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ORIGINAL ARTICLE

Correlations of recurrence of gastric cancer in patients after radical surgery with serum gastrointestinal hormones, vascular endothelial growth factors and serum anti-helicobacter pylori IgG antibody

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Summary

Purpose: *To study the correlations of the recurrence of gastric cancer in patients after radical surgery with serum gastrointestinal hormones, serum anti-Helicobacter pylori (anti-HP) immunoglobulin G (IgG) antibody and vascular endothelial growth factors (VEGFs).*

Methods: *According to whether gastric cancer recurred within five years after surgery, the patients were divided into recurrence group (RE group, gastric cancer recurred within five years after surgery, n=78) and non-recurrence group (NR group, gastric cancer did not recur within five years after surgery, n=69). Differences in lymph node metastasis, gastrointestinal hormones, VEGFs, anti-HP IgG antibody and the tumor-node-metastasis (TNM) stage between RE group and NR group were detected and compared, so as to analyze the correlations of these factors with the recurrence of gastric cancer in patients after radical surgery.*

Results: *The levels of gastrin (GAS) and motilin (MTL) after meals in RE group and NR group were slightly higher than those before meals. The levels of GAS and MTL in RE group were higher than those in NR group in the two periods ($p<0.05$). Besides, compared with NR group, RE group had lower pepsinogen (PG) I, PG II and PG I/II ratio (PGR), but a higher positive value of anti-HP IgG antibody ($p<0.05$) and higher levels of VEGF-A, VEGF-C and VEGF-D ($p<0.05$). Moreover, there were markedly more cases of gastric cancer in stage III, remarkably few cases of gastric cancer in stage I and obviously more cases of lymph node metastasis in RE group than those in NR group ($p<0.05$). Multivariate analysis showed that gastrointestinal hormones, lymph node metastasis, VEGFs, the TNM stage of gastric cancer and anti-HP IgG antibody were all risk factors for the recurrence of gastric cancer after radical surgery ($p<0.05$).*

Conclusions: *The recurrence of gastric cancer in patients after radical surgery is related to the TNM stage of gastric cancer, gastrointestinal hormones, VEGFs, lymph node metastasis, anti-HP IgG antibody and other factors.*

Key words: *gastric cancer, growth factors, serum gastrointestinal hormones, IgG antibody, recurrence*

Introduction

Gastric cancer is a malignant tumor growing in gastric mucosa, whose incidence rate ranks top among malignant tumors [1]. No obvious symptoms appear in the early stage of gastric cancer, and only a few patients have mild symptoms such as stomach ache and anorexia that can only be treated as general stomach diseases and are difficult to be diagnosed as gastric cancer, so the patients will

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miss the optimal treatment time. Therefore, if gastric cancer is found, more than 80% of the patients are in the middle or advanced stages, and there is a slim hope for cure [2]. Gastric cancer evolves from chronic gastritis, which is also an important process for normal cells to transform into cancer cells [3]. In 1988, some experts revealed the development process of gastric cancer. It mainly develops from normal gastric dynamics superficial gastritis, atrophic gastritis, metastasis to the large intestine and epithelial metaplasia into atypical hyperplasia, leading to gastric cancer. As the economy and society constantly develop and the pressure increases, gastric cancer patients gradually tend to be younger [4]. Gastric cancer results from various causes and may be related to factors such as the environment, genes and diets. The incidence rate of the disease is relatively high in eastern Asia but extremely low in northwestern regions such as Europe and northern Asia [5]. Gastric cancer is clinically treated by surgery assisted by chemotherapy and other comprehensive treatment methods, but it is likely to recur due to the unsatisfactory treatment efficacy [6]. In fact, however, even in developed countries, over 50% of the definitely diagnosed patients are in advanced stage, and the possibility of complete elimination of lesions and metastases by surgery is below 50%. Helicobacter pylori (HP) exerts a crucial effect in the formation of gastric cancer [7]. The expression level and significance of anti-HP IgG antibody in the body of gastric cancer patients have a relatively remarkable correlation with the recurrence after treatment, and anti-HP IgG antibody may be an independent risk factor for the recurrence of gastric cancer [8]. Gastric cancer is a malignant tumor in the digestive system, whose occurrence and development are closely associated with gastrointestinal hormones. Vascular endothelial growth factors (VEGFs) play a major role in the angiogenesis process, and they are involved in every physiological activity of the body. Multiple studies have manifested that VEGFs are detected to be abnormally expressed in gastric cancer patients, exerting a vital effect in the disease progression [9]. Therefore, this study aimed to investigate the correlations of the recurrence of gastric cancer in patients after radical surgery with lymph node metastasis, gastrointestinal hormones, VEGFs, anti-HP IgG antibody and TNM stage by detecting and analyzing these factors in patients in RE group and NR group.

