Original Article

The MMP-7-181*A/G* gene polymorphism is a prognostic indicator in patients with gastric cancer

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Background: This study was designed to investigate the prognostic role of the MMP-7-181*A/G* gene polymorphism in patients with gastric cancer and to correlate the genotype with clinicopathological features.

Methods: The polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method was used to detect the MMP-7-181*A/G* gene polymorphism, and prognostic analyses were performed to elucidate the prognostic role of the gene polymorphism.

Results: The MMP-7-181*A/A* genotype was detected in 83.8% (176/210) of cases, *A/G* genotype in 16.2% (34/210) of cases and *G/G* genotype in 0% (0/210) of cases. The MMP-7-181*A/G* polymorphism was closely correlated with lymph node metastasis (P=0.037). *A/G* genotype carriers exhibit lymph node metastasis more frequently than *A/A* genotype carriers. The MMP-7-181*A/G* polymorphism was also strongly correlated with vascular invasion (P=0.003), and *A/G* genotype carriers show an increase in vascular invasion over *A/A* genotype carriers. The 5-year overall survival rates of *A/A* genotype carriers and *A/G* genotype carriers were 59.56% and 33.33%, respectively. The discrepancy was significant (P=0.0164). The prognosis of *A/G* genotype carriers was significantly worse than that of *A/A* genotype carriers. Multivariate survival analysis by Cox regression model confirmed that the MMP-7-181*A/G* genotype was an independent prognostic factor of gastric cancer (HR =2.10; 95% CI: 1.09–4.05; P=0.027).

Conclusions: The MMP-7-181*A/G* genotype was closely correlated with malignant biological behaviors and prognosis of gastric cancer. The MMP-7-181*A/G* genotype may serve as valuable prognostic indicator of gastric cancer.

Keywords: MMP-7; gene polymorphism; gastric cancer; prognosis

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Introduction

Gastric cancer still ranks as one of the most prevalent malignancies worldwide with remarkably high fatality (1). And *Cancer Statistics in China*, 2015 indicated that an estimated 679,100 new gastric cancer cases and 498,000 gastric cancer deaths would occur in China in 2015 (2). The prognosis of gastric cancer is not reliably predicted using current clinicopathological indicators. Molecular markers to optimize the individualized therapy and predict the prognosis of this malignant disease are under extensive investigation. Genetic markers of RFLP (restriction fragment length polymorphism), microsatellite and SNP (single nucleotide polymorphism) comprise three molecular genetics tools for the study of disease. Present researches have showed genetic polymorphisms confer susceptibility both to several types of cancer and to malignant biological features (3,4). The role of these genetic polymorphisms in cancer susceptibility has been most extensively evaluated for isozymes of cytochrome P450 (CYP1A1, CYP2D6, and CYP2E1), N-acetyltransferase (NAT1 and NAT2), glutathione S-transferase (GSTM1, GSTT1, and GSTP1), microsomal epoxide hydrolase, and NAD(P)H:quinone oxidoreductase (5). And early monogenic association studies focusing on candidate genes with strong biological hypothesis have demonstrated an increased risk of cancers associated with polymorphisms in genes involved in cell cycle control, carcinogen metabolism, DNA (deoxyribonucleic acid) repair, apoptosis, inflammation and epigenetic regulation (5,6). Thus, they may have prognostic value.

MMPs regulate multiple biological processes: they can degrade extracellular matrix proteins, are implicated in connective tissue destruction and remodeling associated with cancer invasion and metastasis, contribute to cartilage destruction in arthritis and are involved in atherosclerotic plaque rupture (7-10). Genetic polymorphisms in the promoter of MMP genes have allele-specific effects on transcriptional activities, are associated with susceptibility to multiple cancers and confer aggressive or metastatic biological features. These polymorphisms may serve as markers to predict the susceptibility and prognosis of cancers and have potential to facilitate the diagnosis, therapeutic decisions and prognostication of cancer patients (11-30).

