

ORIGINAL ARTICLE

점액성 위선암과 비점액성 위선암 및 위반지세포암종의 임상적 비교

안홍근, 정우철, 김연지, 유성열, 임은선

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Clinical Outcomes of Mucinous Gastric Carcinomas Compared with Non-mucinous and Signet Ring Cell Carcinomas

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Background/Aims: This study examined the clinical features and prognosis of patients with mucinous gastric carcinoma (MGC), non-mucinous gastric carcinoma (NMGC), and signet ring cell gastric carcinoma (SRC).

Methods: A retrospective cohort study was performed, enrolling 65 patients with MGC from January 2007 to December 2016. During the same period, 1,814 patients with histologically proven gastric cancers underwent curative or palliative operations. One hundred and ninety-five NMGC patients were selected as the 1:3 age- and sex-matched control groups. In addition, 200 SRC patients were identified. This study evaluated the demographic features of the patients, pathologic features of the tumor, and the predictive factors, such as the recurrence-free survival and overall survival.

Results: The recurrence rates were significantly high in MGC than in NMGC or SRC (both $p < 0.01$). The proportion of early gastric cancer was lower in the MGC group than in the other groups ($p < 0.01$). In addition, metastatic lymph nodes were found more frequently in the MGC group ($p < 0.01$), and the proportion of initial pT4, M1 stage, was highest in the MGC group. The recurrence-free survival and overall survival in the MGC group were significantly lower than those in the NMGC or SRC. Subgroup analysis showed that patients with the same American Joint Committee on Cancer (AJCC) stage of each cancer group showed a similar prognosis.

Conclusions: MGC frequently presents an advanced stage with an unfavorable prognosis compared to NMGC or SRC. On the other hand, MGC of the same AJCC stage had a similar prognosis to NMGC and SRC. (Korean J Gastroenterol 2020;76:297-303)

Key Words: Stomach neoplasms; Mucins; Prognosis

INTRODUCTION

Gastric cancer accounts for 5.7% of all new cases of cancers identified, representing the sixth most common cancer worldwide in 2018.¹ This cancer is responsible for 8.2% of cancer deaths, representing the third most common cause of cancer-related death.¹ Gastric cancer can be divided into

several histologic subtypes, including mucinous gastric cancer (MGC) and signet ring cell carcinoma (SRC). These two subtypes are classified as undifferentiated gastric cancer, accounting for 3.5-3.8%^{2,3} and 10-15% of gastric cancers,^{4,5} respectively.

MGC is defined as gastric adenocarcinoma with a substantial amount of extracellular mucin (>50% of tumor vol-

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ume) within the tumors by the World Health Organization.⁶ MGC is generally believed to be associated with a poor prognosis.^{6,7} Its prognosis is even worse than SRC.^{8,9} To date, there are limited studies on MGC because of its rarity. Previous studies have shown controversial results. Several studies have reported that MGC patients have a poorer prognosis than patients with non-mucinous gastric carcinomas (NMGC).^{2,6,10,11} On the other hand, other studies have suggested no significant prognostic difference between MGC and NMGC.¹²⁻¹⁴ This study examined the clinical features and prognosis of patients with MGC compared to those with NMGC or SRC.

SUBJECTS AND METHODS

1. Subjects

A retrospective cohort study was conducted, enrolling patients aged more than 18 years who underwent gastric cancer surgery at St. Vincent Hospital, The Catholic University of Korea (Suwon, Korea) from January 2007 to December 2016. Patients who did not have histologically confirmed adenocarcinoma were excluded. Patients with insufficient follow-up data were also excluded. The follow-up data were collected until December 2018. One thousand eight hundred and fourteen patients with a histologically proven gastric adenocarcinoma underwent curative or palliative operations. Patients with cancer above T2 stage were treated with neo-adjuvant chemotherapy and adjuvant therapy as appropriate protocols before and after surgery. For stage IV patients, chemotherapy was administered individually after palliative surgery.

There were 65 patients with MGC, 1,549 patients with NMGC, and 200 patients with SRC. Patients in the NMGC group were selected randomly as controls at a 3:1 ratio for the MGC group. The age and sex were matched between MGC and NMGC groups using the match macro program of SAS software for Windows (release 9.2; SAS Institute, Cary, NC, USA). Sixty-five MGC patients and 195 age- and sex-matched NMGC patients at a 1:3 ratio were recruited for this study. The number of SRC patients was relatively small. Thus, matching was not performed (Fig. 1).

