Original paper

Clinicopathology and Prognosis of Mucinous Gastric Carcinoma

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Abbreviations: Mucinous gastric carcinoma (MGC), Non-mucinous gastric carcinoma (NGC)

Abstract

Background/Aims: Mucinous gastric carcinoma (MGC) is a rare histopathological type of gastric carcinoma, for which the clinicopathological features and prognosis remain controversial. To clarify the clinical significance of mucinous histological type in gastric cancer, we studied clinicopathological characteristics of MGC tumors and prognosis of patients.

Methodology: Forty-one patients with MGC and 1,407 patients with non-mucinous gastric carcinoma (NGC) were included in the study. Tumors were evaluated against patient gender and age, tumor location, size, and macroscopic type, depth of gastric wall invasion, lymph node metastasis, liver metastasis, peritoneal dissemination, distant metastasis, stage, and operative curability.

Results: Compared with NGC tumors, MGC tumors were larger, showed more serosal invasion, were associated with a higher incidence of lymph node metastasis, and peritoneal dissemination, and tended to be at a more advanced stage. However, multivariate analysis demonstrated that the mucinous histological type was neither an independent prognostic factor nor an independent risk factor for lymph node metastasis in patients with gastric cancer.

Conclusions: The mucinous histological type had no influence on patient outcome or the frequency of lymph node metastasis. MGC tumors are therefore biologically similar to those in NGC.

INTRODUCTION

Mucinous gastric carcinoma (MGC) is a rare histopathological type of gastric tumors, comprising approximately 3-5% of gastric cancers (1-5). Mucinous gastric adenocarcinoma has been associated with a worse prognosis than the non-mucinous type (4), although other studies ruled out the mucinous histological classification as an independent prognostic factor in gastric cancer (1-3). Moreover, several groups have reported a higher frequency of lymph node metastasis with MGC than with non-mucinous gastric carcinoma (NGC) (2-4). To clarify clinical significance of this controversial mucinous histological type of gastric cancer, we studied the clinicopathological features of MGC tumors including predisposition to lymph node metastasis, as well as the prognosis of patients with MGC.

METHODOLOGY

Patients

A total of 1,448 Japanese patients with gastric cancer who underwent gastrectomy in the First Department of Surgery, Nagasaki University Hospital, from 1984 to 2004 were entered into this study. All specimens obtained from the patients were stained by hematoxylin-eosin and examined histopathologically. Informed consent was obtained from all patients. We defined MGC as a tumor in which more than 50% of the tumor area contained extracellular mucin pools, as described previously (2). Forty-one cases (2.8%) were classified as MGC, with the remaining cases classified as NGC. We examined patient gender and age, tumor location, size, and macroscopic type, depth of wall invasion, lymph node metastasis, liver metastasis, peritoneal dissemination, distant metastasis, as well as stage of the disease and operative curability. These clinicopathological findings were analyzed according to the Japanese classification system for gastric carcinoma outlined by the Japanese Gastric Cancer Association (6).

Statistical Analysis

Statistical analysis of the clinicopathological data was evaluated by the χ^2 test and Student's *t*-test. Survival curves were calculated by the Kaplan-Meier method, and statistical differences were evaluated by log-rank tests. Prognostic factors were analyzed using the Cox proportional hazards model. Logistic regression analysis was used for a multivariate analysis of the risk factors for lymph node metastasis. A P value of <0.05 was considered to indicate a statistically significant difference. All statistical analyses were performed on a personal computer using StatView software (StatView, version 5.0J, SAS Institute Inc., NC).

RESULTS

Table 1 lists the clinicopathological data for the 41 patients with MGC and 1,407 patients with NGC. There were no significance differences between MGC and NGC cases with respect to gender, age, tumor location, macroscopic type, metastasis to distant organs (including liver), and operative curability. Depth of wall invasion greater than T3 (tumor penetrates serosa) was found more frequently in MGC tumors than non-mucinous types (66% vs. 27%); one case of tumor invasion of the mucosa and two cases with tumor invasion of the submucosa were identified in T1 MGC. MGC tumors tended to be significantly larger in size than NGC tumors, as well as showing

significantly more peritoneal dissemination, a higher incidence of lymph node metastasis, and appearing at a more advanced stage

The overall survival rate was significantly lower in the MGC group than in those patients with NGC **(Figure 1)**. However, when all patients were stratified according to depth of invasion, lymph node metastasis, and stage, there was no significant difference between the 5-year survival rate of patients with MGC and NGC **(Table 2)**. The Cox proportional hazards model was used to re-evaluate some of the clinicopathological parameters including patient gender and age, tumor location, tumor size, macroscopic and histological type of tumor, depth of gastric wall invasion, lymph node metastasis, and operative curability. Multivariate analysis identified tumor location, tumor size, depth of wall invasion, lymph node metastasis, and operative curability as significant independent prognostic factors in gastric cancer **(Table 3)**. The histological classification of a gastric tumor as mucinous was not an independent prognostic factor for patients with gastric cancer in this study.

