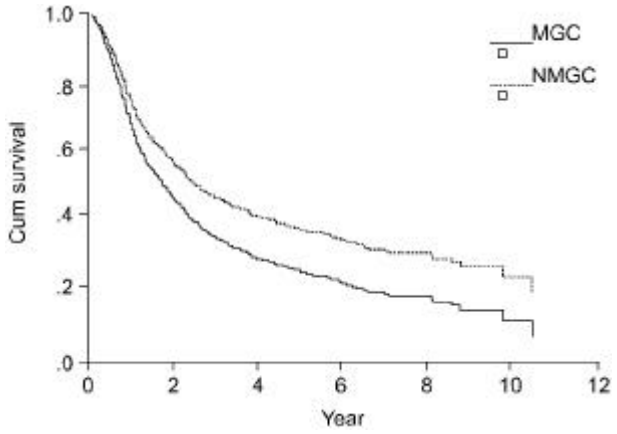

Fig. 1. Survival curves for patients with mucinous gastric carcinoma (MGC) and non-mucinous gastric carcinoma (NMGC). The survival rate for patients with MGC was significantly lower than for those with NMGC.

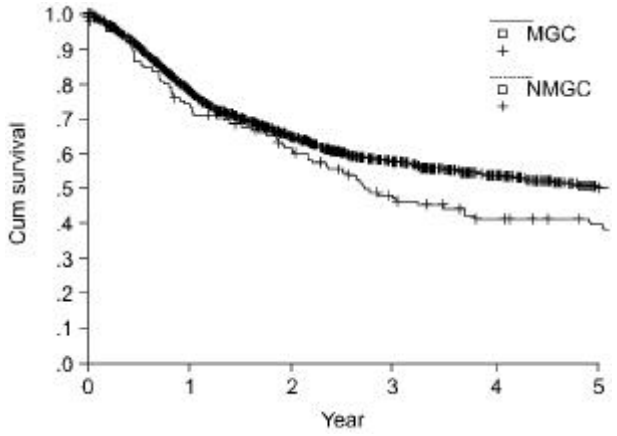

Fig. 2. The Kaplan-Meier survival curves for the MGC and NMGC groups ($P<0.05$).

DISCUSSION

Although gastric carcinoma is an important cause of death, the histologic classification of gastric carcinoma is con-

Table 2. Cox proportional hazard model for the covariates analysis

Variable		Risk ratio	95% CI		P
T factor					
	T1	1.6839	0.7588	3.7515	.0000
	T2	4.3098	2.1423	8.6703	.202
	T3	9.4053	4.8062	18.4052	.0000
	T4	25.2695	12.6490	50.4821	.0000
N factor					
	N1	1.5182	1.2282	1.8766	.0001
	N2	2.1082	1.7145	2.5924	.0000
	N3	2.9333	2.2975	3.7450	.0000
Age		1.0034	0.9961	1.0108	.375
Sex		0.9624	0.8208	1.1284	.637
Mucinous histology		0.9482	0.7367	1.2205	.679

CI = confidence interval.

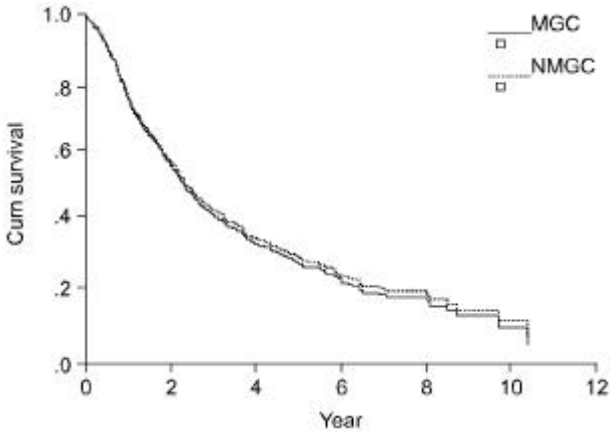

Fig. 3. The survival curves of the MGC and NMGC groups after performing multivariate analysis using the Cox proportional hazards model to determine whether the mucinous-type histology was an independent prognostic factor.

troversial. (*1-6*) The most common systems in use include the World Health Organization, Lauren, and Ming classifications. (*5*) No system is ideal, because tumors are not uniform and mixtures of histologic patterns exist. Mucinous gastric carcinoma is a histopathologic subtype of gastric adenocarcinoma with an incidence of 3 to 10% of stomach cancers and was thought to have a poor prognosis. In 1966, Hoerr et al. (*6*) first reported that a mucin- producing tumor did not necessarily have an adverse outcome if there were no lymph node metastases. The definition of MGC by the WHO international histologic classification is: "an adenocarcinoma in which a substantial amount of extracellular mucin (more than 50% of the tumor) is retained within the tumor". (*2*) The Japanese Research Society for Gastric Cancer (*3*) defines MGC as "an adenocarcinoma characterized by a sustantial amount of mucous lakes due to mucin pooling in the tumor stroma". In our study, using the Japanese Research Society for Gastric Cancer definition, MGC was diagnosed in 6.6% of gastrectomy specimens. This data only included MGC found after gastrectomy, but it is possible that the true incidence would be higher if biopsy and autopsy cases were included.