2. Methods

The demographic features of patients, pathological features

of the tumor, and predictive factors, such as recurrence and overall survival of MGC, NMGC, and SRC groups were evaluated. The cancer stage was classified by the pathologic stage after surgery, according to the American Joint Committee on Cancer (AJCC) 8th edition.¹⁵ Recurrence was defined as the re-appearance of the tumor in a follow-up examination after resection of the primary tumor. Patients with M1 stage who had palliative surgery were excluded when evaluating the recurrence.

For statistical analysis of the clinicopathologic factors, analysis of variance was performed for the continuous variables while a Fisher's exact test or Pearson's χ^2 test was used for the categorical variables. The baseline characteristics are presented as the frequency (percentage) for the categorical variables or mean±standard deviation for the continuous variables. The recurrence-free survival (RFS) and overall survival (OS) rates were analyzed using the Kaplan-Meier method. A Log-rank test was used for the comparisons between the groups. In multivariate analysis, Cox proportional hazards model was used to identify the prognostic factors. A p-value <0.05 was considered significant. All statistical analyses were performed using SPSS 22.0 software (SPSS Inc., Chicago, IL, USA). The Ethics Committee of the Catholic University approved the study design and procedures (IRB No. VC20RISI0051).

RESULTS

1. Baseline characteristics

The incidence of MGC and SRC was 3.6% (65/1,814) and 11.0% (200/1,814), respectively. Table 1 lists the baseline

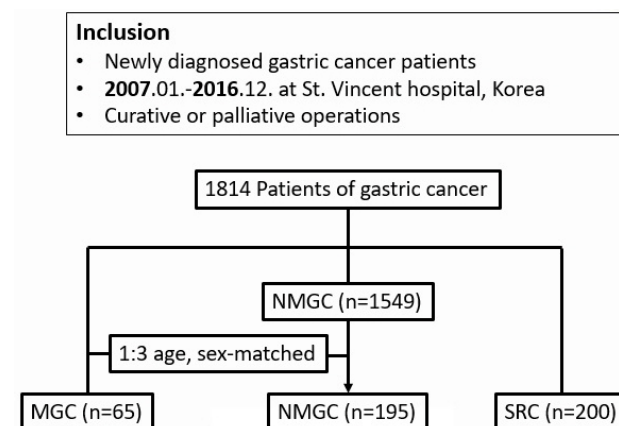


Fig. 1. Flow diagram showing patient selection for this study.

characteristics of each group. The mean age of all patients was 58.4 ± 13.2 years. Males accounted for 70.8% in the MGC group, 70.8% in the NMGC groups, and 50% in the SRC group. The BMI and tumor location did not show significant differences among the three groups. The MGC group had a larger tumor size than the NMGC or the SRC group (5.30 ± 2.56 cm, 4.06 ± 3.13 cm, and 4.32 ± 3.71 cm, $p < 0.01$).

2. Initial prognostic factors and recurrence rate

The proportions of early gastric cancer (EGC), metastatic lymph node, and initial pT4, M1 stage of each group were analyzed. Table 2 lists the results. The proportion of EGC was significantly lower in the MGC group (13.8% in MGC vs. 47.7% in NMGC and 57.5% in SRC, $p < 0.01$). The MGC group showed metastatic lymph nodes more frequently (66.2% in MGC vs.

Table 1. Baseline Characteristics of the Enrolled Patients

Variables	MGC (n=65)	NMGC (n=195)	SRC (n=200)	p-value
Age (years)	60.0 ± 13.4	59.9 ± 13.3	56.5 ± 12.8	0.021
Male	46 (70.8)	138 (70.8)	100 (50)	<0.001
BMI (kg/m^2)	23.1 ± 2.9	23.4 ± 3.1	23.9 ± 3.7	0.119
Tumor size (cm)	5.30 ± 2.56	4.06 ± 3.13	4.32 ± 3.71	0.007
Tumor location				0.117
Upper	4 (6.2)	16 (8.2)	12 (6.0)	
Middle	19 (29.2)	65 (33.3)	88 (44.0)	
Lower	42 (64.6)	111 (56.9)	95 (47.5)	
Whole	0 (0)	3 (1.5)	5 (2.5)	
Depth of invasion				<0.001
T1	9 (13.8)	93 (47.7)	115 (57.5)	
T2	8 (12.3)	20 (10.3)	15 (7.5)	
T3	23 (35.4)	50 (25.6)	17 (8.5)	
T4	25 (38.5)	32 (16.4)	53 (26.5)	
Lymph node metastasis				<0.001
N0	22 (33.8)	116 (59.5)	134 (67.0)	
N1	10 (15.4)	28 (14.4)	12 (6.0)	
N2	14 (21.5)	14 (7.2)	20 (10.0)	
N3	19 (29.2)	37 (19.0)	34 (17.0)	
AJCC Stage				<0.001
I	12 (18.5)	99 (50.8)	120 (60.0)	
II	19 (29.2)	44 (22.6)	27 (13.5)	
III	28 (43.1)	47 (24.1)	42 (21.0)	
IV	6 (9.2)	5 (2.6)	11 (5.5)	

