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Original Article

Expression of c-MET, EGFR and HER-2 in gastric adenocarcinoma tissue and its relationship with clinicopathological characteristics

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Abstract: Objective: To determine the expression of tyrosine protein kinase Met (c-MET), epidermal growth factor receptor (EGFR), and human epidermal growth factor receptor 2 (HER-2) in cases with gastric adenocarcinoma (GA). Methods: The positive rates of the c-MET, EGFR, and HER-2 proteins between cancerous tissues and normal tissues sampled from 87 patients with GA were compared. The patients were assigned to different subgroups according to their clinicopathological characteristics and analyzed. Then the relationship between the above three indexes and the positive expression of Ki-67 were analyzed. In addition, the patients were assigned to positive and negative groups based on the situation of c-MET, EGFR and HER-2 proteins, and followed up for three years. These groups were compared in terms of recurrence-free survival, overall survival, and risks factors of prognosis. Results: The positive rates of c-MET, EGFR and HER-2 proteins in GA tissues were all higher than those in corresponding non-tumor tissues (all P<0.001), and the positive rates of them were greatly different in subgroups with different differentiation, invasion depth, TNM stage, lymph node metastasis (LNM), distant metastasis and presence of tumor thrombus (all P<0.05) and were positively correlated with the expression of Ki-67 protein (P<0.05). Moreover, the survival analysis results revealed lower recurrence-free survival and overall survival rates in groups with negative expression of c-MET, EGFR, and HER-2 than those in groups with positive expression of them (both P<0.001). Furthermore, the positive EGFR was an independent prognostic factor affecting the survival of patients with GA. Conclusion: The expression of c-MET, EGFR and HER-2 proteins is correlated with clinical characteristics of patients with GA, and patients with positive expression of them face a higher recurrence rate. Additionally, EGFR protein may affect patients' survival.

Keywords: Gastric adenocarcinoma, tyrosine protein kinase Met, epidermal growth factor receptor, human epidermal growth factor receptor 2

Introduction

Gastric adenocarcinoma (GA) is a prevalent malignant tumor of the digestive tract, with morbidity and mortality ranking at the forefront of those of malignant tumors [1, 2]. With the development of society, the incidence of GA is increasing year by year. Patients with GA have no obvious clinical manifestations in the early state, so more than half of them have already entered the later phase at the time of diagnosis, and have missed the optimal therapy time [3-6]. Over the past few years, as molecular biology advances rapidly, the roles of signal pathways in tumor development have gradually captured the attention of medical researchers and have provided new ideas for the treatment of GA [7, 8]. Receptor tyrosine kinases (RTKs) include tyrosine protein kinase Met (c-MET), epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER-2). According to previous studies, RTKs pathway is closely related to the growth and reproduction of many kinds of tumor cells. c-MET is a hepatocyte growth factor receptor, with a main biological function of activating RTKs pathway, which plays an important role in cell proliferation and differentiation. HER-2, a

member of the human epidermal growth factor receptor family, can lead to over-expression of corresponding proteins when it increases in large quantities and can thus promote cell proliferation and inhibit apoptosis, resulting in rapid growth of tumor cells. Studies have confirmed that c-MET and HER-2 in solid tumor tissue such as breast cancer tissues increase notably, and overexpression of the two can stimulate the activity of various signal pathways, thus accelerating the proliferation and infiltration of tumor cells [9, 10]. EGFR is a specific protein capable of promoting vascular proliferation and increasing vascular permeability. It can regulate the vascular permeability of tumor tissues to a certain extent and its positive expression in tumors can promote angiogenesis in tumor tissues, and then regulate the growth of tumor tissues [11]. One earlier study has investigated the expression of RTKs family members in cases with GA, but the difference of their expression in patients with different clinical characteristics is still controversial [12]. Therefore, this study analyzed the expression of c-MET, EGFR and HER-2 in cases with GA and its correlation with clinicopathological features, and determined its clinical value in evaluating prognosis, with the purpose of providing relevant basis for diagnosis and prognosis evaluation of GA.

Materials and methods

General data

A total of 87 patients with GA who received radical gastrectomy in our hospital from January 2016 to January 2018 were enrolled, and their general data were collected. In our study, all enrolled participants voluntarily participated in the study after they and their families were informed of the study and signed informed consent forms. This study was approved by the ethics committee of our hospital. Cases enrolled in this study were evaluated according to the GC staging (8-th edition) formulated by the American Joint Committee on Cancer [13].

