Int J Clin Exp Pathol 2017;10(2):2024-2029
www.ijcep.com /ISSN:1936-2625/IJCEP0042923

Original Article

Clinicopathological characteristics and prognosis in patients with mucinous gastric carcinomaafter D2 radical gastrectomy

Lei Cai[1*], Yan Li[2*], Li Sun[1*], Man Guo[1], Xiao Lian[1], Shu-Ao Xiao[1], Jian-Jun Yang[1], Liu Hong[1], Meng-Bin Li[1], Hong-Wei Zhang[1]

[1]Division of Digestive Surgery, Xijing Hospital of Digestive Diseases, Fourth Military Medical University, Xi'an, Shaanxi, China; [2]Department of Anesthesiology, Northwest Women's and Children's Hospital, Xi'an, Shaanxi, China. [*]Equal contributors and co-first authors.

Received October 26, 2016; Accepted December 24, 2016; Epub February 1, 2017; Published February 15, 2017

Abstract: Background: Mucinous gastric carcinoma (MGC) is a special histological type of gastric adenocarcinoma and its clinic-pathologic characters, especially features of molecular markers, and prognosis are still obscure. Thus, we tried to explore the clinic-pathologic characters and prognosis of this special histological type. Method: Between 2008. 09 and 2015. 05, gastric adenocarcinoma patients given D2 radical gastrectomy were enrolled. The clinic and pathologic data, especially tumor and pathology molecular markers, and 5-year overall survival rate was collected and analyzed between MGC and pure gastric adenocarcinoma without mucinous component (PGA). Results: Of 6205 patients, 176 patients were confirmed to be MGC. And MGC was mostly found in Borrmann type III and IV, T4 stage, and positive for dissected lymph nodes. When MGC came to T4 phage, the rate of lymph nodes metastasis was increasing significantly. There were more positive CEA, CA19-9, and less positive AFP, EGFR and HER-2 (>++) in MGC patients compared with PGA. The 5-year survival rate was not different between MGC and PGA when compared with same tumor location, Borrmann type, T stage and lymph nodes metastasis after D2 radical gastrectomy. Multivariate analysis showed T and N stage and positive expression of CEA were the independent prognostic factors. Conclusion: MGC was a rare histologic subtype in gastric adenocarcinoma and diagnosed mostly in an advanced stage, but was not a prognostic significance in patients after D2 radical gastrectomy. The significantly changed tumor and pathologic molecular markers might provide some new strategies for the diagnosis and treatment of MGC.

Keywords: Mucinous gastric carcinoma (MGC), pure gastric adenocarcinoma without mucus ingredient (PGA), D2 radical gastrectomy, clinic-pathologic characters, prognosis

Introduction

Mucinous component was produced in a various organs tract adenocarcinomas included gastric cancer [1, 2]. The mucinous gastric carcinoma (MGC) is a special histologic subtype of gastric adenocarcinoma and defined as a gastric adenocarcinoma with a substantial amount of extracellular mucin (≥50% of tumor volume) within tumors by the World Health Organization (WHO) [3]. Mucinous is a histological type only according to the observation by the microscope, but not by the biological behavior [4]. Although many studies had focused on MGC [2, 5-7], its clinic-pathologic characteristics and prognosis is still controversial, especially based on bulk data.

Thus, in this study, we compared the difference of clinic-pathologic characteristics, especially tumor and pathology molecular markers, and 5-year overall survival rate between MGC patients and pure gastric adenocarcinoma without mucinous component (PGA) patients.

Patients

Candidate patients, who were given D2 radical gastrectomy for gastric adenocarcinoma in Division of Digestive Surgery of Xijing Digestive Hospital from September 2008 to May 2015, were enrolled. All patients were evaluated carefully for the safety of anesthesia and operation. A signed informed consent was obtained from all participants before the sur-