Values are presented as mean \pm standard deviation or n (%).

AJCC, American Joint Committee on Cancer; BMI, body mass index; MGC, mucinous gastric carcinoma; NMGC, non-mucinous gastric carcinoma; SRC, signet ring cell carcinoma.

Table 2. EGC, LN Metastasis, Initial T4, and M1 Stage Proportions and Recurrence

	MGC (n=65)	NMGC (n=195)	SRC (n=200)	p-value
EGC	9 (13.8)	93 (47.7)	115 (57.5)	<0.001
LN metastasis	43 (66.2)	79 (40.5)	66 (33.0)	<0.001
Initial T4	25 (38.5)	32 (16.4)	53 (26.5)	0.001
Initial M1	6 (9.2)	5 (2.6)	11 (5.5)	0.076
Recurrence	22 (37.3)	32 (16.8)	31 (16.5)	0.001

Values are presented as n (%).

EGC, early gastric cancer; MGC, mucinous gastric carcinoma; NMGC, non-mucinous gastric carcinoma; SRC, signet ring cell carcinoma.

40.5% in NMGC and 33.0% in SRC, $p<0.01$). The proportion of the initial pT4, M1 stage was also the highest in the MGC group. The MGC group had a significantly higher recurrence rate than the NMGC and SRC groups (37.3% in MGC vs. 16.8% in NMGC and 16.5% in SRC, $p<0.01$).

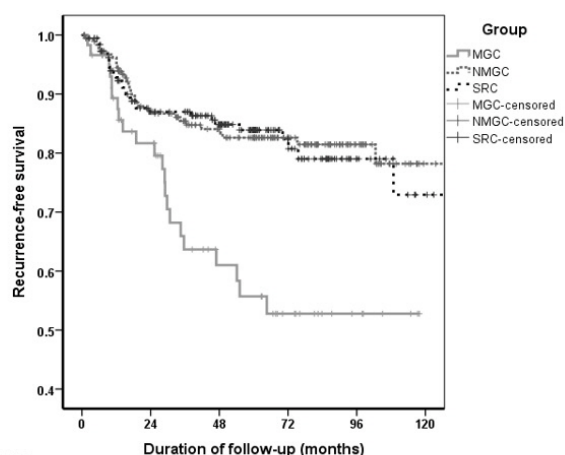


Fig. 2. Kaplan-Meier curves of the recurrence-free survival of MGC, NMGC, and SRC groups. MGC, mucinous gastric carcinoma; NMGC, non-mucinous gastric carcinoma; SRC, signet ring cell carcinoma.

3. Postoperative survival and related factors

The median follow-up duration was 53.8 months (42.4 months in MGC, 61.0 months in NMGC, 50.1 months in SRC). The mean RFS was 75.6 ± 6.8 months for the MGC group, 114.3 ± 3.8 months for the NMGC group, and 117.4 ± 4.3 months for the SRC group ($p<0.01$, log-rank test, Fig. 2). Univariate analysis also showed that MGC was a significant risk factor associated with RFS compared to NMGC or SRC (Table 3). Multivariate analysis showed that the cancer type (MGC, NMGC, SRC) did not have a significant association with RFS. Multivariate Cox regression analysis demonstrated that the tumor size and AJCC stage were independent risk factors for tumor recurrence.

