

Original Article

Mucinous gastric carcinoma: an update of clinicopathologic features and prognostic value from a retrospective study of clinical series

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Received July 3, 2017; Accepted July 24, 2017; Epub February 1, 2018; Published February 15, 2018

Abstract: Mucinous gastric carcinoma (MGC) is a specific type of gastric carcinoma, but its clinicopathologic characteristics remains obscured. Our study aimed to explore clinical features and prognostic value of MGC. This retrospective study included a total of 996 patients with primary gastric carcinoma from June 1994 to December 2006. Patients with gastric carcinoma were divided into MGC, other poorly differentiated (PD), and well or moderately differentiated groups. In all, 68 (6.8%) of 996 patients had MGC, with 599 (60.2%) cases for PD. Our study found that MGC had older age, more distant and peritoneal metastasis, but less radical gastrectomy than PD. Furthermore, the overall survival rate of MGC declined compared with PD gastric cancer (22.3% vs. 28.8%, $P=0.032$). Younger age (≤ 60 ys), smaller size (≤ 5 cm), Bormann III type, and lymph node metastasis were linked to poorer prognosis of MGC. However, MGC itself was not an independent prognostic factor of gastric carcinoma. In conclusion, MGC was associated with poorer prognosis than other types of gastric carcinoma but was not an independent predictive factor for survival, which called for further lucubration of this distinctive type of gastric carcinoma.

Keywords: Clinical pathology, gastric cancer, mucinous carcinoma, prognosis

Introduction

Despite advances in surgical treatments, gastric carcinoma (GC) remains an important public health burden worldwide. Histologically, human GC can be mainly divided into well differentiated (intestinal) and poorly differentiated (diffuse) types according to the presence or absence of tubular tissues [1, 2]. In brief, the well differentiated carcinomas contain papillary, well-differentiated, and moderately-differentiated subtypes. While, the poorly differentiated carcinomas include mucinous, signet ring cell, poor-differentiated and undifferentiated subtypes. Mucinous gastric carcinoma (MGC) is a specific subtype of poorly differentiated gastric carcinoma [3].

Up to the present, MGC remains a rarely found GC subtype, only making up 2.6-6.6% of all GCs [4-9]. Although the stomach is one of the

most susceptible organs for mucinous carcinoma, other organs, such as colon and breast, are also vulnerable to this specific carcinoma. The incidence of mucinous colorectal cancer is a little higher than that of MGC. This specific subtype accounts for approximately 5.7-11.7% of all colorectal cancer, and often indicates larger size, deeper invasion, and poorer outcomes than other subtypes [10, 11].

Pathologically, MGC was characterized by abundant mucus accumulation in tumor tissues, with nest-like or mass-shape neoplasm in cancer nests [12]. The pathological appearance of MGC was various due to its expansive growth pattern. Generally, more than 50% of tumor areas contained extracellular mucin pools in microscopic view of MGC. Of note, tumor with only intracellular mucin pools or below 50% mucin pools was out of the range of MGC [13]. Moreover, the surrounding areas of MGC were

often encapsulated by collagen fibers and argyrophil fiber contents. Thus, MGC could be considered as poorly differentiated carcinoma.

Due to the low incidence, the clinical characteristics and prognostic value of MGC remain unclear and controversial [14]. Most of relevant studies just investigated its features in comparison with non-MGC [15, 16]. Some found that MGC had poorer prognosis than non-MGC subtype, but others got no significant difference in survival between two histological subtypes [3, 17-19]. In fact, the non-MGC was comprised of well- and poorly-differentiated types in histopathology, with various ratios in reported studies. We herein investigated the clinical manifestation and prognosis of MGC by comparing it with well and moderated differentiated GCs, as well as other poorly differentiated subtypes, respectively. The aim of this study was to further understand the features of this rare subtype.

Material and methods

Population selection

From June 1994 to December 2006, a consecutive series of 1042 patients who had primary gastric carcinoma and underwent palliative or radical gastrectomy at our department, were retrospectively reviewed. In all, 996 patients were enrolled in this study, with 46 patients excluded due to inadequate follow-up. Among the enrolled, 68 (6.8%) patients were confirmed with MGC, 329 (33.0%) cases for well or moderately-differentiated carcinoma (WMD), and 599 (60.2%) cases for poorly-differentiated carcinoma (PD).