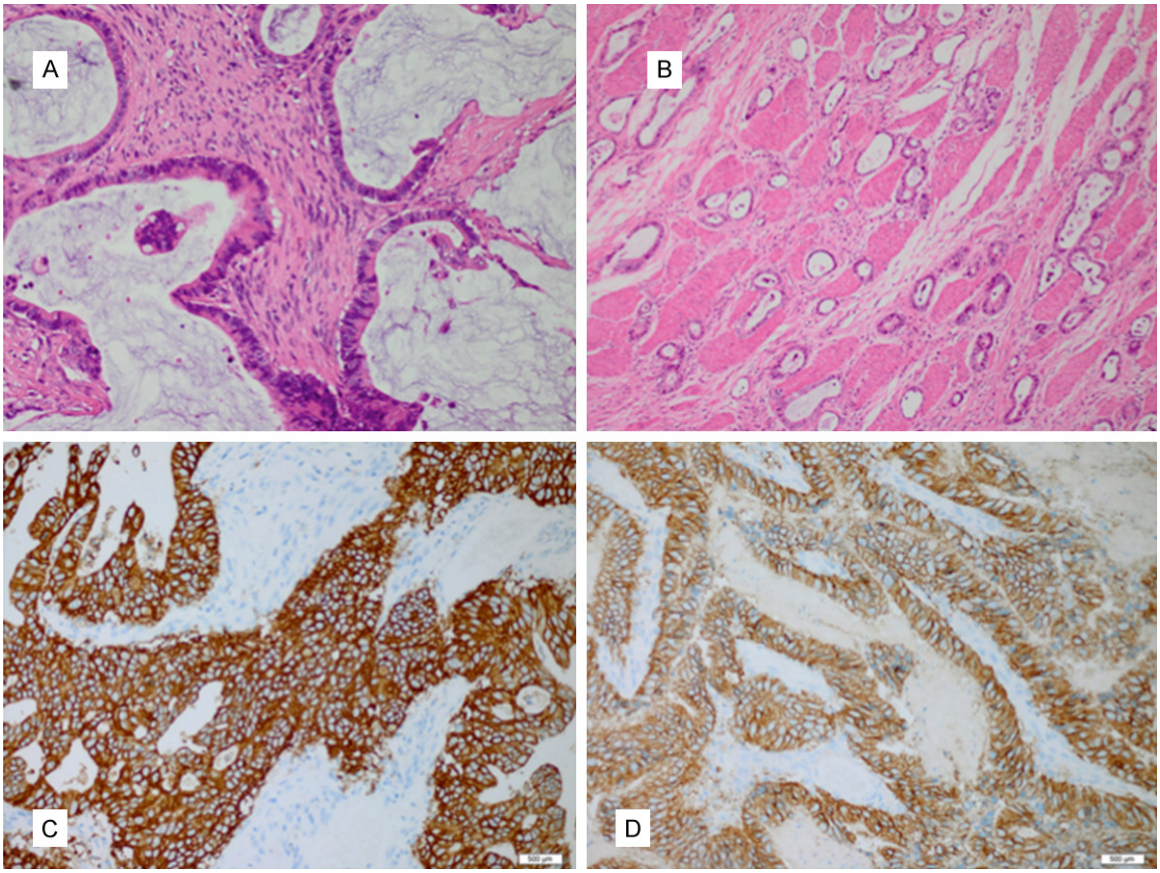

Figure 1. Pathological data of the enrolled MGC and PGA patients. A. Histological features of MGC. B. Histological features of PGA. C. Phenotypes of HER-2 in MGC by Immunohistochemical staining. D. Phenotypes of HER-2 in PGA by immunohistochemical staining. Bar =500 μm.

gery. This study adhered to the guideline established by the Declaration of Helsinki and was approved by the institutional review board.

All patients had undergone curative resection surgery as the standard approach, and pathologic diagnosis was made by at least two experienced trained gastrointestinal pathologists.

Exclusion criteria

Patients with the following items were excluded from the study: 1. Other gastric tumors expect adenocarcinoma confirmed by post-operative histopathology reports; 2. No pre-operative neoadjuvant chemotherapy; 3. Tumor cross two part of stomach; 4. Tumor recurrence; 5. Incomplete follow-up data.

Patients' clinicopathologic characteristics

Histologic types were classified by the pathologists using the World Health Organization (WHO) criteria [8, 9]. Demographics collected for each patient included age, gender, history of drinking and smoking. The tumor-specific information included tumor location, Borrmann type, tumor bio-markers (AFP, CEA, CA-125, CA19-9), depth of gastric wall invasion, lymph nodes metastasis and features of molecular-pathology markers (S-100, EGFR, HER-2) were obtain from surgical records, medical charts and histopathology reports.

Follow-up and statistical analysis

Patients between MGC and PGA were matched based on tumor location, T and N stage and Borrmann type in order to reduce the differences of clinic-pathological characteristics.