The mean OS was 91.2 ± 7.5 months for the MGC group, 116.8 ± 3.8 months for the NMGC group, and 118.1 ± 4.1 months for the SRC group ($p<0.01$, log-rank test, Fig. 3). Univariate analysis also revealed MGC to be a significant risk factor associated with OS compared to NMGC or SRC (Table 4). On the other hand, cancer type (MGC, NMGC, and SRC) did not show a significant association with OS in multivariate analysis. Multivariate Cox regression analysis showed that the AJCC stage was an independent risk factor for survival.

Subgroup analyses were performed according to the AJCC stage. Stage IV was excluded because of the small number

Table 3. Risk Factors Associated with the Recurrence-free Survival

Variables	Parameter	Univariate analysis		Multivariate analysis	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Age		0.996 (0.979-1.013)	0.640		
Sex	Male	1.000 (reference)			
	Female	1.052 (0.677-1.634)	0.822		
BMI		0.940 (0.877-1.006)	0.075		
Size		1.276 (1.218-1.336)	<0.001	1.095 (1.028-1.167)	0.005
Group	MGC	1.000 (reference)		1.000 (reference)	
	NMGC	0.376 (0.218-0.649)	<0.001	0.763 (0.437-1.332)	0.341
	SRC	0.380 (0.219-0.657)	0.001	0.933 (0.526-1.656)	0.812
AJCC Stage	I	1.000 (reference)		1.000 (reference)	
	II	11.347 (3.792-33.950)	<0.001	9.336 (3.089-28.214)	<0.001
	III	58.654 (21.286-161.621)	<0.001	38.949 (13.499-112.380)	<0.001
Location	Upper	1.000 (reference)		1.000 (reference)	
	Middle	0.474 (0.222-1.012)	0.054	0.451 (0.207-0.982)	0.045
	Lower	0.608 (0.297-1.244)	0.173	0.425 (0.204-0.885)	0.022
	Whole	3.620 (1.107-11.836)	0.033	0.528 (0.149-1.870)	0.322

AJCC, American Joint Committee on Cancer; BMI, body mass index; HR, hazard ratio; CI, confidence interval; MGC, mucinous gastric carcinoma; NMGC, non-mucinous gastric carcinoma; SRC, signet ring cell carcinoma.

of patients. No significant difference in RFS was found among MGC, NMGC, and SRC groups at each stage (Fig. 4). Similarly, there was no significant difference in OS among MGC, NMGC, and SRC groups at each stage (Fig. 5).

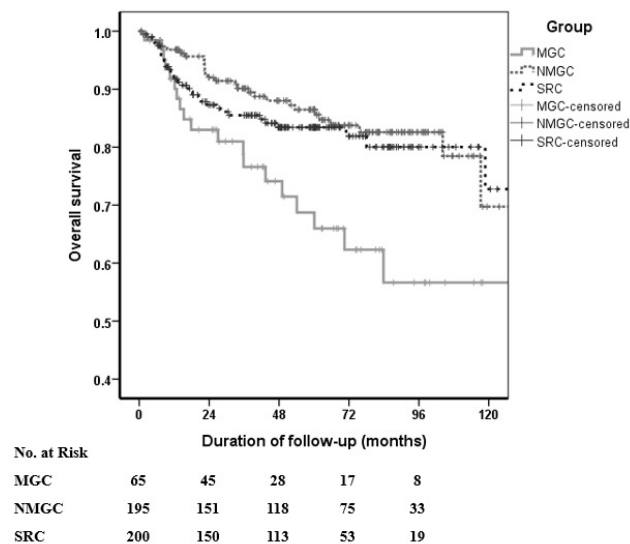


Fig. 3. Kaplan-Meier curves of the overall survival of MGC, NMGC, and SRC groups. MGC, mucinous gastric carcinoma; NMGC, non-mucinous gastric carcinoma; SRC, signet ring cell carcinoma.

DISCUSSION

This study analyzed the clinical features and prognoses of patients with MGC compared to patients with other types of gastric cancer. In the cohort of 1,814 patients with gastric cancer, the incidence of MGC was 3.6%, similar to previous reports.^{2,3,10} The proportion of advanced stage and recurrence rate was higher in the MGC group than in the other pathological types of gastric cancer. In Kaplan-Meier analysis, the MGC group showed significantly shorter RFS and OS than the NMGC or SRC groups. The MGC group showed even lower survival rates than the SRC group, similar to the findings of previous studies.^{8,9} The present study findings showed that MGC patients have a significantly poorer prognosis than patients with other types of gastric cancer.