Study design

As mentioned above, the study was designed as a retrospective analysis to investigate the features of clinicopathologic variables, such as age, gender, tumor size, tumor location, Borrmann types, invasion depth, lymph node metastasis, distant metastasis, peritoneal metastasis, liver metastasis, TNM stage and the percentage of radical gastrectomy, in various histological types of GC in our faculty. All details were obtained from surgical records, case report forms and histopathology reports. The radical resection was confirmed if no residues or negative margin (R0 dissection) was reported in the postoperative pathological results, otherwise considered as non-radical operation

(R1 or R2 resection). In our unit, the tumor with peritoneal dissemination or hepatic metastasis can be resected radically when their metastasis confirmed with clear borders during the operation. The tumor invasion and lymph node metastasis were categorized according to the 7th edition of UICC/AJCC TNM stage. The tumor invasion, lymph node metastasis, degree of differentiation and histopathological type were assessed by two experienced pathologists. The protocol was approved by the ethics committee of the first affiliated hospital of Sun Yat-sen University.

Follow-up program

The follow-up program included the routine body check, laboratory tests, X-ray, abdominal CT scan/abdominal ultrasound, and endoscopic exam. The latest follow-up date last to December 2011. Generally, patients were followed once every 3 months for the first 2 years, every 4-5 months up to the fifth year and thereafter once every year. All patients were required to follow up at least 5 years or until the death. Specifically, patients who failed to track within the first year of postoperative follow-up or lost contact during the follow-up period should be excluded from this study.

Statistical analysis

All data were expressed as mean \pm SD if no specific statement. Mann-Whitney U-test or Fischer's exact test was performed to compare the difference of individual variables among three groups. All survival data shown in current study were cancer-specific survival, while death with no relationship to GC would be considered as the lost in the follow-up and marked as time of death. Survival curves were conducted using the Kaplan-Meier method, and survival difference was compared using the log-rank test. While the cumulative overall survival was estimated from the date of diagnostic biopsy to the latest follow-up date or the death as the endpoint. In the multivariate analysis, Cox's proportional hazard regression model through forward stepwise manner was used to identify significant factors correlated with the prognosis. Only prognostic factors with statistical significance in the univariate analysis were employed for further multivariate analysis. All statistical analyses were performed, and graphs were constructed by using the SPSS software (Version 16.0, Chicago, IL, USA). *P* value below 0.05 was considered statistically significant.

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Table 1. Characteristics of gastric carcinoma in all registered patients

Variables	MGC (n=68)	PD (n=599)	WMD (n=329)
Age, ys (mean ± SD)	59.2±11.8	54.1±12.9 ^b	60.8±10.8
≤60	34 (50.0%)	382 (63.8%)	148 (45.0%)
>60	34 (50.0%)	217 (36.2%)	181 (55.0%)
Gender, M:F	44:24	381:218	249:80 ^a
Size, cm (mean ± SD)	6.81±3.22	6.31±3.94	5.18±2.73 ^a
≤5	28 (41.2%)	305 (50.9%)	200 (60.8%)
>5	40 (58.8%)	294 (49.1%)	129 (39.2%)
Location ^p			
Upper third	24 (35.3%)	131 (21.9%)	130 (39.5%)
Middle third	7 (10.3%)	145 (24.2%)	45 (13.7%)
Lower third	36 (52.9%)	299 (49.9%)	150 (45.6%)
Whole	1 (1.5%)	24 (4.0%)	4 (1.2%)
Borrmann type ^{a,b}			
I	8 (11.8%)	21 (3.5%)	30 (9.1%)
II	12 (17.6%)	146 (24.4%)	113 (34.3%)
III	41 (60.3%)	326 (54.4%)	162 (49.2%)
IV	7 (10.3%)	106 (17.7%)	24 (7.3%)
Depth of invasion ^a			
T1	2 (2.9%)	59 (9.8%)	60 (18.2%)
T2	7 (10.3%)	47 (7.8%)	47 (14.3%)
T3	33 (48.5%)	331 (55.3%)	155 (47.1%)
T4	26 (38.2%)	162 (27.0%)	67 (20.4%)
Lymph node metastasis ^a			
Positive	55 (80.9%)	161 (26.9%)	208 (63.2%)
Negative	13 (19.1%)	438 (73.1%)	121 (36.8%)
Distant metastasis ^{a,b}			
Positive	25 (36.8%)	137 (22.9%)	56 (17.0%)
Negative	43 (63.2%)	462 (77.1%)	273 (83.0%)
Peritoneal dissemination ^{a,b}			
Positive	20 (29.4%)	104 (17.4%)	42 (12.8%)
Negative	48 (70.6%)	495 (82.6%)	287 (87.2%)
Hepatic metastasis			
Positive	3 (4.4%)	27 (4.5%)	21 (6.4%)
Negative	65 (95.6%)	572 (95.5%)	308 (93.6%)
Stage ^a			
Ia	2 (2.9%)	45 (7.5%)	50 (15.2%)
Ib	4 (5.9%)	42 (7.0%)	33 (10.0%)
II	9 (13.2%)	85 (14.2%)	54 (16.4%)
IIIa	13 (19.1%)	100 (16.7%)	55 (16.7%)
IIIb	11 (16.2%)	138 (23.0%)	61 (18.5%)
IV	29 (42.6%)	189 (31.6%)	76 (23.1%)
Radical Operation ^{a,b}			
Radical	41 (60.3%)	463 (77.3%)	265 (80.5%)
Non-radical	27 (39.7%)	136 (22.7%)	64 (19.5%)