Recent studies found that the MMP-7 promoter region near -181 in the *A/G* polymorphism is functional and closely related to gastric cancer risk, which revealed that this gene polymorphism might serve as a susceptibility marker for gastric cancer. Among the multiple gene polymorphisms of MMPs and TIMPs, the MMP-7-181*A/G* polymorphism is one of the most differentially distributed between gastric cancer patients and healthy controls. Functional analysis *in vitro* has shown that nuclear proteins bind with higher affinity to the -181*G* allele than to the -181*A* allele and promoter activity variation of the -181*G* allele was about 2–3 times than that of the -181*A* allele, which may induce elevation of MMP-7 mRNA transcription and subsequently increase its protein levels, so individuals with *GG* genotype may have a higher risk of the gastric cancer than with *GA* genotype. Furthermore, the MMP-7-181*A/G* polymorphism is significantly correlated with helicobacter pylori (Hp) infection, which is a key aetiological factor in gastric cancer. The *G* allele may serve as a promoting factor for tumor growth and lymph node invasion. Thus, it may have prognostic value (31-34).

In this study, we detected the polymorphism of MMP-7-181*A/G* in lymph node tissue samples collected from 210 gastric carcinoma patients with no confirmed metastasis. Subsequently, we analyzed the association of the potential molecular marker with clinicopathological characteristics and prognosis of patients, intending to investigate the potential role of the MMP-7-181*A/G* polymorphism as a prognosticator.

Methods

Subjects

Gastric cancer patients (n=210) who underwent clinical surgery were recruited from the Beijing Cancer Hospital between January 1999 and December 2000. Patients were excluded if without adequate histological specimens or lacking clinical information. Lymph nodes tissue samples from the patients with pathological symptoms but no confirmed signs of metastasis were suitable for DNA extraction and subsequently collected. None of the enrolled patients received neo-adjuvant chemo-radiotherapy. The study was conducted under the assent of the ethics and research committee of Peking University School of Oncology. Tumor staging was according to the 2002 sixth edition of AJCC/UICC TNM staging criteria for gastric cancer. All patients were followed up at regular intervals of 6 months after surgery with a minimum of 5 years of follow-up. Tumor recurrence was clinically based on the reappearance of the tumor after curative surgery. The overall survival time was evaluated from the surgery date to the last visit or death.

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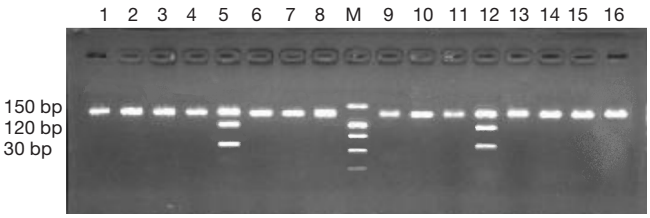

Figure 1 Genotyping of the MMP-7-181*A/G* genotype by PCR-RFLP. 1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 13, 14, 15, 16, A/A genotype; 5, 12, *A/G* genotype; M, molecular marker (160 bp, 115 bp, 100 bp, 25 bp, 15 bp). PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism.

Genotyping

Genomic DNA was extracted from paraffin-embedded tissue sections (three to five 10 μm sections) using a Genomic DNA Extraction Kit (Tiangen Biotech, Beijing, China) according to the manufacturer's protocol. The MMP-7-181*A/G* polymorphism was identified by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). The primers used to amplify MMP-7 were the following: forward primer *TGG TAC CAT AAT GTC CTG AAT G* and reverse primer *TCG TTA TTG GCA GGA AGC ACA CAA TGAATT*, as described by Jormsjö *et al.* (33). The reaction conditions used were an initial denaturation at 94 ℃ for 5 minutes, followed by 35 step cycles of denaturation at 94 ℃ for 30 seconds, annealing at 62 ℃ for 30 seconds, and extension at 72 ℃ for 30 seconds, followed by a terminal extension time of 5 minutes. PCR products were digested with the EcoRI restriction enzyme (New England Biolabs, Inc.) for 2 hours at 37 ℃. The digestion products were then resolved on a 3% agarose gel containing ethidium bromide. The *A/A* variant was identified by a single band (150 bp), and the *A/G* variant displayed three bands (150, 120, and 30 bp; *Figure 1*).