The matched-patients were followed up according to our standard protocol (3 months intervals for the first two years, every six months for the subsequent three years and yearly thereafter). Comparisons of the Clinic-pathological features

Table 1. Clinic-pathological features of MGC versus PGA

Variables	MGC N=176	PGA N=2847	*P* value
Age			0.911
<30	2 (1.1%)	32 (1.1%)	
31-40	7 (2.7%)	153 (5.4%)	
41-50	33 (18.8%)	524 (18.4%)	
51-60	66 (37.5%)	913 (32.1%)	
61-70	47 (26.7%)	857 (30.1%)	
71-80	20 (11.4%)	350 (12.3%)	
>80	1 (0.6%)	18 (0.6%)	
Gender			0.821
Male	138 (78.4%)	2244 (78.8%)	
Female	38 (21.6%)	603 (21.2%)	
Location			0.128
Upper	61 (34.7%)	998 (35.1%)	
Middle	25 (14.2%)	513 (18.0%)	
Lower	84 (47.7%)	1295 (45.5%)	
Whole	6 (3.4%)	41 (1.4%)	
Macroscopic type			0.000
Early GC	13 (8.2%)	518 (19.0%)	
Borrmann I	6 (3.8%)	207 (7.6%)	
Borrmann II	32 (20.1%)	686 (25.2%)	
Borrmann III	83 (52.2%)	1070 (39.3%)	
Borrmann IV	25 (15.7%)	240 (8.8%)	
Depth of invasion			0.000
T1	15 (8.5%)	550 (19.1%)	
T2	20 (11.4%)	451 (16.0%)	
T3	55 (31.8%)	1030 (36.2%)	
T4	85 (48.3%)	816 (28.7%)	
Lymph node metastasis			0.000
N0	37 (21.3%)	1057 (37.4%)	
N1	82 (41.7%)	551 (19.5%)	
N2	17 (9.8%)	491 (17.4%)	
N3	38 (21.8%)	727 (25.7%)	
CEA			0.000
Positive	58 (36.3%)	450 (17.6%)	
Negative	102 (63.8%)	2106 (82.4%)	
AFP			0.011
Positive	2 (1.3%)	151 (6.1%)	
Negative	156 (98.7%)	2312 (93.9%)	
CA19-9			0.000
Positive	63 (39.1%)	446 (17.9%)	
Negative	98 (60.9%)	2048 (82.1%)	
CA125			0.328
Positive	10 (6.5%)	116 (4.8%)	
Negative	143 (93.5%)	2212 (95.2%)	
S-100			0.156

and the lymph-node metastasis in T-stages between MGC and PGA were assessed using the chi-squared test for dichotomous and categorical variables.

The overall survival rate was estimated by the Kaplan-Meier methods and values were compared by long-rank test. Covariates that remained significant through univariate analysis were selected for multivariate analysis using the Cox proportional hazard model. All statistical analyses were performed by SPSS software (vision 19.0). *P* values less than 0.05 were considered as statistically significant, and all tests were 2-sided.

Results

Patients' characteristics

A total of 6205 patients with gastric cancer, 3537 adenocarcinoma patients were enrolled and 176 patients were defined as MGC (**Figure 1A**), 2847 patients were pure gastric adenocarcinoma without mucinous component (PGA) (**Figure 1B**) and 514 patients were gastric adenocarcinoma with mucinous component (GAM). The clinic-pathologic features of MGC and PGA patients are listed in **Table 1**. Compared with PGA, MGC occurred more frequencies in Borrmann type III and IV, more T4 stage, and positive for dissected lymph nodes. When MGC came to T4 phage, the rate of lymph nodes metastasis was increasing significantly ($P< 0.05$) (**Table 2**). As for the molecular markers, the positive expression of CEA and CA19-9 in MGC was higher than that of PGA ($P<0.05$), while the positive rate of AFP, EGFR and HER-2 (>++) in MGC was less than that of PGA ($P< 0.05$) (**Figure 1C**, **1D**). And there was no significant differences was obtained in age, gender, blood type, smoking and drinking history, tumor location and CA125 between MGC and PGA ($P>0.05$) (**Table 1**).

Survival analysis

One hundred and fifty one pairs of matched-patients between MGC and PGA were selected and analyzed based on same tumor location, T and N stage and Borrmann type. The follow-up data ranged from 1 to 75 months with an overall rate of visits available for analysis at 98.7%.