Multivariate analysis revealed the AJCC stage to be the only independent risk factor for RFS and OS. No significant difference in RFS or OS was observed among the MGC, NMGC, and SRC groups at each stage by subgroup analysis according to the AJCC stage. These findings suggested that the shorter RFS and OS of the MGC group might be due to the more advanced cancer stage at the initial diagnosis.

MGC is often found in a more advanced stage than NMGC,^{7,16,17} which was also found in the present study. MGC

Table 4. Risk Factors Associated with the Overall Survival

Variables	Parameter	Univariate analysis		Multivariate analysis	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Age		1.010 (0.992-1.027)	0.283		
Sex	Male	1.000 (reference)			
	Female	1.201 (0.769-1.874)	0.421		
BMI		0.907 (0.844-0.974)	0.007	0.965 (0.896-1.038)	0.337
Size		1.241 (1.181-1.305)	<0.001	1.034 (0.956-1.120)	0.402
Group	MGC	1.000 (reference)		1.000 (reference)	
	NMGC	0.397 (0.223-0.705)	0.002	0.786 (0.433-1.427)	0.429
	SRC	0.479 (0.275-0.836)	0.010	1.000 (0.551-1.813)	1.000
AJCC Stage	I	1.000 (reference)		1.000 (reference)	
	II	6.009 (2.588-13.953)	<0.001	5.833 (2.511-13.553)	<0.001
	III	19.859 (9.120-43.242)	<0.001	19.106 (8.721-41.856)	<0.001
	IV	113.519 (45.066-285.949)	<0.001	113.945 (45.087-287.963)	<0.001
Location	Upper	1.000 (reference)		1.000 (reference)	
	Middle	0.597 (0.272-1.312)	0.199	0.715 (0.321-1.593)	0.412
	Lower	0.607 (0.284-1.298)	0.198	0.560 (0.257-1.219)	0.144
	Whole	4.809 (1.559-14.832)	0.006	1.999 (0.630-6.346)	0.240

AJCC, American Joint Committee on Cancer; BMI, body mass index; HR, hazard ratio; CI, confidence interval; MGC, mucinous gastric carcinoma; NMGC, non-mucinous gastric carcinoma; SRC, signet ring cell carcinoma.

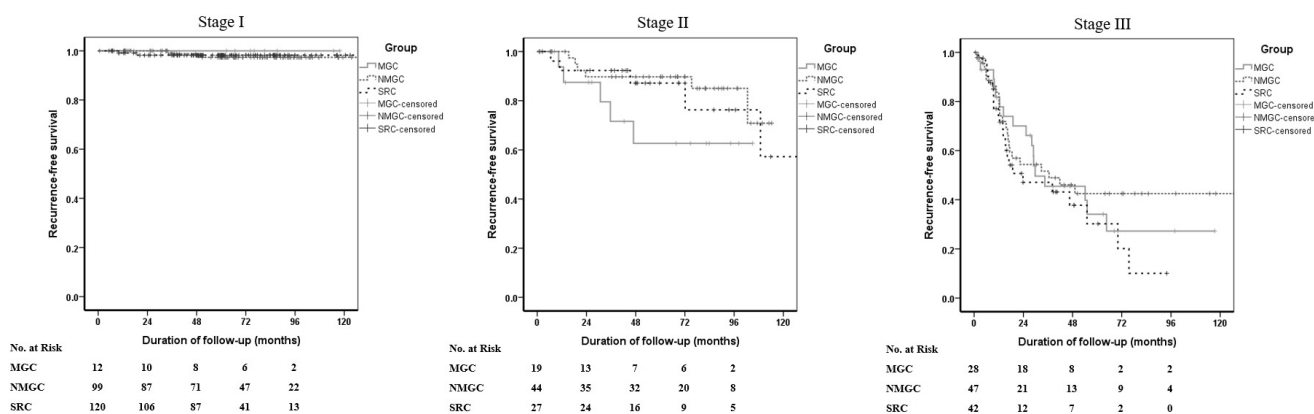


Fig. 4. Kaplan-Meier curves of recurrence-free survival of MGC, NMGC, and SRC groups at each AJCC stage. MGC, mucinous gastric carcinoma; NMGC, non-mucinous gastric carcinoma; SRC, signet ring cell carcinoma; AJCC, American Joint Committee on Cancer.