Data are presented as mean ± SD or number (%), if no other is noted.

^aP<0.05 WMD vs. MGC group; ^bP<0.05 PD vs. MGC group.

Results

During the period of follow-up, 996 patients with gastric carcinoma met entry criteria and were included for final analysis. The clinico-pathologic characteristics of enrolled subjects were listed in **Table 1**. As mentioned in the Methods section, all patients were categorized into MGC, PD and WMD groups. There was no statistical difference between MGC and WMD groups in age, with mean age of 59.2 and 60.8 years respectively, as well as the proportion of the elder (>60 ys). However, the average age of MGC patients was significantly older than that of PD patients (P=0.001), as well as the elder age (P=0.034). Moreover, the gender ratios in all groups indicated that the male would be more vulnerable than the female for gastric carcinomas.

The difference of tumor size between MGC and PD groups was not significant (6.81 vs. 6.31 cm, P=0.315), similar to the percentage of large size (>5 cm, P=0.128). However, the average size in WMD group was significantly smaller than that in MGC group (5.18 vs. 6.81 cm, P=0.001), as well as the larger size (P=0.003). In addition, tumor location and Borrmann type were similar to each other group. Of note, the lower third part of stomach was the most susceptible location to any type of GCs, as the same for Borrmann III/IV type.

On basis of stratified analysis, the serous layer is shown to be most frequently intruded layer for any types of GCs, with the percentage of 48.5%, 47.1% and 55.3% for MGC, WMD and PD, respectively. There was no significant difference in depth of invasion among three groups. Specifically, as compared with PD and WMD types, MGC was associated with more III+IV TNM stages (77.9% vs. 71.3% vs. 58.3%, respectively) and positive peritoneal metastasis (29.4% vs. 17.4% vs.

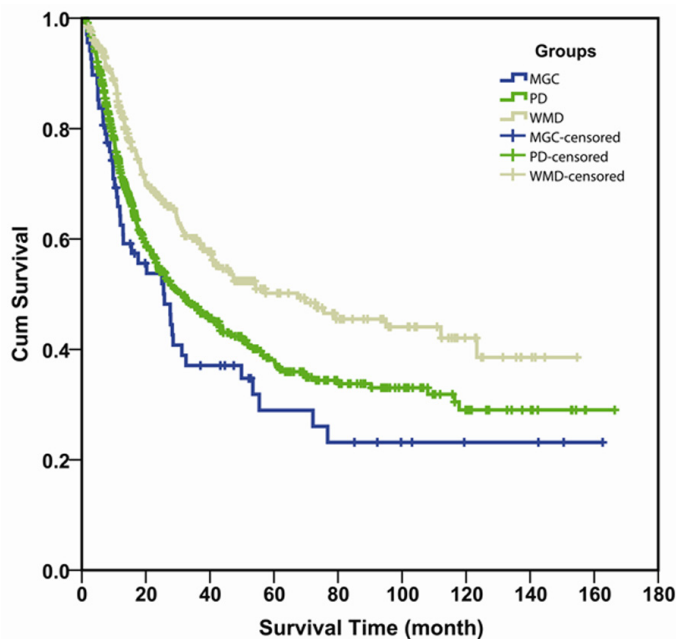


Figure 1. The cumulative survival after tumor resection in all GC groups. The Kaplan-Meier Survival Analysis was performed to compare the difference among the groups. The period of follow-up after tumor resection ranged from 3-167 months. The survival rate for patients with MGC was significantly lower than that for those with PD (P=0.032) or WMD (P<0.001).

