RESEARCH ARTICLE

Preoperative Serum CEA and CA19-9 in Gastric Cancer - a Single Tertiary Hospital Study of 1,075 Cases

Yang-Chun Zhou, Hai-Jian Zhao, Li-Zong Shen*

Abstract

To evaluate the clinical impact of preoperative serum CEA and CA19-9 on resectable gastric cancer (GC), a total of 1,075 consecutive cases with gastric adenocarcinoma were obtained retrospectively from January 2012 and December 2013 in a single tertiary hospital, and the relationships between serum CEA, CA19-9 and clinicopathologic features were investigated. Positive preoperative serum rates of CEA and CA19-9 were 22.4% and 12.3% respectively, levels significantly correlating with each other and depth of invasion, lymph node involvement, pTNM and stage. The CEA level also presented a remarkable association with lymphovascular invasion. Both CEA and CA19-9 positivity significantly and positively correlated with depth of invasion, nodal involvement, pTNM stage, lymphovascular invasion, tumor size and tumor location. Stratified analyses according to gender or tumor location showed preoperative CEA or CA19-9 had different associations with clinicopathologic features in different gender subgroups or location subgroups. Preoperative serum CA19-9 positivity may be more meaningful for tumor size rather than CEA. In conclusion, preoperative serum CEA and CA19-9 correlate with disease progression of GC, and may have applications in aiding more accurate estimation of tumor stage, decision of treatment choice and prognosis evaluation.

Keywords: Gastric cancer - tumor markers - CEA, CA19-9 - clinicopathologic feature

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Introduction

In spite of the fact that the incidence and mortality rate of gastric cancer (GC) have declined markedly over the past decades in western and eastern countries, gastric cancer remains one of the most common and lethal malignancies worldwide (Jemal et al., 2011). The incidence of early gastric cancer is rather low, and most patients are diagnosed at advanced stage and of poor prognosis in China (Chen et al., 2008). Endoscopy and other imaging technology have improved the detection of GC.

Tumor markers (TMs) are circulating substances that can be measured quantitatively and that have a causal relationship with malignant diseases (Sikaroodi., et al 2010) and tumor markers are often used for early detection of various carcinomas and during follow-up after surgery (Choi et al., 2006; Huang et al., 2014). There are no specific TMs for gastric cancer by far, and carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) are the most commonly used alternatives (Fan et al., 2011; Dilege et al., 2010; Shimada et al., 2014). Both CEA and CA19-9 have shown little benefit to screen early primary GC in the general population due to low sensitivity and specificity, they mainly be used for the monitoring of tumor recurrence and used as prognostic factors (Park et al., 2008; Marrelli et al., 1999; Shimada et al., 2014). These two markers are currently widely measured in patients with GC preoperatively (Dilege et al., 2010; Fan et al., 2011; Shimada et al., 2014), however, their clinical correlation with clinicopathologic features remains controversial (Huang et al., 2014; Polat et al., 2014). To reevaluate the clinical impact of preoperative serum CEA and CA19-9 on resectable GC, we collected the clinical data of large volume of patients with GC in a single tertiary hospital, and investigated the correlation of preoperative serum CEA, CA19-9 with clinicopathologic features in the present retrospective study.

Materials and Methods

Patient population

There were consecutive 1313 patients diagnosed with gastric adenocarcinoma between January 2012 and December 2013 at the Department of General Surgery, First Affiliated Hospital, Nanjing Medical University, China. All patients underwent surgical treatment with curative intent for GC, and were diagnosed pathologically according to the American Joint Committee on Cancer (AJCC) criteria. The curative intent means that the surgical approaches are performed with the goal of achieving complete tumor resection. The medical records

*Division of Gastrointestinal Surgery, Department of General Surgery, First Affiliated Hospital, Nanjing Medical University, Nanjing, Jiangsu, China *For correspondence: shenlz@163.com.*

of these patients, including demographic, laboratory, pathologic, and treatment-related variables, were collected retrospectively. Patients who underwent neoadjuvant chemotherapy or radiotherapy, and patients with other malignancies before surgery were excluded from the analysis. Therefore, 1075 patients were enrolled in this study, and the patient characteristics were listed in Table 1. This study was approved by the Nanjing Medical University Institutional Review Board. Written consent was given by the patients for their information and samples to be stored in the hospital database and used for research. This study was also in compliance with the Helsinki Declaration.

Preoperative serum CEA and CA19-9 determination

Preoperative serum CEA and CA19-9 levels were determined by electrochemiluminescence immunoanalyzer (Roche, Cobas e602, Germany). Blood sample were measured within one week preoperatively. The cut-off levels of serum tumor markers were 4.7 ng/ml for CEA and 39.0 U/ml for CA19-9 according to the manufacturer's instructions.

Statistical analysis

Statistical analyses were carried out by SPSS for Windows, version 20.0 (Statistical Package for the Social Sciences, SPSS, Inc., Chicago, IL). The association between preoperative serum CEA or CA19-9 positivity and clinicopathological features was analyzed by Kruskal-Wallis test. Qualitative data were compared with Pearson's chi-squared test. A P value less than 0.05 was considered statistically significant.