Inclusion and exclusion criteria

The inclusion criteria: Patients who were confirmed with GA and received surgical resection; patients ≥18 years old; patients who had not received treatments affecting our experimental results such as radiotherapy, chemotherapy, biological immunotherapy and targeted therapy before operation.

The exclusion criteria: Patients with other comorbid tumors; patients who had taken immunosuppressants and other drugs with possible impacts on the experimental results within the last 3 months; those without detailed pathological data.

Methods

Cancerous tissues and corresponding non-tumor tissues were sampled, paraffined, and cut into 4 μm sections. Then immunohistochemistry was adopted to determine the positive status of ki-67, c-MET, EGFR and HER-2 in them. Immunohistochemical antibodies and kits were all purchased from Beijing Zhongshan Golden Bridge Biotechnology Co., Ltd.

Result determination

The sections were scored according to the following criteria. 0 point: no observed cells were stained; 1 point: 1-25% observed cells were stained; 2 points: 26-50% observed cells were stained; 3 points: over 50% observed cells were stained. 0 point was adopted to indicate negative expression, while 1-3 points indicate positive expression [14-16].

Follow-up observation

The follow-up ended on January 2021. The postoperative recurrence time and survival time of patients were calculated from the time of the first surgical resection of GA in our hospital to the time of death or the last follow-up time, namely January 2021 (for patients who did not die).

Outcome measures

Primary outcome measures: The positive expression rates of c-MET, EGFR and HER-2 proteins in GA tissues from the 87 enrolled patients were compared with those in corresponding non-tumor tissues. The K-M survival curve was adopted to analyze the difference of recurrence-free survival (RFS) and overall survival (OS) rates between positive and negative groups, and the COX proportional hazard model (PHM) was adopted to conduct multivariate survival analysis.

Table 1. Immunohistochemical results of c-MET, EGFR and HER-2 proteins [n (%)]

Parts	c-MET	EGFR	HER-2
Gastric adenocarcinoma tissues (n=87)	37 (42.53)	33 (37.93)	39 (44.83)
Paracancerous tissues (n=87)	10 (11.49)	9 (10.34)	10 (11.49)
χ^2	21.521	18.408	23.891
P	<0.001	<0.001	<0.001

Note: c-MET: tyrosine protein kinase Met; EGFR: epidermal growth factor receptor; HER-2: human epidermal growth factor receptor 2.

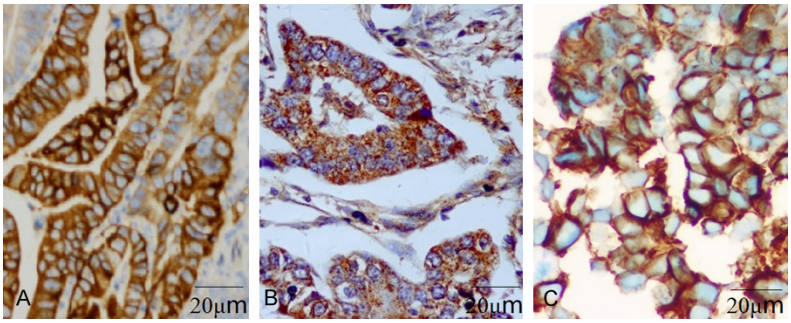

Figure 1. Immunohistochemical results of c-MET, EGFR and HER-2 proteins (×400). A. Gastric adenocarcinoma tissue is positive for c-MET protein. B. Bastric adenocarcinoma tissue is positive for EGFR protein. C. Gastric adenocarcinoma tissue is positive for HER-2 protein. c-MET: tyrosine protein kinase Met; EGFR: epidermal growth factor receptor; HER-2: human epidermal growth factor receptor 2.

Secondary outcome measures: The patients were assigned into different subgroups according to their gender, age, tumor location, tumor diameter, differentiation, invasion depth, TNM stage, lymph node metastasis (LNM), distant metastasis, and presence of tumor thrombus. The subgroups were compared in positive expression rates of c-MET, EGFR and HER-2 proteins. Additionally, Spearman's rank correlation was adopted for correlation analysis between the positive expression of c-MET, EGFR and HER-2 proteins and that of Ki-67 protein.

Statistical analyses

SPSS22.0 was used for statistical analyses. The study also compared enumeration data, expressed as the number of cases and percentage, between groups via the χ^2 test. Spearman's rank correlation method was used for correlation of two indices, and COX proportional hazard model (PMH) for multivariate survival analysis. P<0.05 indicates a significant difference.