Methods

General data

A total of 147 patients with gastric cancer treated in our hospital from January 2013 to July 2014 and undergoing radical surgery were selected. According to whether gastric cancer recurred within five years after surgery, these patients were divided into recurrence group (RE group, gastric cancer recurred in patients within five years after surgery, n=78) and non-recurrence group (NR group, gastric cancer did not recur within 5 years after surgery, n=69). There were no differences in general data (Table 1) between patients in RE group and NR group. This study was approved by the Ethics Committee of Affiliated Hospital of Yan'an University. Signed written informed consents were obtained from all participants before the study.

Inclusion and exclusion criteria

Inclusion criteria: 1) patients who met the diagnostic criteria for gastric cancer; 2) those who received only radical surgery for gastric cancer; and 3) those who signed the informed consent. Exclusion criteria: 1) patients suffering from other digestive system diseases; 2) those who quit studies without reason during the investigation; or 3) those who were in poor mental state.

Detection of gastrointestinal hormones by enzyme-linked immunosorbent assay

The levels of serum gastrointestinal hormones in patients were detected before and after meals, respectively, using the following methods: Venous blood of patients in RE group and NR group was collected and centrifuged by conventional methods, and the supernatant was taken to measure the levels of gastrin (GAS) and plasma motilin (MTL). This experiment was required to be completed within 20 min, and the average value was recorded.

Detection of VEGFs by chemiluminescence

Venous blood of patients in RE group and NR group was collected at the same time. Serum was diluted 2 times with bovine serum albumin (BSA) solution. The diluted VEGF monoclonal antibody was added to a chemiluminescent microplate for incubation, after which phosphate buffered saline-tween (PBST) was utilized for washing. Then, chemiluminescence substrates A and B were mixed evenly and added to the microplate for 5 min of reaction, followed by detection using a chemiluminescent analyzer. Finally, the levels of VEGF-A, VEGF-C and VEGF-D were calculated.

Examination of anti-HP IgG antibody via enzyme-linked immunosorbent assay

Venous blood of patients in RE group and NR group was collected and detected according to the instructions of enzyme-linked immunosorbent assay kit (R&D Systems, Minneapolis, MN, USA). The levels of pepsinogen (PG) I and PG II in serum were detected. Determination of positive results: 1) pepsinogen I/II ratio (PGR) ≥4.5 and 2) PG II ≤70 g/L.

TNM stage and lymph node metastasis of gastric cancer

The TNM stage of gastric cancer: stage I: cancer cells grow on the surface of the gastric mucosa and do not invade the lamina propria of the mucosa; stage II:

cancer cells penetrate connective tissues but do not invade the visceral peritoneum; and stage III: cancer cells invade the surrounding tissue structures, with signs of metastasis. If lymph node metastasis occurred in patients it was pathologically examined.

Observational indexes

Gastrointestinal hormones, VEGFs and anti-HP IgG antibody of patients in RE group and NR group were detected and analyzed. The TNM stage of gastric cancer and whether lymph node metastasis occurred were determined by the pathological examination of tumor size, growth site and degree of lymph node invasion, and the multivariate analysis was performed for the recurrence after surgery.

Statistics

SPSS 22.0 (IBM, Armonk, NY, USA) was used for statistical analyses. The differences in anti-HP IgG antibody, gastrointestinal hormones, the TNM stage and VEGFs between RE group and NR group were detected via t-test. Univariate Cox regression analysis was carried out, while variables with significant values in univariate analysis were further subjected to multivariate analysis. P<0.05 suggested statistically significant differences.