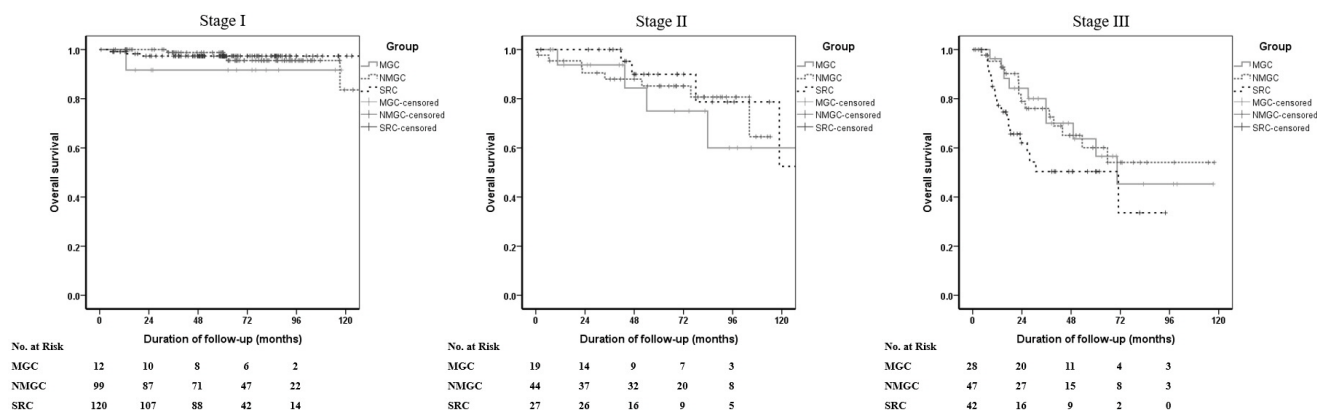


Fig. 5. Kaplan-Meier curves of the overall survival of MGC, NMGC, and SRC groups at each AJCC stage. MGC, mucinous gastric carcinoma; NMGC, non-mucinous gastric carcinoma; SRC, signet ring cell carcinoma; AJCC, American Joint Committee on Cancer.

is found mainly in advanced stages and is believed to be related to the characteristics of MGC. MGC is characterized by abundant extracellular mucin within the tumors. Extracellular mucin is thought to act as a medium to infiltrate the surrounding matrix and help tumor cells penetrate deeper.⁶ In practice, however, it is difficult to diagnose MGC through endoscopy. MGC is characterized by an elevated lesion resembling a sub-mucosal tumor because of abundant mucin pools in the sub-mucosa,¹³ making an endoscopic evaluation of MGC difficult. Endoscopic evaluation of invasion depth is also difficult for MGC. Therefore, pathologically confirmed that AGC could initially be considered as submucosal tumor or EGC by endoscopy.^{18,19}

There are some hypotheses about the mechanism of occurrence of MGC. First, typical gastric adenocarcinoma proceeds to MGC through dedifferentiation. Second, as the tumor invades the gastric wall, mucin could not be excreted into the

lumen, but deposited in the intramural area.^{16,20} The pathogenesis of MGC is also believed to contribute to the diagnosis of MGC in advanced stages.

On the other hand, the SRC group did not show a poorer prognosis than the NMGC group. Recent studies have indicated that the survival rate of SRC is equivalent to or better than that of NMGC in early gastric cancer.^{21,22} In contrast, the prognosis of the SRC group was considered to be unfavorable if the disease was at the advanced stage. In the present study, the proportion of EGC in the SRC group was higher than that in MGC or NMGC. This might have affected the prognosis of patients in the SRC group.

This study had some limitations. First, the present study had a retrospective observational design. Although MGC and NMGC groups were matched for age and sex at a ratio of 1:3, the SRC group was not. Therefore, there were some differences in several of the baseline characteristics. In addition,

patients undergoing curative or palliative operations were included in this study. These heterogeneities might have interfered with the definitive conclusions. Future large-scale prospective studies will be needed to confirm the results of the present study. Studies involving patients who receive other treatment modalities will also be needed in the future.