Results

Immunohistochemical results

The positive rates of c-MET, EGFR and HER-2 proteins in GA tissues were 42.53%, 37.93% and 44.83%, respectively, and those in corresponding non-tumor tissues were 11.49%, 10.34% and 11.49%, respectively. Therefore, the positive rates of them in the two different tissues were significantly different (P<0.001, **Table 1** and **Figure 1**).

Comparison of positive rates of c-MET, EGFR and HER-2 proteins in patients with different clinicopathological features

Among the 87 cases of GA tissues, patients with low differentiation showed higher positive rates of c-MET, EGFR and HER-2 proteins than those with moderate or high differentiation (all *P*<0.05); patients with T3 or T4 infiltration depth showed higher positive rates of them than those with T1 or T2 infiltration depth (all *P*<0.05); patients with higher TNM staging showed higher positive rates of them (all *P*<0.05); patients without LNM, distant metastasis or cancer thrombus showed higher positive rates of them than those with the condition (all *P*<0.05; **Table 2**).

Correlation analysis between the positive expression of c-MET, EGFR and HER-2 proteins and that of Ki-67 protein

The positive expression of c-MET, EGFR and HER-2 proteins were positively correlated with that of Ki-67 protein (all P<0.05, **Table 3**).

Comparison of OS rate between positive and negative groups of c-MET, EGFR and HER-2 proteins

By the time of follow-up, the survival rate was 64.37%, with 31 deaths. The median survival time of positive groups of c-MET, EGFR, and

Table 2. Comparison of positive rates of c-MET, EGFR and HER-2 protein in patients with different clinicopathological characteristics

Project	Numbers	c-MET expression			EGFR expression			HER-2 expression		
		Positive (%)	χ^2	P	Positive (%)	χ^2	P	Positive (%)	χ^2	P
Gender (n)										
Male	54	24 (44.44)	0.214	0.644	18 (33.33)	1.278	0.258	25 (46.30)	0.124	0.725
Female	33	13 (39.39)			15 (45.45)			14 (42.42)		
Age (years)										
<55	30	12 (40.00)	0.12	0.729	10 (33.33)	0.411	0.521	13 (43.33)	0.041	0.839
≥55	57	25 (43.86)			23 (40.35)			26 (45.61)		
Tumor location (n)										
Cardia	26	12 (46.15)	0.199	0.655	11 (42.31)	0.302	0.583	12 (46.15)	0.026	0.871
Non cardia	61	25 (40.98)			22 (36.01)			27 (44.26)		
Tumor diameter (CM)										
>5	51	23 (45.10)	0.333	0.564	20 (39.22)	0.086	0.769	25 (49.02)	0.876	0.349
≤5	36	14 (38.89)			13 (36.11)			14 (38.89)		
Differentiation degree (n)										
Medium high differentiation	35	9 (25.71)	6.774	0.009	7 (20.00)	7.997	0.005	9 (25.71)	8.649	0.003
Low differentiation	52	28 (53.85)			26 (50.00)			30 (57.69)		
Infiltration depth (n)										
T1+t2	42	11 (26.19)	8.868	0.003	10 (23.81)	6.878	0.009	11 (26.19)	11.404	0.001
T3+t4	45	26 (57.78)			23 (51.11)			28 (62.22)		
TNM staging (n)										
Phase I	13	2 (15.38)	13.086	0.001	2 (15.38)	10.133	0.006	3 (23.08)	12.526	0.002
Phase II	32	9 (28.13)			8 (25.00)			9 (28.13)		
Phase III	42	26 (61.90)			23 (54.76)			27 (64.29)		
Lymph node metastasis (n)										
Yes	50	27 (54.00)	6.33	0.012	24 (48.00)	5.063	0.024	28 (56.00)	5.934	0.015
No	37	10 (27.03)			9 (24.32)			11 (29.73)		
Distant metastasis (n)										
Yes	24	23 (95.83)	38.529	<0.001	22 (91.67)	40.649	<0.001	23 (95.83)	34.863	<0.001
No	63	14 (22.22)			11 (17.46)			16 (25.40)		
Tumor thrombus (n)										
Yes	51	29 (56.86)	10.361	0.001	26 (50.98)	8.915	0.003	30 (58.83)	9.762	0.002
No	36	8 (22.22)			7 (19.44)			9 (25.00)		
Histological type (n)										
Tubular adenocarcinoma	67	29 (43.28)	0.436	0.509	27 (40.30)	0.694	0.405	31 (46.27)	0.245	0.621
Non tubular adenocarcinoma	20	7 (35.00)			6 (30.00)			8 (40.00)		

Note: c-MET: tyrosine protein kinase Met; EGFR: epidermal growth factor receptor; HER-2: human epidermal growth factor receptor 2.