Table 2. The survival of patients with gastric carcinoma after a long-term follow-up program

Variable	MGC (n=68)	PD (n=599)	WMD (n=329)	Overall (n=996)
Mean ST, month	54.9±8.6	68.0±3.6 ^a	81.5±4.4 ^b	73.0±2.8
Median ST, month	26.7±5.9	32.7±4.1	67.4±16.4 ^b	37.0±3.7
1-year SR, %	64.3	72.2	83.4 ^b	75.4
3-year SR, %	37.1	47.9 ^a	60.5 ^b	51.3
5-year SR, %	29.4	38.4 ^a	50.9 ^b	41.9

Data for survival time are presented as mean (median) ± SEM. ^aP<0.05 PD vs. MGC group; ^bP<0.05 WMD vs. MGC group. ST: survival time; SR: survival rate.

12.8%). Nevertheless, patients with MGC had less radical gastrectomy rate than other types of GCs. In details, there were 769 patients who underwent radical gastrectomy, with only 47 (6.1%) cases from MGC group.

The comparison of survival outcome between MGC and other GCs

Kaplan-Meier survival curves were used to investigate survival time of patients with MGC and other GCs (Figure 1). The overall survival rate was markedly lower in patients with MGC than that in patients with PD (22.3% vs. 28.8%,

P=0.032), with more details in Table 2. Of note, the overall 5-year survival rate in PD patients was much higher than that in MGC ones (38.4% vs. 29.4%, P=0.040).

To find out the factors that may have impacts on overall survival rate, we compared each group in different clinical variables by stratification analysis. The findings indicated that age (P<0.001), tumor size (P<0.001), Borrmann type (P<0.001) and lymph node metastasis (P<0.001) were significantly correlated with cumulative survival (Figure 2). While, gender, tumor location, depth of invasion, distant metastasis, peritoneal metastasis, liver metastasis, TNM stage, and radical gastrectomy were not correlated with survival outcomes. Specifically, for patients younger than 60 years, both median survival time and survival rate in each follow-up survey were distinctly lower in MGC group compared with PD or WMD group. The similar finding was obtained when tumor size less than 5 cm, Borrmann III type, or positive lymph node metastasis (Table 3).

Cox regression analysis for outcomes

To confirm the factors that may influence outcomes, univariate regression analysis was performed and indicated that age, Borrmann type, histological type, tumor size, depth of invasion, lymph node metastasis, distant metastasis, peritoneal metastasis, liver metastasis, TNM stage, and radical operation were associated with the prognosis of overall survival. The further multivariate Cox's proportional hazard model analysis confirmed that age, tumor size, depth of invasion, lymph node metastasis, distant metastasis, peritoneal metastasis, and radical resection were independent prognostic factors (Table 4). However, the histological type was not an independent prognostic factor (P=0.073).

Discussion

In the present study, we mainly explored the clinical features of mucinous gastric carcinoma