The factors influencing the prognosis of gastric carcinoma are depth of invasion, lymph node metastasis, distant metastasis, age, location of primary tumors, and gross appearance of advanced cancer (Borrmann type). Histologic type itself as a prognostic factor is still controversial. (*9,10*) We investigated clinicopathologic variables such as age, sex, tumor size, tumor location, depth of invasion, number of lymph node involvement, hepatic or peritoneal metastasis, regional lymph-node metastasis, stage at presentation, estimate of surgical cure, and TNM stage based on the UICC classification.

Adachi et al. (*1*) found that the characteristics of MGC patients who died of a recurrence within 3 years included total gastrectomy, upper location, large size, infiltrative growth, extraserosal invasion, lymph node metastasis, more advanced stage, and a non-curative operation, but no correlation was found between the degree of mucin content and the prognosis. These authors concluded that the 5-year survival rate for curatively treated patients was almost the same in MGC (58%) and NMGC (56%), and that clinicopathologic features, except for lymphatic permeation, were not significantly different in MGC and NMGC patients. Hoerr et al. (*6*) also reported that there is no difference in prognosis between MGC and NMGC groups when there are no regional lymph node metastases, and a mucin-producing tumor did not necessary mean a worse outcome if there were no lymph node metastases. In our study, 54 out of 157 (34.4%) patients had no lymphatic metastasis in the MGC group and 1,099 out of 2,226 (49.4%) patients had no lymph node metastasis in the NMGC group. In our study, there was no significant difference in survival rates of the two groups when there was no lymph node metastasis. Kinosita et al. (*11*) found no significant difference in the 5-year survival rates of patients with different histologic types, but reported that individuals with NMGC had an improved survival rate compared with MGC patients when followed for more years. Wu et al. (*12*) reported that MGC cases had larger tumors, tumors located in the proximal stomach, more serosal invasion, more lymph node involvement, more advanced stages, and worse 5-year survival rates than NMGC cases. They reported that curative surgery, adjuvant chemotherapy, or radiation therapy did not reverse the poorer outcome for MGC patients. Hyung et al. (*8*) reported that MGC had a greater metastasis rate to the peritoneum and lymph nodes, more serosal invasion, larger size, and was more frequently Borrmann type III and IV. In that study, the survival rates for patients with MGC was significantly lower than for those with NMGC ($P<0.05$). In our study, we also found that MGC is more often larger, has more lymph node metastasis, is in a more advanced stage when diagnosed, and has a slightly worse survival rate than NMGC. In our study, however, there was no significant difference between MGC and NMGC groups in the number with peritoneal and hepatic metastasis.

Although MGC behaves more aggressively than NMGC, a similar outcome after surgery was found in some studies. Koufuji et al. (*13*) reported that the incidence of early stage MGC was only 19% of cases compared to 42% in NMGC, and they concluded that more effective radical gastrectomy, and aggressive immunochemotherapy should be selected for stage III MGC to improve the outcome. We also found there was no significant difference in the estimate of surgical curability between the two groups (MGC : NMGC, 77.1% : 80.1%). Hyung et al. (*8*) reported that there was no significant difference in prognosis between a dominant type MGC (mucin content involving over 50% of the tumor) and partial type (mucin content less involving than 50% of the tumor) when the mucin content and other pathologic variables were compared. Caruso (*14*) suggested a histogenetic heterogeneity in MGC because well and poorly differentiated mucinous intramucosal early gastric cancers have a histogenesis similar to that of gastric carcinoma of the intestinal and diffuse type respectively, and he hypothesized that MGC develops during progression of an ordinary adenocarcinoma. Several hypotheses have been proposed to explain why MGC is diagnosed at late stage: first,

MGC is thought to arise initially as a typical adenocarcinoma that becomes mucinous as the tumor progresses; second, as the tumor invades the gastric wall, the intraluminal secretion of mucin decreases and an increasing deposition of mucin leads to the intramural accumulation; third, MGC is located mainly in the submucosal or deep layer, and this also may be explained by the intraluminal accumulation of mucin. (*15,16*) Adachi et al. (*1*) reported that the biologic behavior of MGC is similar to that of NMGC and behavior was determined by the histologic subtype, not by the mucin content, since they found no difference in clinicopathologic characteristics between tumors with a mucin content from 50 to 80% and those with over 80%.

Caruso (*14*) reported that of 168 cases of early gastric cancer, only 18 cases were of the MGC subtype, and in 11 patients the mucinous tumor was found mainly in the submucosal layer of stomach. In this study, 10 of 574 (1.74%) of patients with early gastric carcinoma had a MGC, and 7 of these 10 patients (70%) had submucosal lesions.

In our study, 135 out of 157 (86.0%) patients with MGC had advanced gastric carcinoma. We performed a multivariate analysis and found the worse prognosis with MGC to be related to the depth of invasion and the stage of the tumor, but not to the mucinous histology. Further study of the clinicopathologic characteristics, prognosis and mucin content of MGC is warranted.

CONCLUSION

In conclusion, we confirmed that the factors influencing the lower 5-year survival rate of MGC compared with NMGC are the advanced stage of MGC at time of diagnosis and lymph node metastasis. The histologic type itself was not an independent prognostic factor.

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