

## **The expression difference of CEA, CA19-9, CA72-4 and CA125 in patients with different staging of gastric cancer and the relationship with metastasis and recurrence.**

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### **Abstract**

**Objective:** To analyse the expression difference of Carcino-Embryonic Antigen (CEA), Carbohydrate Antigen 72-4 (CA72-4), CA19-9, and CA125 in patients with different staging of Gastric Cancer (GC) and the relationship with metastasis and recurrence.

**Methods:** 284 cases of GC patients with surgery were selected from July 2013 to June 2014 in our hospital. After follow-up of 3 y, the metastasis and recurrence of GC patients was observed. And the expressions of CEA, CA19-9, CA72-4 and CA125 antigens in GC patients with different staging were measured. The relationship of CEA, CA19-9, CA72-4 and CA125 with metastasis and recurrence was analysed.

**Results:** The positive expression rates and the mean serum levels of CEA, CA19-9, CA72-4 and CA125 in T3/T4 staging GC patients were both higher than T1/T2 staging GC patients ( $P<0.05$ ). And the positive expression rates and the mean serum levels of CEA, CA19-9, CA72-4 and CA125 antigens in T1/T2/T3 patients after surgery for 3 months were decreased than before surgery ( $P<0.05$ ). After followed-up of 3 y, the positive expression rates of CEA, CA19-9, CA72-4 and CA125 antigens of patients with metastasis and recurrence before surgery were higher than patients without metastasis and recurrence ( $P<0.05$ ).

**Conclusion:** The expressions of CEA, CA19-9, CA72-4 and CA125 antigens in patients with gastric cancer could be related with different staging, which would be the reference index for the diagnosis and prognosis of gastric cancer.

**Keywords:** Gastric cancer, Carcino-embryonic antigen, Carbohydrate antigen, Recurrence, Tumor staging.

*Accepted on October 5, 2017*

### **Introduction**

Gastric Cancer (GC) is one of common malignant tumor in alimentary system in our country. The incidence rate and fatality rate are relatively high, which threat economic development and health of residents in out of country [1]. At present, iconography, endoscope and pathological examination are the main diagnostic methods in clinic. But early manifestations of GC is not obvious, including abdominal pain, appetite decreases, nausea and abdominal distention, there are relatively high omission diagnostic rate and misdiagnosis rate. In our country, diagnostic rate in early stage of GC is only about 10% [2]. When patients have obvious clinical symptoms, the conditions have progressed to middle-advanced stage, missing the best time for treatment, which will cause poor prognosis [3]. Therefore, early treatment and diagnosis are the key strategies for promoting GC prognosis and treatment effects.

In recent years, combing some certain GC specificity makers in clinic to be assistant diagnostic methods, including expressions of tumor specific antigen, such as CEA, CA72-4, CA19-9 and

CA125, thus, promoting accuracy and sensitivity of early clinical diagnosis, effects monitor and prognosis judge of GC furtherly [4-6]. This study provides a certain theoretical reference for clinical working by detecting expressions and changes of CEA, CA72-4, CA19-9 and CA125 of serum in 284 GC patients.

### **Clinical Data and Methods**

#### ***Main instruments and reagents***

Cobas® e411 full automatic electrochemical luminescent instrument was bought from American Roche Diagnostics GmbH. CEA, CA72-4, CA19-9 and CA125 quantitative detection kit from American Roche Diagnostics GmbH.

#### ***Clinical data of patients***

Ethical approval was given by the medical ethics committee of Huangshi Central Hospital of Edong Health Group with the following reference number: 2013006. This study selected 284 GC patients who had received surgery in gastrointestinal

surgery department or oncology department in our hospital from July, 2013 to June, 2014, of which, there were 151 male patients and 133 female patients. The age was from 22 to 79 y old. The average age was  $51.86 \pm 7.39$  y old. The course was from 3 months to 17 y. The average course was  $4.97 \pm 5.51$  y. According to the location of GC, there were 91 cancer in cardia and fundus of stomach, 47 gastric body cancer, 146 gastric antral cancer. According to condition progress, 36 patients had early GC, 248 patients had GC in progressive stage. According to TNM pathological staging of International Union against Cancer, there were 113 cases in T1 stage, 70 cases in T2 stage, 69 cases in T3 stage and 32 cases in T4 stage. All patients after admitting hospital were given radical gastrectomy or palliative surgery, gastroscopy examination and pathological examination before surgery. The viscera carcinoma is excluded. All patients after surgery were given follow-up from 6 months to 3 years.

### Examination methods and diagnostic criteria

**Blood sample collection:** all subjects were given 3 to 5 ml vein blood sample collection from cubital veins in emptiness in the morning, given centrifugation. The serum was separated. Then it is stored at  $-80^{\circ}\text{C}$  for prepared application.