To further assess whether the histological type of MGC was a predisposing factor for lymph node metastasis in gastric cancer, we analyzed the following factors by logistical regression: gender, age, tumor location, tumor size, macroscopic type, histological type, and

depth of tissue invasion. Multivariate analysis identified tumor size and depth of tumor invasion as the only significant independent factors associated with lymph node metastasis **(Table 4)**. The mucinous histological type was not related to lymph node metastasis.

DISCUSSION

MGC is a rare histological type constituting approximately 3% of gastric cancers (2-4). The prognosis of patients with MGC remains under discussion, with several studies finding a poorer prognosis for patients with MGC (4, 7-9), while others showing no significant prognostic difference between MGC and NGC cases (2, 10-12). The present study demonstrated a worse overall prognosis for patients with MGC compared with those with NGC; however, multivariate analysis indicated that a mucinous histological classification was not a significant independent prognostic factor. Previous comparisons of MGC with NGC ascribed the following clinicopathological features to MGC: larger tumor size (2-4, 7, 9, 11, 13), higher position in stomach (2, 9), higher incidence of lymph node metastasis (2-4, 8, 9, 11-14), more frequent serosal invasion (2, 3, 8, 9, 12), more extensive peritoneal dissemination (3, 4, 8, 11, 14), and more advanced in stage (2, 3, 9, 11, 12). Our study also demonstrated that the majority of diagnosed MGC cases were at an advanced stage. It is therefore possible that the poorer outcome of MGC patients was not associated with the mucinous histological type, but with the tumor stage at diagnosis. Only 0.4% of early-stage gastric cancers detected in this study were of a mucinous histological type. The reported frequencies of MGC among early-stage gastric cancers range from 0.7% to 9.2% (2, 3, 13, 15, 16), and it remains unclear why MGC is predominantly associated with cancers detected at a more advanced stage compared with other histological-type gastric carcinoma. Some hypotheses have been advocated as follows. MGC is thought to arise initially as a typical adenocarcinoma and then becomes mucinous during tumor progression. As the tumor invades the gastric wall, the intraluminal excretion of mucin decreases, leading to intramural mucin accumulation. MGC is located mainly in the submucosal or deeper gastric layer, and this also may also be explained by the intramural accumulation of mucin (16, 17). We identified only one tumor that showed mucosal invasion and two submucosal tumors in early MGC. This agrees with the findings of

Adachi et al. (13) that mucosal invasion of MGC (17%) was much less frequent than invasion of the submucosa (83%) in early-stage cancers, suggesting that reduced intraluminal excretion of mucin is accompanied by an increasing intraluminal accumulation of mucin during tumor invasion.

Several studies have reported a higher frequency of lymph node metastasis with MGC than with NGC (2-4, 8, 9, 11-14). In particular, a stratified comparison according to depth of tumor invasion showed that lymph node metastasis in MGC was observed more frequently in patients with tumor invasion of at least the submucosal layer (4). Our results also demonstrated that MGC tumors were associated with a higher rate of lymph node metastasis than NGC tumors, but also implicated other clinicopathological factors as predisposing to lymph node metastasis, in addition to depth of tumor invasion. It remains unclear as to the significance of the mucinous histological type as a risk factor for lymph node metastasis in gastric cancer, although our regression analysis found no statistical evidence for such an association. In addition, Adachi et al. (13) reported no difference in the frequency of lymph node metastasis between early-stage MGC and early-stage NGC, further suggesting that a higher incidence of lymph node metastasis in MGC could be related to the extent of tumor invasion and tumor size rather than histological type. Therefore, the mere finding of a mucinous histological type does not present an extra risk factor for lymph node metastasis in gastric carcinoma. This finding has implications for the surgical treatment of patients with MGC regarding the need for extended lymph node dissection.

In conclusion, the histological classification of a gastric carcinoma as mucinous does not in itself have an impact on lymph node metastasis or prognosis in patients with MGC. Although mucinous gastric carcinoma tends to be more advanced in stage at diagnosis, the malignant potential of this tumor type is not different from that of non-mucinous gastric cancers.