Results

Gastrointestinal hormone levels in the patients in RE group and NR group

As shown in Table 2, the levels of gastrointestinal hormones (GAS and MTL) in the patients in RE group and NR group after meals were slightly higher than before meals (p<0.05), and those in RE group were higher than those in NR group in two periods (p<0.05).

Levels of VEGFs in the patients in RE group and NR group

The patients in RE group had higher levels of VEGF-A, VEGF-C and VEGF-D than those in NR group (p<0.05) (Table 3).

Table 1. General data (n)

Item	*RE group (n=78)*	*NR group (n=69)*	x^2	*p*
Gender			0.108	0.742
Male	43	40		
Female	35	29		
Age (years)			0.065	0.798
30-49	32	30		
50-74	46	39		
Lesion site			0.021	0.884
Gastric antrum	23	24		
Gastric body	26	21		
Cardia	29	24		

Table 2. Gastrointestinal hormone levels in the patients in RE group and NR group (x±s)

Group	*n*	*GAS (μmol/L)*		*MTL (ng/L)*	
		Before meals	*After meals*	*Before meals*	*After meals*
RE group	78	117.93±9.38	121.34±10.66*	302.94±28.46	317.92±29.93*
NR group	69	90.37±7.35	103.45±10.35*	241.49±20.65	253.56±25.72*
t		19.658	10.296	14.813	13.893
p		<0.001	<0.001	<0.001	<0.001

*p<0.05 *vs.* before meals

Table 3. Levels of VEGFs in the patients in RE group and NR group (x±s)

Group	*n*	*VEGF-A*	*VEGF-C*	*VEGF-D*
RE group	78	138.04±12.47	1793.45±298.84	1474.64±197.03
NR group	69	89.03±6.93	1036.47±174.07	937.05±138.46
t		29.664	18.453	18.901
p		<0.001	<0.001	<0.001

Anti-HP IgG antibody in the patients in RE group and NR group

The results revealed that the patients in RE group had lower PG I, PG II and PGR than those in NR group. Meanwhile, the positive value of anti-HP IgG antibody in RE group was higher than in NR group (p<0.05) (Table 4).

Pathological TNM stage of patients in RE group and NR group

It was found that there were significantly more cases of gastric cancer in stage III and remarkably few cases of gastric cancer in stage I in RE group than those in NR group (p<0.05) (Table 5).

Lymph node metastasis in the patients in RE group and NR group

The number of patients with lymph node metastasis in RE group was notably larger than in NR group (p<0.05) (Table 6).

Cox regression analyses

Multivariate analysis revealed that the TNM stage, gastrointestinal hormones, lymph node metastasis, VEGFs and anti-HP IgG antibody were all risk factors for the recurrence of gastric cancer in patients after radical surgery (p<0.05) (Table 7).

Discussion

Gastric cancer is a clinically common tumor of the digestive system, whose incidence rate varies among regions, and is relatively high mainly in eastern Asia. The number of gastric cancer cases and deaths in rural areas is markedly higher than that in cities [10]. Gastric cancer can arise in any part of the stomach, whose pathogenesis is complex and variable and associated with many factors such as food, genes and heredity [11]. The cause of cancer is a rather complicated bio-pathological process, including multiple genes and molecular

Table 4. Anti-HP IgG antibody in patients in RE group and NR group (x±s)

Group	*n*	*PG I (μg/L)*	*PG II (μg/L)*	*PGR*
RE group	78	146.83±15.47	21.84±8.73	4.63±1.64
NR group	69	218.93±21.39	13.04±5.94	19.93±3.85
t		23.346	7.052	31.983
p		<0.001	<0.001	<0.001

Table 5. Pathological TNM stage of patients in RE group and NR group (n)

Group	*n*	*I*	*II*	*III*	x^2	*p*
RE group	78	9 (11.53)	38 (48.71)	31 (39.74)	27.227	<0.001
NR group	69	32 (46.37)*	29 (42.03)*	8 (11.59)*		