Statistical analysis

All statistical analyses were performed using SPSS version 10.0 software (SPSS Inc., Chicago, IL, USA). Associations between the MMP-7-181 genotype and clinicopathologic characteristics were analyzed using Pearson's χ^2 test. Cumulative survival probability as a function of time was estimated using the Kaplan-Meier method, and the statistical significance of difference between survival curves was evaluated by the log-rank test. Differences with a two-sided P value of 0.05 or less were considered to be statistically significant. Cox's proportional hazards modeling of the factors including the MMP-7-181*A/G* genotype and established clinicopathologic characteristics which may potentially related to survival was performed in order to identify which factors might have a significant influence on survival.

Results

Patient characteristics

Our study group consisted of 142 male and 68 female patients, the median age of the study population was 56 years (range, 25–78 years). There were 34 cases of patients were classified as stage I, 52 cases of stage II, 64 cases of stage III and 60 cases of stage IV. Among them 133 cases were poorly differentiated, 43 cases were moderately differentiated and 34 cases were well differentiated. According to the Lauren classification, 70 tumors were intestinal, 97 were diffuse and the remaining 43 were mixed. The follow-up period for survivors ranged from 2 to 120 months (median: 34 months). The 5-year overall survival rate for the entire study population was 43.7% with 92.7% in stage I, 75.2% in stage II, 34.3% in stage III and 13.5% in stage IV patients.

The association between MMP-7-181 polymorphic variants and clinicopathologic characteristics

Of the 210 patients analyzed in this study, 83.8% (176 of 210) were homozygous for the *A/A* variant, 16.2% (34 of 210) were heterozygous for *A/G*, and none were homozygous for *G/G* variant. The correlation between the polymorphic variants and the clinicopathologic factors was carefully analyzed (*Table 1*). Patients with the MMP-7-181*A/G* genotype were significantly more likely to have lymph node metastasis (P=0.037) and lymphovascular invasion (P=0.003) than those with the *A/A* genotype. Other variants, including gender, age, tumor size, tumor site, differentiation, Lauren classification, depth of invasion and distant metastasis, had no significant correlation with the MMP-7-181 genotype.

The association between MMP-7-181 polymorphic variants and prognosis of patients

Univariate analysis detected that 5-year overall survival rates of patients with A/A and A/G genotypes were 59.56% and 33.33%, respectively, and this difference is statistically

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Table 1 Association between the MMP-7-181 genotype and the clinicopathological factors

Factors	Patients	MMP-7-181 genotype		P value
		A/G No. (%)	*A/A* No. (%)	
Gender				0.899
Male	142	22 (10.5)	120 (57.1)	
Female	68	12 (5.7)	56 (26.7)	
Age (years)				0.256
≥60	111	21 (10.0)	90 (42.9)	
<60	99	13 (6.1)	86 (41.0)	
Tumor size (cm)				0.836
≥5	133	21 (10.0)	112 (53.3)	
<5	77	13 (6.2)	64 (30.5)	
Depth of Invasion				0.360
T1/T2	49	10 (4.8)	39 (18.6)	
T3/T4	161	24 (11.4)	137 (65.2)	
Lymph node metastasis				0.037*
N0	83	8 (3.8)	75 (35.7)	
N1	127	26 (12.4)	101 (48.1)	
Distant metastasis				0.104
M1	21	6 (2.9)	15 (7.1)	
M0	189	28 (13.3)	161 (76.7)	
Lymphovascular invasion				0.003*
V(+)	94	23 (11.0)	71 (33.8)	
V(–)	116	11 (5.2)	105 (50.0)	
Lauren classification				0.341
Intestinal type	70	11 (5.2)	59 (28.1)	
Diffuse type	97	13 (6.2)	84 (40.0)	
Mixed type	43	10 (4.8)	33 (15.7)	
Differentiation				0.894
Poorly	133	22 (10.5)	111 (52.9)	
Moderately	43	6 (2.9)	37 (17.6)	
Well	34	6 (2.9)	28 (13.3)	
TNM stage				0.502
I	34	5 (2.4)	29 (13.8)	
II	52	6 (2.9)	46 (21.9)	
III	64	10 (4.8)	54 (25.7)	
IV	60	13 (6.2)	47 (22.3)	