The 5-year survival rate for MGC patients had no significant difference compared to PGA (41%

Positive	94 (82.5%)	1585 (76.7%)	
Negative	20 (17.5%)	481 (23.3%)	
EGFR			0.020
Positive	61 (50.8%)	1342 (61.5%)	
Negative	59 (49.2%)	840 (38.5%)	
HER-2			0.000
>++	39 (32.3%)	1109 (50.8%)	
≤++	82 (67.7%)	1075 (49.2%)	

Table 2. Comparison of lymph-node metastasis in T-stages between MGC and PGA

Lymph-node metastasis	MGC (n=176)	PGA (n=2847)	*P* value
T1			0.121
Positive	4 (28.6%)	75 (13%)	
Negative	10 (71.4%)	465 (86.1%)	
T2			0.262
Positive	9 (42.9%)	226 (52.8%)	
Negative	12 (57.1%)	211 (47.2%)	
T3			0.269
Positive	44 (80.0%)	757 (73.7%)	
Negative	11 (20.0%)	270 (26.3%)	
T4			0.021
Positive	80 (95.2%)	705 (86.4%)	
Negative	4 (4.8%)	111 (13.6%)	

vs 61.6%, P=0.185). When 5-year overall survival rates were compared by T stage, no significant differences were found between MGC and PGA (**Figure 2**).

Six factors evaluated in the univariate analysis had a significant influence on the long-term survival. And the multivariate analysis indicated that independent prognostic factors were T stage, lymph node status, and positive expression of CEA, and the histologic type of MGC was not a prognostic factor (**Table 3**).

Discussion

Mucinous gastric carcinoma (MGC) is a rarely histologic subtype of gastric carcinomas [10, 11]. There were already some studies about MGC in recent years [1, 2, 12-14], but controversy still exists on the clinic-pathologic features and prognosis, especially in bulk data.

Clinical-pathological features of MGC were reported included as followed [1-3, 10, 15]: poor prognosis, deeper invasion, lower location, and more lymph node metastasis. Kunisaki [3] reported MGC was not a clinically significant variable in patients treated by curative resection surgery (45 MGC vs 1255 non-MGC). The poor prognosis of MGC was correlated with advanced stage at diagnosis. One hundred and ninety-six MGC patients were compared with 2573 non-MGC patients, which showed MGC was of advanced stage at the time of diagnosis and less curative gastrectomy, but the prognosis of MGC did not have significant difference compared with non-MGC after curative gastrostomy [1]. Zhang (48 MGC vs 1230 non-MGC) revealed 72.9% MGC patients were detected at the higher stage than stage II and more frequently in the lower portion of the stomach (66.7%). The 5-year overall survival rate was significant different (MGC 27.2% vs non-MGC 42.8%, P<0.05); but as for the same stage, the OS between the two groups showed no significant difference. But neither of these studies had clarified whether the group of non-MGC contains the gastric adenocarcinoma patients with mucinous component [4].

So, unlike other researches, our research analyzed 6205 Chinese patients underwent D2 radical gastrectomy including 176 MGC patients, perhaps one of the largest number of tested patients reported, and 2847 pure gastric adenocarcinoma without mucinous component (PGA) and we believed that the research could resulted in some clarification of MGC features.

Our results indicated MGC occurred more frequently in Borrmann type III and IV, more T4 stage, and positive for dissected lymph nodes. In contrast, the age, gender, blood type distribution, smoking and drinking history, tumor location showed no significant difference between MGC and PGA.

Also, the total T and N stage showed significant difference (P<0.05). As for relationship between T and N stage, unlike the stage of T1, T2 and T3, when the tumor came to T4 stage, the positive lymph nodes increased rapidly (MGC 95.2% vs PGA 86.4%, P<0.05), indicated that when breakthrough serosa layer, the MGC might be easier to have lymph nodes metastasis.

Further, we focused on the tumor and pathology molecular markers and had some interest-