In conclusion, this study suggests that MGC frequently shows an advanced stage with an unfavorable prognosis compared to NMGC or SRC. On the other hand, patients with MGC, NMGC, and SRC at the same AJCC stage had a similar prognosis. The poor prognosis of MGC was associated mainly with its advanced stage at the initial diagnosis.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394-424.
2. Kunisaki C, Akiyama H, Nomura M, et al. Clinicopathologic characteristics and surgical outcomes of mucinous gastric carcinoma. *Ann Surg Oncol* 2006;13:836-842.
3. Zhang M, Zhu GY, Zhang HF, Gao HY, Han XF, Xue YW. Clinicopathologic characteristics and prognosis of mucinous gastric carcinoma. *J Surg Oncol* 2010;102:64-67.
4. Zhang M, Zhu G, Zhang H, Gao H, Xue Y. Clinicopathologic features of gastric carcinoma with signet ring cell histology. *J Gastrointest Surg* 2010;14:601-606.
5. Kwon KJ, Shim KN, Song EM, et al. Clinicopathological characteristics and prognosis of signet ring cell carcinoma of the stomach. *Gastric Cancer* 2014;17:43-53.
6. Choi JS, Kim MA, Lee HE, Lee HS, Kim WH. Mucinous gastric carcinomas: clinicopathologic and molecular analyses. *Cancer* 2009;115:3581-3590.
7. Jian-Hui C, Shi-Rong C, Hui W, et al. Gastric mucinous cancer histology: clinicopathological characteristics and prognostic value. *Gastroenterol Res Pract* 2016;2016:8947505.
8. Jiang H, Zhang H, Tian L, Zhang X, Xue Y. The difference in clinic-pathological features between signet ring cell carcinoma and gastric mucinous adenocarcinoma. *Tumour Biol* 2013;34:2625-2631.
9. Bu Z, Zheng Z, Li Z, et al. Clinicopathological and prognostic differences between mucinous gastric carcinoma and signet-ring cell carcinoma. *Chin J Cancer Res* 2013;25:32-38.
10. Kawamura H, Kondo Y, Osawa S, et al. A clinicopathologic study of mucinous adenocarcinoma of the stomach. *Gastric Cancer* 2001;4:83-86.
11. Lim SW, Kim DY, Kim YJ, Kim SK. Clinicopathologic features of mucinous gastric carcinoma. *Dig Surg* 2002;19:286-290.
12. Adachi Y, Mori M, Kido A, Shimono R, Maehara Y, Sugimachi K. A clinicopathologic study of mucinous gastric carcinoma. *Cancer* 1992;69:866-871.
13. Yasuda K, Shiraishi N, Inomata M, Shiroshita H, Ishikawa K, Kitano S. Clinicopathologic characteristics of early-stage mucinous gastric carcinoma. *J Clin Gastroenterol* 2004;38:507-511.
14. Ryu SY, Kim HG, Lee JH, Kim DY. Prognosis of early mucinous gastric carcinoma. *Ann Surg Treat Res* 2014;87:5-8.
15. Ajani JA IH, Sano T, Gaspar LE, et al. Stomach. In: Amin MB, Greene FL, Edge SB, et al. ed. *AJCC cancer staging manual*. 8th ed. New York: Springer, 2017:203-220.
16. Isobe T, Hashimoto K, Kizaki J, et al. Characteristics and prognosis of mucinous gastric carcinoma. *Mol Clin Oncol* 2015;3:44-50.
17. Yuan Y, Chen Z, Chen J, et al. Mucinous gastric carcinoma: an update of clinicopathologic features and prognostic value from a retrospective study of clinical series. *Int J Clin Exp Pathol* 2018;11:813-821.
18. Shin SH, Bae JM, Jung H, et al. Clinical significance of the discrepancy between preoperative and postoperative diagnoses in gastric cancer patients. *J Surg Oncol* 2010;101:384-388.
19. Yu BC, Lee WK. Two cases of mucinous adenocarcinoma of the stomach mistaken as submucosal tumor. *J Korean Surg Soc* 2013;84:118-122.
20. Hyung WJ, Noh SH, Shin DW, et al. Clinicopathologic characteristics of mucinous gastric adenocarcinoma. *Yonsei Med J* 1999;40:99-106.
21. Pernot S, Voron T, Perkins G, Lagorce-Pages C, Berger A, Taieb J. Signet-ring cell carcinoma of the stomach: impact on prognosis and specific therapeutic challenge. *World J Gastroenterol* 2015;21:11428-11438.
22. Chon HJ, Hyung WJ, Kim C, et al. Differential prognostic implications of gastric signet ring cell carcinoma: stage adjusted analysis from a single high-volume center in Asia. *Ann Surg* 2017;265:946-953.