*, P<0.05.

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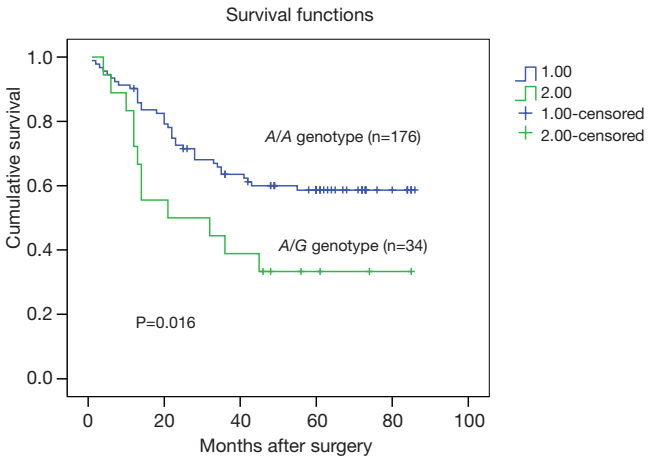

Figure 2 Kaplan-Meier overall survival curves based on genotype of MMP-7-181 polymorphism in the patients of gastric cancer. It showed the significant differences between the *A/A* and *A/G* genotype groups.

Table 2 Multivariate survival analysis of the prognostic effect of MMP-7-181 polymorphism using the Cox proportional hazard model with a backward stepwise procedure

Variables	P value	Relative risk	95% CI
Tumor size	0.654	0.868	0.469–1.608
Lymphovascular invasion	0.423	1.295	0.688–2.436
Differentiation	0.427	1.169	0.795–1.720
Lauren classification	0.728	0.920	0.577–1.468
TNM stage			
II/I	0.191	2.812	0.597–13.246
III/I	0.016*	6.075	1.407–26.233
IV/I	0.001*	11.061	2.579–47.447
III/II	0.043*	2.377	1.029–5.488
II/IV	0.001*	0.254	0.112–0.579
III/IV	0.065	0.549	0.291–1.037
MMP-7-181*A/G* genotype	0.027*	2.098	1.088–4.045

*, P<0.05.

significant (P=0.016, *Figure 2*). Patients with the *A/G* genotype had worse prognoses than those with the *A/A* genotype. TNM stage and lymphovascular invasion were also significantly correlated with 5-year overall survival, while other variants demonstrated no significant correlation. Multivariate analysis adjusting for sex, age, tumor size, tumor location, depth of invasion, lymph node metastasis, distant metastasis, TNM stages and grade of differentiation revealed that the MMP-7-181*A/G* genotype (RR =2.098; 95% CI: 1.09–4.05; P=0.027, *Table 2*) and TNM stage were significant prognostic indicators.

Discussion

This retrospective study detected the MMP-7-181*A/G* genotype in gastric cancer and found that there were close correlations between the MMP-7-181*A/G* genotype and lymph node metastasis and lymphovascular invasion. Univariate and multivariate analyses revealed that the MMP-7-181*A/G* genotype was a powerful prognosticator for overall survival with gastric cancer patients. Patients with the MMP-7-181*A/G* genotype are at a higher risk for lymph node metastasis, lymphovascular invasion and poorer prognosis than those with the *A/A* genotype. Our data strongly suggest that the MMP-7-181*A/G* genotype may serve as a valuable prognostic indicator for predicting poor prognosis in patients with gastric cancer.