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TABLE 1 Clinicopathological Features of Mucinous Gastric Carcinoma and Non-mucinous Gastric Carcinoma

Variable	MGC n=41 (%)	NGC n=1407 (%)	P value
Gender			
Male	24 (59)	954 (68)	NS
Female	17 (41)	453 (32)	
Age			
(mean ± SD) (years)	60.9 ±11.2	63.1±11.6	NS
Tumor location			
Upper	11 (27)	296 (21)	NS
Middle	16 (39)	566 (40)	
Lower	14 (34)	545 (39)	
Tumor size			
(mean ± SD) (mm)	74.2 ± 34.1	50.0 ± 38.0	<0.0001
Macroscopic type			
Elevated	12 (29)	324 (23)	NS
Depressed	29 (71)	1083 (77)	
Depth of invasion			
T1	3 (7)	703 (50)	<0.0001
T2	11 (26)	328 (23)	
T3	22 (54)	256 (18)	
T4	5 (12)	120 (9)	
Lymph node metastasis			
Negative	13 (32)	838 (60)	<0.001
Positive	28 (68)	566 (40)	
Liver metastasis			
Negative	40 (98)	1357 (96)	NS
Positive	1 (2)	50 (4)	
Peritoneal dissemination			
Negative	32 (78)	1278 (91)	<0.05
Positive	9 (22)	129 (9)	
Distant organ metastasis			
Negative	41 (100)	1379 (98)	NS
Positive	0 (0)	28 (2)	
TNM classification			
Stage I	8 (20)	849 (60)	<0.0001
Stage II	10 (24)	174 (12)	
Stage III	16 (39)	226 (16)	
Stage IV	7 (17)	158 (11)	
Operative curability			
Curative	40 (98)	1357 (96)	NS
Noncurative	1 (2)	50 (4)	

MGC; mucinous gastric carcinoma, NGC: non-mucinous gastric carcinoma, NS; not significant, SD; standard deviation

TABLE 2 Five-year Survival Rates of Patients with Mucinous Gastric Carcinoma and Non-mucinous Gastric Carcinoma

Variables	MGC		NGC		P value
	n	5-year survival rate (%)	n	5-year survival rate (%)	
Depth of invasion					
T1, T2	14	79.6	1028	88.9	NS
T3, T4	27	40.2	369	26.2	NS
Lymph node metastasis					
Negative	13	88.9	838	95.6	NS
Positive	28	33.3	566	39.4	NS
TNM classification					
Stage I, II	18	78.5	1023	90.5	NS
Stage III, IV	23	31.5	387	23.5	NS

MGC; mucinous gastric carcinoma, NGC: non-mucinous gastric carcinoma , NS; not significant

TABLE 3 Multivariate Analysis of Prognostic Factors in Patients with Gastric Carcinoma

Variable	Odds ratio (95%CI)*	P value
Gender		
Male	1	
Female	0.90 (0.71-1.14)	0.3772
Age		
<65 years	1	
≥65 years	1.00 (0.80-1.25)	0.9867
Tumor location		
Upper	1	
Middle	0.64 (0.48-0.86)	0.0028
Lower	0.81 (0.62-1.06)	0.1229
Tumor size (10mm)	10.06 (10.03-10.09)	<0.0001
Macroscopic type		
Elevated	1	
Depressed	1.10 (0.83-1.46)	0.5296
Histopathological type		
NGC	1	
MGC	0.97 (0.56-1.67)	0.9052
Depth of invasion		
T1, T2	1	
T3, T4	2.42 (1.83-3.20)	<0.0001
Lymph node metastasis		
Negative	1	
Positive	7.57 (5.01-11.43)	<0.0001
Operative curability		
Curative	1	
Noncurative	4.58 (3.53-5.95)	<0.0001

*CI; confidence interval, MGC; mucinous gastric carcinoma, NGC; non-mucinous gastric carcinoma

TABLE 4 Logistic Regression Analyses for Factors Associated with Lymph Node Metastasis in Gastric Carcinoma

Variable	Odds ratio (95%CI)*	P value
Gender		
Male	1	
Female	0.89 (0.67-1.19)	0.4391
Age		
<65 years	1	
≥65 years	0.93 (0.71-1.23)	0.6191
Tumor location		
Upper	1	
Middle	0.85 (0.59-1.22)	0.3642
Lower	0.99 (0.69-1.43)	0.9582
Tumor size		
<5cm	1	
≥5cm	4.54 (3.35-5.93)	<0.0001
Macroscopic type		
Elevated	1	
Depressed	1.28 (0.91-1.81)	0.1543
Histopathological type		
NGC	1	
MGC	0.93 (0.40-2.14)	0.8562
Depth of invasion		
T1, T2	1	
T3, T4	9.48 (6.75-13.51)	<0.0001

*CI; confidence interval, MGC; mucinous gastric carcinoma, NGC; non-mucinous gastric carcinoma

Figure Legends

FIGURE 1 Overall Survival Curves for 1,448 Patients with Mucinous Gastric Carcinoma and Non-mucinous Gastric Carcinoma