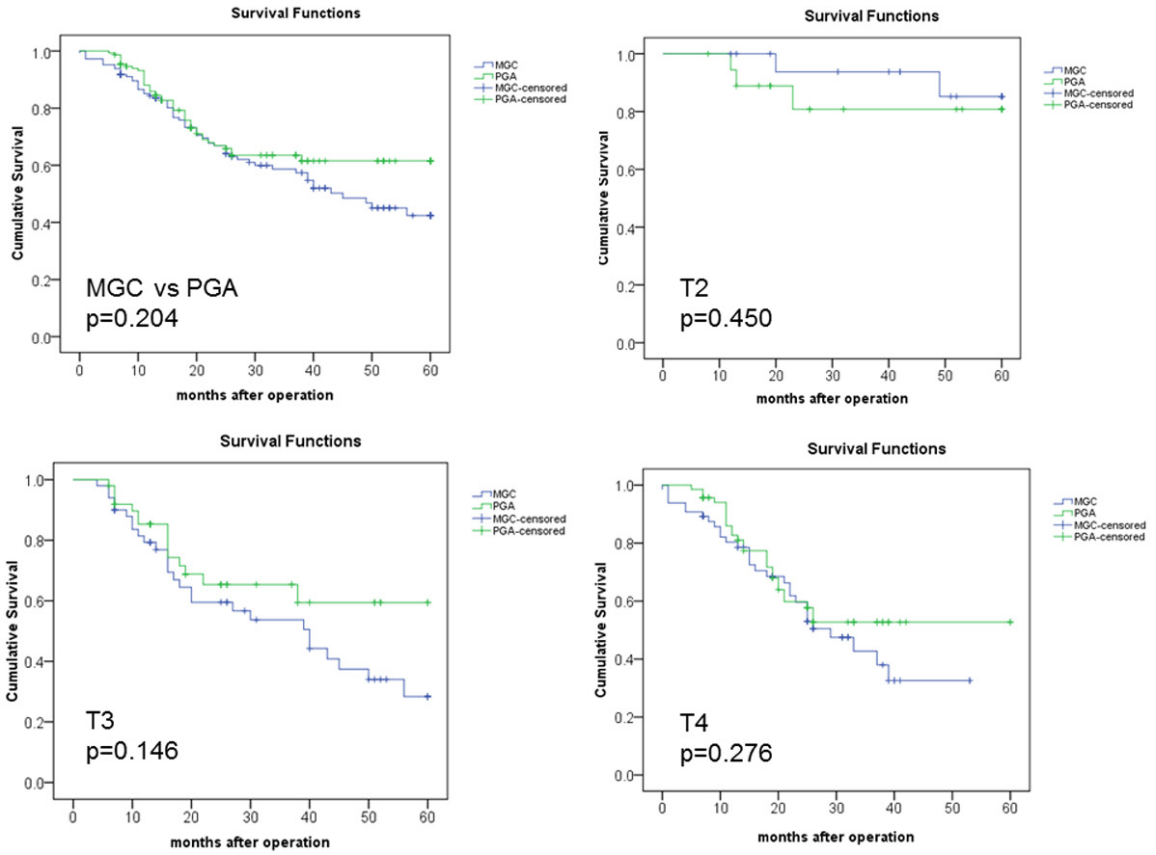

Figure 2. Survival curve for patients of MGC and PGA.

Table 3. Univariateand Multivariate analyses of prognostic factors

Characteristics	β	Hazard ratio (95% CI)	*P* value
Univariate analyses			
Age	0.210	1.234 (1.027-1.482)	0.025
Tumor depth	0.594	1.811 (1.401-2.341)	0.000
Lymph node metastasis	0.682	1.978 (1.865-2.098)	0.000
CEA	0.706	2.025 (1.345-3.050)	0.001
CA19-9	0.503	1.653 (1.105-2.475)	0.015
Multivariate analyses			
Tumor depth	0.476	1.609 (1.208-2.143)	0.001
Lymph node metastasis	0.375	1.455 (1.192-1.776)	0.000
CEA	0.433	1.542 (1.010-2.356)	0.045

ing results. The positive tumor marker CEA (36.3% vs 17.6%), AFP (1.3% vs 6.1%) and CA19-9 (39.1% vs 17.9%) had significant difference between MGC and PGA (P<0.05). The positive rate of molecular pathological markers EGFR and HER-2 (>++) was less in MGC than in PGA. These results might indicate the cellular molecular phenotype of MGC had its own characteristics, which was not clear for now.

It is well known that the 5-year survival rate after D2 radical gastrectomy was influenced by tumor location, Borrmann type, T and N stage. Thus, we compared the outcomes of patients with MGC or PGA in same location, Borrmann type, depth of invasion and lymph node status and the results indicated the 5-year survival rate shows no significant difference between MGC and PGA. Furthermore, the multivariate analysis confirmed the T stage, lymph node metastasis and positive expression of tumor molecular marker CEA were the independent prognostic indicators.

In conclusion, although it is widely accepted we confirmed the MGC had poor prognosis,

we assume the biological characteristics and prognosis of MGC are similar to that of PGA after D2 radical gastrectomy. And the T and N stage, positive expression of CEA are the independent factors for prognosis. Also, the positive molecular markers might provide a potential diagnosis and treatment strategy for MGC, which still need further exploration.