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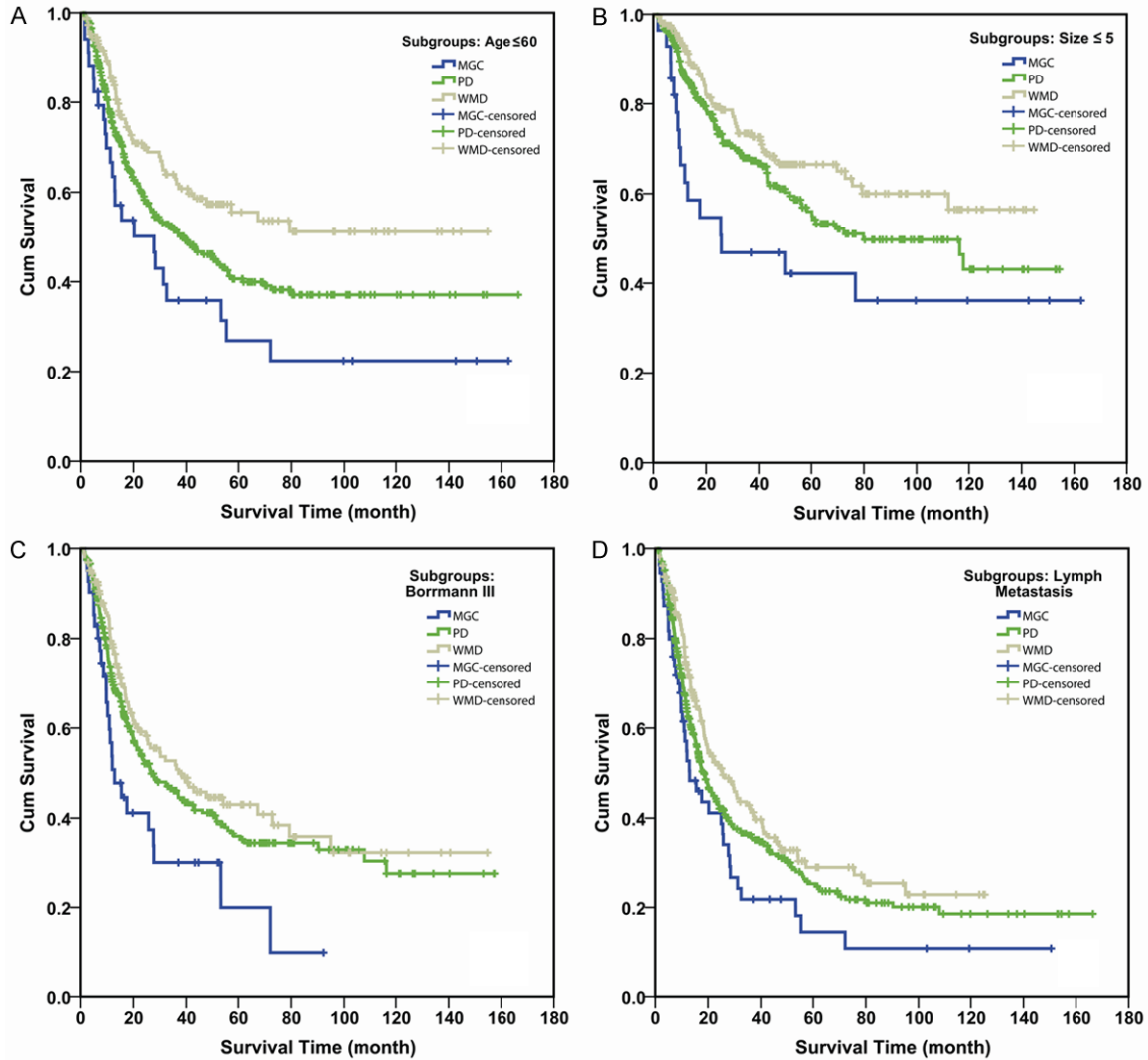


Figure 2. The stratification analysis of survival in different subgroup variables. The Kaplan-Meier Survival Analysis was used to compare the difference among MGC, PD, and WMD groups. The stratification analysis was performed by Age ≤ 60 ys (A), Size ≤ 5 cm (B), Borrmann III (C), and positive Lymph node metastasis (D).

and compared this specific subtype with other histopathological subtypes. Our findings indicated that MGC subtype shared common features with other poorly differentiated types of GC in some fields, such as age, tumor size, tumor location, depth of invasion and Borrmann type. Whereas, MGC was associated with much poorer clinical outcomes than other subtypes. Both the overall survival rate and radical resection rate were markedly lower in MGC than those in other poor-differentiated GCs. Beyond that, as a rarely found subtype, MGC was not an independent prognostic factor for overall survival of GC patients.

Actually, gastric cancer can be classified with various classification systems, such as Lauren

and Ming classification [20, 21]. Some of those systems were popularly used in clinical practice, but with specific controversies unresolved. Davessar et al. [22]. reported that Lauren and Ming classification recommended histological type as an independent prognostic factor, but other studies suggested an opposite result [8, 16]. Our study further evaluated the role of histological classification in predicting the prognosis of GC.