Table 3. Correlation results

Statistics	c-MET	EGFR	HER-2
r	0.319	0.338	0.374
P	0.017	0.029	0.005

Note: c-MET: tyrosine protein kinase Met; EGFR: epidermal growth factor receptor; HER-2: human epidermal growth factor receptor 2.

HER-2 proteins was 19.95, 19.28 and 21.49 months, respectively, while that of negative groups was 33.84, 33.10, and 33.26 months, respectively. Therefore, the positive and negative groups were significantly different in OS (χ^2=41.435, 38.314, 29.538; all P<0.001, **Figure 2**).

Comparison of RFS rate between positive and negative groups of c-MET, EGFR and HER-2 proteins

All patients were followed up for three years, and the RFS rate was 64.37%, with 35 patients suffering recurrence. The median RFS of positive groups of c-MET, EGFR and HER-2 proteins was 14.59, 13.84, and 15.35 months, respectively, while that of negative groups was 27.83, 27.37, and 27.57 months, respectively.

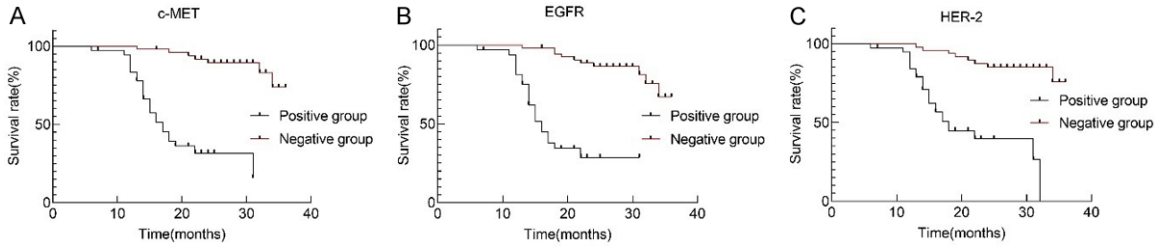

Figure 2. The overall survival curves of c-MET, EGFR and HER-2 protein positive and negative groups. A. c-MET. B. EGFR. C. HER-2. c-MET: tyrosine protein kinase Met; EGFR: epidermal growth factor receptor; HER-2: human epidermal growth factor receptor 2.

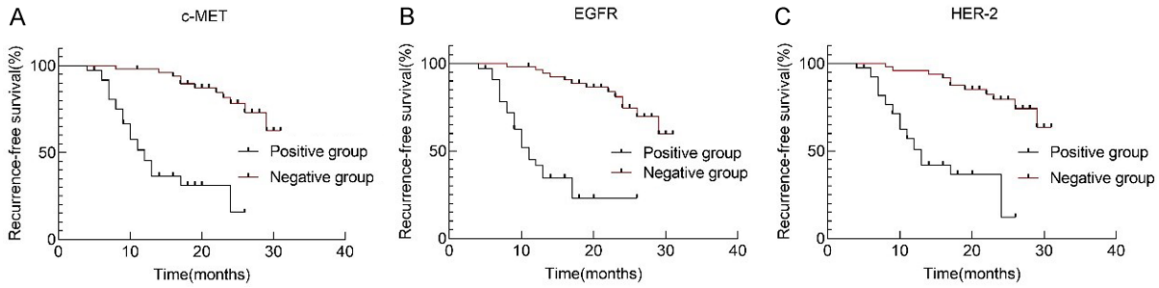

Figure 3. Recurrence-free survival curves of c-MET, EGFR and HER-2 protein positive and negative groups. A. c-MET. B. EGFR. C. HER-2. c-MET: tyrosine protein kinase Met; EGFR: epidermal growth factor receptor; HER-2: human epidermal growth factor receptor 2.

Table 4. COX proportional hazard model analysis results

Index	EGFR positive
B	1.453
Se	0.363
Wald	16.024
P	<0.001
Rr	4.277
95ci	
Lower limit	2.099
Upper limit	8.713

Note: EGFR: epidermal growth factor receptor.

Therefore, the positive and negative groups were greatly different in RFS (χ^2=37.778, 39.991, 31.006; all P<0.001, **Figure 3**).