**ECLIA:** this study fetched reagents and sample from refrigerator, then placed at room temperature for 30 min. Giving full mixing after dissolution for standby application. Samples before detection, monoclonal antibody of biotinylation anti-CEA, CA72-4, CA19-9 and CA 125 submit were mixed with Ru markers anti-CEA, CA72-4, CA19-9 and CA 125 submit of another location monoclonal antibody in reaction systems, which form double-antibody sandwich antigen and antibody compounds. Then magnetic particle wrapped by streptavidin were added, under the effects of magnetic field, catching magnetic particles of antigen and antibody compounds which had absorbed to electrode, and various free ingredients were absorbed and abandoned. After

compression, optical signal produced, its intensity was proportional to CEA, CA72-4, CA19-9, CA125 level in a certain range of detection samples.

**Judge criteria:** CEA:  $\leq 3.4$  ng/ml; CA72-4:  $\leq 6.9$  U/ml; CA19-9:  $\leq 27$  U/ml; CA125:  $\leq 35$  U/ml. If it higher than this critical value, can be positive.

### Curative judge

**Recurrence:** observe new swelling by gastroscope and identify existence of malignant tumor cells by pathological examination.

**Metastasis:** there were new cancer focus beyond regional lymph nodes, including remote visceral metastasis, positive cytologic examination of BLAF in abdominal cavity, peritoneal metastasis, which had been identified by color ultrasound, CT, PET-CT and cytologic examination etc.

### Statistical management

These data used SPSS 19.0 software to do management. Measurement data was represented by average value  $\pm$  standard deviation ( $\bar{x} \pm s$ ). Using t-test to do comparison between groups, variance analysis to do comparison within groups. Enumeration data represented by percentage and given  $\chi^2$  test. Average value in multiple groups using variance analysis.  $P < 0.05$ , there were statistical differences.

### Results

#### Expressions of tumor markers of patients in different TNM staging

According to clinical data and detection results of patients, it showed CEA, CA72-4, CA19-9, CA125 positive expression rate and the average level higher than patients in T1 and T2 stage, there were statistical differences (Table 1).

**Table 1.** Expressions of tumor markers of patients in different TNM staging.

TNM	n	CEA		CA72-4		CA19-9		CA125					
		(Case)	Positive rate	Average (ng/ml)	value	Positive rate	Average (U/ml)	value	Positive rate	Average value (U/ml)			
T1/T2	183	39 (21.31)		$2.31 \pm 1.24$	6 (3.29)		$9.86 \pm 2.75$	14 (7.65)		$11.42 \pm 2.76$	31 (16.94)		$3.76 \pm 1.04$
T3/T4	101	36 (35.64)*		$3.72 \pm 1.53^{\dagger}$	28 (27.72)*		$38.01 \pm 4.47^{\dagger}$	30 (29.70)*		$39.15 \pm 3.87^{\dagger}$	47 (46.53)*		$8.45 \pm 1.19^{\dagger}$
Total	284	75 (26.41)		$2.90 \pm 1.52$	34 (11.97)		$22.23 \pm 5.11$	44 (15.49)		$24.78 \pm 4.06$	78 (27.46)		$5.77 \pm 0.96$

Note: \*compared with T1 and T2 groups,  $P < 0.05$ .

#### Expression changes of CEA, CA72-4, CA19-9, CA125 before and after surgery of GC patients

Because most GC patients in T4 cannot finish radical ectomy surgery, there was some residue primary focus or metastatic focus, which will influence expression level of tumor markers. The observation objects of this study were GC patients in T1, T2, T3 stages. 252 patients received GC radical resection

surgery. It began in the third week after surgery. They were given chemotherapy for three months for iconography and tumor markers examination. There were no death patients within three months, of which, 7 patients had recurrence and metastasis. Compared positive expression rate and expression changes of CEA, CA72-4, CA19-9 and CA125 before and in three months after surgery of GC patients. The structure

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showed that positive expression rate and expression changes of CEA, CA72-4, CA19-9, CA125 decreased obviously compared with after surgery of GC patients, there were statistical differences, P<0.05; in addition, CA72-4, CA19-9, CA125

average level decreased obviously of patients compared with before surgery, there were statistical differences, P<0.05. But CEA average expression level before and after surgery of patients had no statistical differences, P>0.05 (Table 2).

**Table 2.** Expression condition comparison of tumor markers before and after surgery of GC patients.

	n	CEA		CA72-4		CA19-9		CA125			
		(Case)	Positive rate	Average (ng/ml)	value	Positive rate	Average value ml)	Positive rate	Average (U/ml)	value	Positive rate
Before surgery	252	57 (22.62)	2.78 ± 1.32	22 (8.73)	17.41 ± 2.87	29 (11.51)	19.83 ± 3.92	60 (23.81)	4.15 ± 1.26		
After surgery	252	21 (8.33)*	2.21 ± 0.78	13 (5.16)	6.36 ± 1.94*	13 (5.16) *	9.27 ± 1.46*	27 (10.71) *	2.79 ± 0.87*		

Note: \*compared with before surgery group, P<0.05.