*p<0.05 *vs.* RE group

Table 6. Lymph node metastasis in the patients in RE group and NR group (n)

Group	*n*	*Lymph node metastasis occurs*	*Lymph node metastasis does not occur*	x^2	*p*
RE group	78	57	21	30.408	<0.001
NR group	69	19*	50*		

*p<0.05 *vs.* RE group

Table 7. Multivariate analysis

Factor	*OR*	*p*	*95%CI*
Gastrointestinal hormone	1.947	0.043	1.175-3.631
VEGF	2.846	0.017	1.761-4.245
Anti-HP IgG antibody	1.173	0.035	1.073-5.319
TNM stage	1.573	0.024	1.131-2.465
Lymph node metastasis	1.355	0.026	1.145-3.736

signal transmission pathways. Numerous gastric cancer-related factors were discovered, but a few of them play a decisive role in the targeted therapy of this disease [12]. Similar to other gastric diseases, gastric cancer in the early stage has no obvious manifestations, so it is difficult to be diagnosed, and patients are likely to miss the optimal time for diagnosis and treatment [13]. The discovery and cure rates of gastric cancer in China are relatively low at present, so the early detection and active treatment are of great significance in the curing process of this condition [14]. According to studies, the positive infection rate of HP in patients with gastric cancer is obviously higher, and the International Cancer Center has designated it as the leading carcinogen of gastric cancer. Hence, early prevention and control is an effective method for gastric cancer, and it is also the priority research direction in the medical field in China [15].

The tables of this paper show that the levels of GAS, MTL, VEGF-A, VEGF-C and VEGF-D in RE group were higher than in NR group, and the positive value of anti-HP IgG antibody in the former was higher than that in the latter. Besides, the above tables also demonstrated that there were significantly more cases of gastric cancer in stage III and remarkably few cases of gastric cancer in stage I in RE group than those in NR group, and the number of patients with lymph node metastasis in RE group was notably larger than that in NR group. The multivariate analysis manifested that the TNM stage, VEGFs and anti-HP IgG antibody were all risk factors for recurrence of gastric cancer in patients after radical surgery. TNM staging is usually performed for all gastric cancer patients in clinical practice. The stage of a disease plays a key role in judging the preoperative condition and the necessity for surgery. The higher the stage, the more serious the condition of the disease and the more difficult the treatment will be. Meanwhile, the stage also substantially affects the recurrence rate of patients after surgery. The higher the stage, the greater the recurrence rate of patients [16]. Research has revealed that HP, a special bacterium, exists in most gastric cancer patients. Its content cannot be directly detected in gastric cancer patients, but can be indirectly reflected by detecting the level of anti-HP IgG antibody, thus revealing the development and recurrence of gastric cancer. It can be seen that the development of gastric disease can be determined by measuring serum PG I and PG II levels and PGR in gastric cancer patients, thus providing a reliable basis for screening gastric cancer and diagnosing its recurrence after treatment [17]. Clinical research has indicated that when gastric cancer occurs, the gastrointestinal wall secretion of patients is abnormal due to the action of the affected part, thus further leading to gastrointestinal hormone disorder and influencing gastrointestinal function. Therefore, the recurrence of patients after surgery is correlated with gastrointestinal hormones to a certain extent [18]. Multiple previous studies have confirmed that the expression of VEGF family in tumor tissues is related to the tumor progression in patients. The concentration of VEGF family in serum has a certain prognostic value, and patients with a high level of VEGF family have a higher recurrence rate [19]. Related literature has shown that lymph node metastasis is a main approach for gastric cancer to deteriorate and recur, and the metastasis will make the treatment more difficult. In the meantime, the recurrence rate in patients with metastasis after surgery is also higher than that in patients without metastasis [20], which is consistent with the results of this study.

Conclusions

To sum up, the recurrence of gastric cancer in patients after radical surgery is related to gastrointestinal hormones, anti-HP IgG antibody, VEGFs, the TNM stage of gastric cancer, lymph node metastasis and other various factors.

Conflict of interests

The authors declare no conflict of interests.

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