Acknowledgements

This work was supported by Natural Science Foundation of China Grants: No. 81300301, 81572306; Shaanxi Province Social Development Research Foundation of China: No. 2014SF2-14; Xijing Zhu-Tui Project of the Fourth Military Medical University: No. XJZT12Z03.

Disclosure of conflict of interest

None.

Address correspondence to: Hong-Wei Zhang, Division of Digestive Surgery, Xijing Hospital of Digestive Diseases, Fourth Military Medical University, 127 West Changle Road, Xi'an 710032, Shaanxi, China. Tel: 86-29-84771506; Fax: 86-29-82539041; E-mail: zhanghw1531@163.com

References

[1] Yin C, Li D, Sun Z, Zhang T, Xu Y, Wang Z and Xu H. Clinicopathologic features and prognosis analysis of mucinous gastric carcinoma. Med Oncol 2012; 29: 864-870.

[2] Jian-Hui C, Shi-Rong C, Hui W, Jian-Bo X, Kai-Ming W, Si-le C and He YL. Gastric mucinous cancer histology: clinicopathological characteristics and prognostic value. Gastroenterol Res Pract 2016; 2016: 8947505.

[3] Kunisaki C, Akiyama H, Nomura M, Matsuda G, Otsuka Y, Ono HA and Shimada H. Clinicopathologic characteristics and surgical outcomes of mucinous gastric carcinoma. Ann Surg Oncol 2006; 13: 836-842.

[4] Zhang M, Zhu GY, Zhang HF, Gao HY, Han XF and Xue YW. Clinicopathologic characteristics and prognosis of mucinous gastric carcinoma. J Surg Oncol 2010; 102: 64-67.

[5] Choi MG, Sung CO, Noh JH, Kim KM, Sohn TS, Kim S and Bae JM. Mucinous gastric cancer presents with more advanced tumor stage and weaker beta-catenin expression than nonmucinous cancer. Ann Surg Oncol 2010; 17: 3053-3058.

[6] Caruso RA. The histogenesis of mucinous adenocarcinoma of the stomach from observations in early gastric cancer. Ann Diagn Pathol 1999; 3: 160-164.

[7] Fang WL, Wu CW, Lo SS, Chen JH, Hsieh MC, Shen KH, Li AF, Tai LC and Lui WY. Mucin-producing gastric cancer: clinicopathological difference between signet ring cell carcinoma and mucinous carcinoma. Hepatogastroenterology 2009; 56: 1227-1231.

[8] Lin X, Zhao Y, Song WM and Zhang B. Molecular classification and prediction in gastric cancer. Comput Struct Biotechnol J 2015; 13: 448-458.

[9] Boltin D and Niv Y. Mucins in gastric cancer - an update. J Gastrointest Dig Syst 2013; 3: 15519.

[10] Jiang H, Zhang H, Tian L, Zhang X and Xue Y. The difference in clinic-pathological features between signet ring cell carcinoma and gastric mucinous adenocarcinoma. Tumour Biol 2013; 34: 2625-2631.

[11] Zu H, Wang H, Li C and Xue Y. Clinicopathologic characteristics and prognostic value of various histological types in advanced gastric cancer. Int J Clin Exp Pathol 2014; 7: 5692-5700.

[12] Leteurtre E, Zerimech F, Piessen G, Wacrenier A, Leroy X, Copin MC, Mariette C, Aubert JP, Porchet N and Buisine MP. Relationships between mucinous gastric carcinoma, MUC2 expression and survival. World J Gastroenterol 2006; 12: 3324-3331.

[13] Tatematsu M, Iwata H, Ichinose M, Kakei N, Tsukada S, Miki K, Imai S and Imaida K. Markers of surface mucous cell type human gastric cancer cells: galactose oxidase-Schiff reactive mucins, monoclonal antibody SH-9 reactive mucins and cathepsin E. Acta Pathol Jpn 1993; 43: 500-506.

[14] Uesugi H and Atari E. [Establishment and pathological study of a new poorly differentiated mucinous gastric cancer cell line]. Nihon Shokakibyo Gakkai Zasshi 1995; 92: 19-25.

[15] Tang X, Zhang J, Che X, Lan Z, Chen Y and Wang C. The clinicopathological features and long-term survival outcomes of mucinous gastric carcinoma: a consecutive series of 244 cases from a single institute. J Gastrointest Surg 2016; 20: 693-699.