**Relevance analysis of expression, recurrence and metastasis of CEA, CA72-4, CA19-9, CA125**

After following-up of three years, 129 patients had metastasis or recurrence by iconography and endoscope, of which, 83 patients died. Through analyzing expressions of CEA, CA72-4, CA19-9, CA125 in serum of GC patients before surgery, metastatic and recurrence conditions following-up for three

years, it showed that positive expression rate of CEA, CA72-4, CA19-9, CA125 in serum of patients with recurrence and metastasis before surgery higher than non-metastasis and recurrence obviously, there were statistical differences, P<0.05. It showed recurrence and metastasis risk of patients with positive CEA, CA72-4, CA19-9 and CA125 in serum before surgery increased obviously (Table 3).

**Table 3.** Relevance of expression positive rate, recurrence and metastasis of tumor markers before surgery of GC patients ( $\chi \pm s$ ).

n	CEA		CA72-4		CA19-9		CA125		
	(case)	Positive rate	Average value (ng/ml)	Positive rate	Average value (U/ml)	Positive rate	Average value (U/ml)	Positive rate	Average value (U/ml)
Without recurrence and metastasis	155	22	133	5	150	12	143	16	139
		-14.19	-85.81	-3.23	-96.77	-7.74	-92.26	-10.32	-89.68
with	129	53	76	29	100	32	97	62	67
		(41.09)*	(58.91)*	(22.48)*	(77.52)*	(24.81)*	(75.19)*	(48.06)*	(51.94)*
Total	284	75	209	34	250	44	240	78	206

Note: \*compared with group which had no recurrence and metastasis, P<0.05.

**Discussion**

At present, the study for GC in clinic and experiment gets more and more profound, but the prognosis of GC is still not optimistic. The main reason may be related to low diagnostic rate of GC. For example, this study included 284 GC patients in total, only 36 patients diagnosed as early progressed to GC in middle-advanced stage. In recent years, with the development of molecular biology, more and more studies begin to aim at tumor molecular markers detection and discussion. Whatever portability, sensitivity of detection, reception degree of patients, serum detection has relatively high development potential.

CEA belongs to soluble acid glycoprotein, is a kind of broad spectrum serum markers, which originate from endoderm. It has high malignant tumor expressions. CEA positive expression rate is high in some benign tumors and other endoderm lesions. Therefore, CEA isn't the specific markers of

GC [7]. CA72-4 belongs to glycosingolipid, is a kind of relatively specific markers antigen of gastrointestinal tract and ovarian tumor. CA72-4 expression of GC patients about 85% to 95% increase. In GC patients, the sensitivity of CA72-4 is relatively high, which can be one of reliable indexes for GC diagnosis [8,9]. CA19-9 is a kind of monocyanate, it exists in serum in the form of saliva mucoprotein, and combines with tumor cells in gastrointestinal tract by specificity [10]. In clinic, for short of iconography and pathological examination support, this study usually selects dynamic monitoring for CA19-9 serum expression level [11]. If CA19-9 expression of patients increases continuously, the chance of malignant lesions is relatively high. CA 125 has high expression in ovarian cancer cells, but has also relatively high expression in serum of patients with endometrial cancer and tumor in alimentary tract [12-15]. There are studies point out that CA 125 has close relations with GC recurrence.

In general, serum tumor markers expression of most tumor patients in T3 or T4 in clinic higher than T1 or T2 [16-19]. In this study, CEA, CA72-4, CA19-9 and CA125 positive expression rate of T3 or T4 patients and its average expression level all higher than T1 or T2 patients ( $P<0.05$ ). And serum CEA, CA72-4, CA19-9 and CA125 of GC patients in T1, T2 and T3 decrease obviously in three months after surgery, its positive expression rate and average expression level lower than before surgery ( $P<0.05$ ). But with the progress of disease, CEA, CA72-4, CA19-9 and CA125 in serum will increase again. After three years' following-up, CEA, CA72-4, CA19-9 and CA125 positive expression rate in serum of patients with recurrence and metastasis all higher than patients without recurrence and metastasis obviously ( $P<0.05$ ). It shows we can predict recurrence and metastasis risk of patients according to detection of expression level of serum tumor markers after surgery. The rise of serum tumor markers will be in advance about 2 to 3 months comparing with symptoms. Therefore, it can be reliable indexes for monitoring GC recurrence or metastasis. Furthermore, the higher the expression of serum tumor markers of patients before surgery, the higher the recurrence and metastasis risk.

In conclusion, serum CEA, CA72-4, CA19-9 and CA125 expression level and positive expression rate of GC patients in T3 or T4 higher than T1 or T2. Serum CEA, CA72-4, CA19-9 and CA125 positive expression rate of patients with recurrence and metastasis all higher than patients without recurrence and metastasis. The higher the expression level of serum tumor markers before surgery, the higher the recurrence and metastasis risk after surgery. Therefore, CEA, CA72-4, CA19-9 and CA125 can be important detection indexes for GC assistant diagnosis and prognosis judge.

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