Actually, the prognostic significance of MGC is still controversial and unclear. MGC was first reported to be correlated with poor prognosis when lymph node metastasis complied [23]. In light of secretory and infiltrating abilities, MGC was considered as a risk factor of unfavorable

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Table 3. The outcome of all patients with gastric carcinoma by stratification analysis

Stratification	MGC	PD	WMD
Age ≤60 ys	(N=34)	(N=382)	(N=148)
ST, month	27.7±9.7	39.1±6.45 ^a	91.3±6.6 ^b
1-year SR (%)	66.7	75.2	86.5
3-year SR (%)	35.7	51.6	69.6
5-year SR (%)	26.8	40.7	65.6
Size ≤5 cm	(N=28)	(N=305)	(N=200)
ST, month	25.8±22.0	79.8±19.8 ^a	98.0±13.2 ^b
1-year SR (%)	63.0	85.9	91.2
3-year SR (%)	47.2	68.3	79.0
5-year SR (%)	42.2	56.6	75.0
Borrmann III type	(N=41)	(N=326)	(N=162)
ST, month	12.9±3.0	26.8±4.3 ^a	37.1±8.6 ^b
1-year SR (%)	55.3	70.8	80.2
3-year SR (%)	30.5	46.4	59.8
5-year SR (%)	22.8	36.6	54.9
Lymph Node Metastasis	(N=55)	(N=438)	(N=208)
ST, month	12.9±3.4	18.4±1.6 ^a	25.5±4.1 ^b
1-year SR (%)	55.3	64.2	75.9
3-year SR (%)	22.0	36.5	52.8
5-year SR (%)	14.7	25.6 ^a	46.1 ^b

Survival time are presented as median ± SEM. ^aP<0.05 PD vs. MGC group; ^bP<0.05 WMD vs. MGC group. ST: survival time; SR: survival rate.

Table 4. Multivariate Cox proportional hazard analysis for prognosis of all patients

Factors	RR	CI	P value
Age >60 ys	1.292	1.077-1.550	0.006
Tumor size >5 cm	1.423	1.165-1.739	0.001
Depth of invasion	1.655	1.415-1.937	0.001
Lymph nodes metastasis	1.662	1.427-1.934	<0.001
Distant metastasis	1.748	1.288-2.372	<0.001
Peritoneal metastasis	1.248	1.008-2.017	<0.001
Adjuvant chemotherapy	0.801	0.647-0.990	0.040
Radical resection	2.536	1.868-3.442	<0.001

RR: relative risk; CI: 95% confidential intervals.

outcomes, as compared with Non-MGC [4, 5]. However, some studies have shown no significant differences in clinicopathologic features and prognosis between MGC and Non-MGC [6, 7]. In fact, the previous comparisons put well and poorly differentiated GC into Non-MGC, with lack of consistent ratios (53.2% and 41%) in two studies [4, 7]. That might be the possible reason of different conclusions for assessing the prognostic value of MGC. In current study, the clinicopathologic characteristics and survival factors were compared among MGC, WMD

and PD patients. This specific design would be helpful to evaluate the role of mucinous histological subtype in determining clinical outcomes of GC patients.

Kawamura et al. found that MGC occurred frequently in young patients, but some scholars indicated that the age was not a risk factor. In our study, the average age of MGC patients was 59.2±11.8 years and half of them were over 60 years old, much higher than the PD patients but similar to the WMD patients. Adachi et al. suggested that WMD gastric cancer often occurred in old male patients, with small size in lower third of stomach; while, the PD type often located in the middle third of stomach, with more serosal invasion, lymph nodes metastasis, advanced TNM stage, and peritoneal metastasis [24]. Our results were basically in accordance with Adachi's study, but had worse outcomes for MGC subtype. The survival rate of MGC in overall and subgroups was markedly lower than WMD or PD gastric carcinoma.

In fact, the difference of clinicopathologic characteristics have been compared between MGC and gastric signet ring cell carcinoma, with few articles comparing those features between MGC and other poorly differentiated gastric cancers [9, 25]. Our findings indicated that tumor biological behaviors of MGC were poorer than other PD subtypes, with more elderly patients, more frequently distant and peritoneal metastasis, but lower radical resection rate.