MMPs play a role in the process of cancer invasion and metastasis. MMP-7 is the smallest known member of the MMP family, possessing the highest extracellular matrix (ECM)-degradative activity against a variety of ECM components, including elastin, gelatin, type IV collagen, fibronectin, vitronectin, laminin, entactin, aggrecan and proteoglycans. MMP-7 is overexpressed in invasive cancers of the digestive tract, including esophageal, gastric, colorectal, pancreatic and liver, and its over expression is implicated in cancer transformation, aggressive phenotype, progression, metastasis and poor patient survival (35-39). MMP-7 is most frequently identified in gastric precancerous lesions and gastric carcinomas, but the underlying mechanism of its overexpression has not been fully investigated. Previous studies showed that MMP-7 expression was up-regulated by HP in gastritis and by gastrin in hypergastrinemia and that both of these lesions are associated with gastric carcinoma (40,41). Studies suggested that the functional polymorphisms in the promoters of MMP genes were strongly associated with the risk of multiple types of cancer. Other studies revealed a significant association of functional MMP-7 gene variants toward susceptibility to Hp-induced precancerous gastric

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lesions (31,32,34,40,41). The MMP-7-181 *G* allele was found to confer gastric cancer susceptibility and higher transcriptional activity, which correlate with MMP-7 over expression.

The frequencies of each MMP-7-181 genotype differ between studies from different ethnicities and countries. The *G* allele frequency was shown to be between 8.8% and 42.0%. Moreover, the correlation between the MMP-7-181 polymorphism and individual types of cancer demonstrated certain discrepancies between different studies. Nevertheless, the value of MMP polymorphisms as susceptibility and prognosis indicators is evident and warrants further exploration. The frequency of the *G* allele in our study is consistent with that of Sugimoto *et al*. The frequencies of the MMP-7-181*A/A*, *A/G*, and *G/G* genotypes in the gastric cancer group were 83.1%, 16.9%, and 0.0%, respectively in Sugimoto *et al*.'s study. The previous study also showed that the *G* allele is associated with an increased risk of gastric cancer (OR =2.31) and that this cancer occurs at a more advanced stage (42). These results are also consistent with our findings, yet Sugimoto *et al*.'s study demonstrated no significant prognostic value of the MMP-7-181*A/G* polymorphism. In a study by Kubben *et al*., the MMP-7-181*A/G* polymorphism was found to be significantly associated with patient survival (32).

The studies exploring the MMP-7-181A/G genotype commonly used fresh blood samples or normal tissue specimens for DNA extraction, which are adequate methods for studies exploring the susceptibility of cancers. Studies of cancer prognostication may need long-term follow-up information, which is not possible to collect when the original sample consists of fresh blood because DNA quality in fresh blood decreases over time. Archival formalin fixation paraffin-embedded tumor tissue may be possible to as good source for regular, molecular marker detection and exploration of new prognosticators in such retrospective studies. Recent researches have showed that the fixation process does not seem to impact the DNA quality for genotype detection. Genotyping results obtained from paraffin-embedded tissue DNA and peripheral blood DNA are strongly consistent (43). We picked lymph node tissue to detect the genotypes of MMP-7, all the chosen patients had complete pathological examination and follow-up information, and the lymph nodes were histopathologically confirmed with no sign of metastasis. These results provide a good point to further explore the polymorphisms of MMPs in gastric cancer prognostication.

In summary, our results reveal that the MMP-7-181*A/G* polymorphism is correlated with lymph node metastasis and vascular invasion. The MMP-7-181*A/G* genotype may serve as a new valuable prognostic indicator in gastric cancer patients.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2016.10.04). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was conducted under the assent of the ethics and research committee of Peking University School of Oncology (approval number: V01&2011-3) and written informed consent was obtained from all patients.

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