COX PMH analysis results

The results indicated that positive EGFR was an independent prognostic factor for the survival of patients with GA (P<0.001, **Table 4**).

Discussion

Currently, RTKs pathway has attracted enormous attention of medical researchers. Studies have pointed out the close association between RTKs overexpression and the development of many solid cancers such as colorectal cancer and glioma [9, 10]. Therefore, the study adopted RTKs pathway-associated proteins as indices to explore their clinical value in evaluating prognosis.

C-MET, a member of the RTKs family, is expressed on various cell surfaces. One study has revealed that under normal physiological conditions, c-MET is able to accelerate growth and healing of damaged tissues [17]. However, under special pathological conditions, it can speed up the proliferation of tumor cells and suppress their apoptosis. According to a previous study, c-MET protein shows overexpression in solid cancers such as breast cancer and liver cancer [18]. In our study, among the enrolled 87 patients with GA, the positive rate of c-MET protein in cancerous tissues was 42.53%, significantly higher than that in normal tissues. However, in cases with low differentiation, high infiltration depth or TNM stage, LNM, distant metastasis or cancer thrombus, the positive expression rate of c-MET protein was higher, and the correlation analysis showed a positive association between positive rate of c-MET protein and that of ki-67. The results

indicate the close association of its positive rate with the severity of disease, and its ability of indicating unfavorable prognosis. HER-2, a RTKS I-type receptor, is in an inactive state under normal physiological conditions, but once stimulated by external factors, it will be activated due to its abnormality in structure and function, and then it will enhance the activity of tumor transformation, thus leading to malignant transformation of cells [19]. In one earlier study, in cases with GC, positive rate of HER-2 protein was approximate 7.1-42.6% [10, 20]. In our study, among the 87 patients with GA, the positive rate of HER-2 protein in GA tissues was significantly different from that in corresponding non-tumor tissues (44.83% vs. 11.49%, $P<0.05$). We also found that in cases with GA, the positive rate of HER-2 protein increased with the decrease of differentiation degree, increase of infiltration depth or TNM stage, or occurrence of LNM, distant metastasis or cancer thrombus. The results are in consistent with previous research results, which suggest that cases with positive HER-2 protein have stronger cancer cell invasion and metastasis, and thus have worse prognosis. EGFR also belongs to the RTKs family. Under normal physiological conditions, it binds to its ligand, which leads to dimerization of receptors, and thus participates in cell biological behaviors including cell proliferation, growth and differentiation [21]. One study has pointed out a significant increase in EGFR in cancerous tissues [22], and another study found that the expression rate of EGFR protein in cases with GA was over 40%, notably higher than that in normal gastric tissues [23]. In contrast, our study showed that the expression rate of EGFR protein in cases with GA was 37.93%, which was significantly higher than that in corresponding non-tumor tissues, but lower than that mentioned above. We believe that reasons for the difference are probably related to factors such as race and detection method. In patients with different clinicopathological features, similar to c-MET and HER-2, the positive rate of EGFR protein increased with the decrease of differentiation, increase of infiltration depth or TNM stage, or occurrence of LNM, distant metastasis or cancer thrombus. The correlation analysis showed a positive association between the positive rate of EGFR protein and that of ki-67. The results indicate an involvement of EGFR in the development of GA. We adopted K-M survival curve for analysis of RFS and OS rates of positive and negative groups, and found that negative groups showed higher RFS and OS rates and experienced longer median RFS time and OS time than those of positive groups. The data indicate that patients with positive expression of c-MET, EGFR and HER-2 proteins may have worse prognosis. Additionally, we adopted COX PMH for analysis, and found that only EGFR protein was an independent prognostic factor for the survival time of patients with GA. The result also suggests the relatively shorter survival of patients with positive EGFR protein, but the specific mechanism needs further study.

This study also has the following limitations: (1) All specimens were taken from a single center, so the sample size was small. (2) It was difficult to discuss the sequential order between the expression of c-MET, EGFR, HER-2 proteins and tumorigenesis, and clarify the specific mechanism between them.

To sum up, in cases with GA, the expression of c-MET, EGFR and HER-2 proteins is correlated with differentiation, TNM stage, LNM, distant metastasis, and presence of tumor thrombus, and patients with positive expression of them face a higher recurrence rate. Furthermore, EGFR protein is an independent prognostic factor for patients' survival.

Disclosure of conflict of interest

None.

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