Besides, the lymph node metastatic rate of MGC was similar to other PD subtypes, but higher than WMD type.

According to the 13th edition of Japanese General Rules for Gastric Cancer Study, the main proportion of metastatic lymph node stage in MGC, WMD and PD carcinoma belonged to N1 and N2 stage, with no statistical difference (90.9%, 91.3% and 90.4% respectively). As known to all, lymph node metastasis and radical resection were independent prognostic factors of gastric cancer. Therefore, to improve clinical outcomes, the extensive D2 lymphadenectomy was crucial for patients with MGC.

The pathogenesis of MGC is complicated and remains obscured. Most of MGC patients were diagnosed in the advanced stage, rarely in the early stage [26]. The MGC might originate from common adenocarcinoma, with progressive growth of the tumor [17]. Besides, the submucosa layer was more vulnerable to the early MGC than the mucosa layer (17 vs. 83%, $P < 0.05$). As a result, the possibility of tumor release to extracavity would decline, with increased intracavity invasion accordingly [7].

Our data showed that the five-year survival rate of MGC was 29.4%, much lower than WMD ($P < 0.05$) but similar to PD ($P = 0.324$). Only when patients with age ≤ 60 years, tumor size ≤ 5 cm, Borrmann III type and lymph node metastasis were compared, was the survival rate of MGC significantly lower than that of PD gastric carcinoma [4]. Kawamura et al. found that the 5-year survival rate of MGC was statistically lower than that of non-MGC (64.7% vs. 75.6%), with 45.1% PD gastric carcinoma. In another study, the 5-year survival rate of MGC was also lower than that of non-MGC, but no statistical difference ($P = 0.113$), and PD type occupied by 50.1% [9].

Kunisaka et al. reported that the 5-year survival rate of MGC could reach to 61.7%. However, as compared with their results, the relatively lower 5-year survival rate (29.4%) in our study might be related to the following conditions: larger proportion of advanced stage (78.0% vs. 44.4%), higher rate of lymph nodes metastasis (80.9% vs. 71.1%), and lower rate of radical resection (60.3% vs. 82.2%). The well-developed screening program of gastric cancer in Japan should be attributed to such high incidence of early gastric cancer. In our study, a larger amount of MGC patients were diagnosed in advanced stage, which was in accordance with poorer tumor biological behaviors [27]. Therefore, early detection and treatment of poorly differentiated types of gastric carcinoma seems much more essential for the prognosis.

Actually, the prognostic factors of gastric cancer included peritoneal metastasis, Borrmann classification, liver metastasis, tumor size, tumor location and lymph node metastasis [28-30]. In current study, age, Borrmann type, histological type, tumor diameter, depth of invasion, lymph node metastasis, distant metastasis,

peritoneal metastasis, liver metastasis, TNM stage, radical resection and chemotherapy affected the prognosis. Resembling the results of We et al., age, tumor diameter, depth of invasion, lymph node metastasis, distant metastasis, peritoneal metastasis, chemotherapy and radical dissection were independent prognostic factors of gastric cancer [31]. Of note, although the confidence intervals of multivariate hazard regression for histological type located below one, the statistical significance was not reached. This might be related to the relatively small number of MGC subjects (6.8%) and unbalanced sample distribution between MGC and PD patients (6.8% vs. 60.2%). In addition, the loss of partial patients during follow-up period may be attributed to the lack of significance. Therefore, in the present study, the mucinous histological type cannot be considered as an independent prognostic factor for overall survival of gastric carcinoma.

In summary, all findings suggest the prognosis of MGC was much poorer than that of non-mucinous gastric carcinoma. MGC, as a rare subtype of GC, should be independently considered from other poorly differentiated subtypes. However, mucinous histological type was not an independent predictive factor for overall survival of gastric carcinoma.

Acknowledgements

This work was supported by grants from the National Natural Science Foundation of China (No. 81401307), The Science and Technology Development Project of Guangzhou (201508-020024), The Natural Science Foundation of Guangdong (2014A030313060), The Science and Technology Planning Project of Guangdong (2016A020215044) and The Support Plan For Major Project Cultivation and Emerging Subject Of Sun Yat-sen university (16YKJC13).

Disclosure of conflict of interest

None.

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