Results

A total of 241 (22.4%) patients were positive for serum CEA (range = 4.7~1000 ng/mL) and 132 (12.3%) patients were seropositive for CA19-9 (range = 39.0~1000 U/mL). The distributions of serum CEA, CA19-9 were skewed (Figure 1), and their distributions according to pathologic T classification, N classification, TNM stage and lymphovascular invasion were shown in Figure 2 and Figure 3 respectively. There was significant associations of preoperative serum CEA level with depth of tumor invasion, lymph node involvement, pTNM stages and lymphovascular invasion ($p<0.001$, $p=0.005$, $p<0.001$ and $p=0.005$, respectively) (Figure 2). Similarly, preoperative serum CA19-9 level presented remarkable association with depth of tumor invasion, lymph node involvement and pTNM stages ($p<0.001$, $p=0.012$ and

Table 1. Clinicopathologic Features of 1,075 Patients with Gastric Cancer According to CEA and CA19-9

Features	N(%)	CEA(-) (N=834)	CEA(+) (N=241)(%)	P	CA19-9(-) (N=943)	CA19-9(+) (N=132) (%)	P
Age(y)	60.4±11.4						
<60	466 (43.3)	374	92(19.7)	0.066	422	44 (9.4)	0.013
≥60	609 (56.7)	460	149(24.5)		521	88 (14.5)	
Sex				0.003			0.868
Male	764 (71.1)	574	190(24.9)		671	93 (12.2)	
Female	311 (28.9)	260	51(16.4)		272	39 (12.5)	
Tumor size				<0.001			<0.001
≥3	710 (66.0)	513	197(27.8)		588	122 (17.2)	
<3	365 (34.0)	321	44(12.1)		355	10 (2.7)	
Tumor location				0.005			0.019
Upper third	344 (32.0)	249	95(27.6)		290	54 (15.7)	
Middle and lower third	731 (68.0)	585	146(20.0)		653	78 (10.7)	
Pathologic T classification				<0.001			<0.001
T1	260 (24.2)	241	19(7.3)		253	7 (2.7)	
T2	123 (11.4)	98	25(20.3)		117	6 (4.9)	
T3	167 (15.6)	135	32(19.2)		150	17 (10.2)	
T4[a]	512 (47.6)	351	161(31.5)		414	98 (19.1)	
T4[b]	13 (1.2)	9	4(30.8)		9	4 (30.8)	
Pathologic N classification				0.001			<0.001
N0	410 (38.1)	354	56(13.7)		389	21 (5.1)	
N1	171 (15.9)	133	38(22.2)		155	16 (9.4)	
N2	203 (18.9)	159	44(21.7)		173	30 (14.8)	
N3[a]	216 (20.1)	138	78(36.1)		174	42 (19.4)	
N3[b]	75 (7.0)	50	25(33.3)		52	23 (30.7)	
Pathologic stage (pTNM)				<0.001			<0.001
I	302 (28.1)	271	31(10.3)		295	7 (2.3)	
II	235 (21.9)	192	43(18.3)		215	20 (8.5)	
IIIA	129 (12.0)	98	31(24.0)		113	16 (12.4)	
IIIB	166 (15.4)	127	39(23.5)		136	30 (18.1)	
IIIC	233 (21.7)	144	89(38.2)		178	55 (23.6)	
IV	10 (1.0)	2	8(80.0)		6	4 (40.0)	
Lymphovascular invasion				0.002			0.008
Absence	801 (74.5)	640	161(20.1)		715	86 (10.7)	
Presence	274 (25.5)	194	80(29.2)		228	46 (16.8)	

p<0.001, respectively), however, it had no association with lymphovascular invasion (p=0.227) (Figure 3).

The correlations of preoperative serum CEA or CA19-9 positivity with clinicopathologic features were summarized in Table 1. Both CEA and CA19-9 positivity significantly and positively correlated with depth of invasion, nodal involvement, pTNM stage and lymphovascular invasion (p<0.05). Furthermore, both CEA and CA19-9 positivity were associated with tumor size and tumor location (p<0.05). CEA and CA19-9 had more positivity in patients with larger tumor or tumors located in upper third of the stomach. However, serum CEA had higher positivity in male patients than in female patients (p=0.003), while serum CA19-9 had higher positivity in older patients (p=0.013). Serum CEA positivity was significantly correlated with serum CA19-9 positivity levels (p=0.000) (Table 2).

We performed further stratified analysis on correlation of preoperative serum CEA or CA19-9 positivity with clinicopathological features according to gender or tumor location. As listed in Table 3, the ratio of male to female was 2.46:1 in this study, and male patients were older than female patients (p<0.001). As in the whole patients, preoperative serum CEA positivity in female ones correlated with tumor location (p<0.001), however, this correlation did not exist in male patients (p=0.257) (Table 4A). Conversely, the association between CEA positivity and lymphovascular invasion in male patients was consistent with that in the whole patients (p=0.005), while CEA positivity did not correlate with lymphovascular invasion in female ones (p=0.115) (Table 4A). As shown in Table 4B, preoperative serum CA19-9 positivity in female patients correlated with age (p=0.014) and lymphovascular invasion (p=0.001), while these correlations did not occur in male patients, and CA19-9 positivity in male ones had slight association with tumor location (p=0.049) other than in female patients (p=0.205). Other associations between CEA or CA19-9 positivity and other characteristics in male or female patients were consistent with that in whole patients.

In this study the percentage of the upper third GC was 32%. In the whole patients, preoperative serum CEA positivity was associated with gender and lymphovascular invasion, and this association did exist in the middle and lower third GC (p<0.001, p<0.001, respectively). However, CEA positivity did not correlate with gender (p=0.919) and lymphovascular invasion in the upper third GC (p=0.997) (Table 5A). In the whole patients, preoperative serum CA19-9 positivity correlated with age of patients, but this correction disappeared both in the upper third subgroup (p=0.210) and the middle

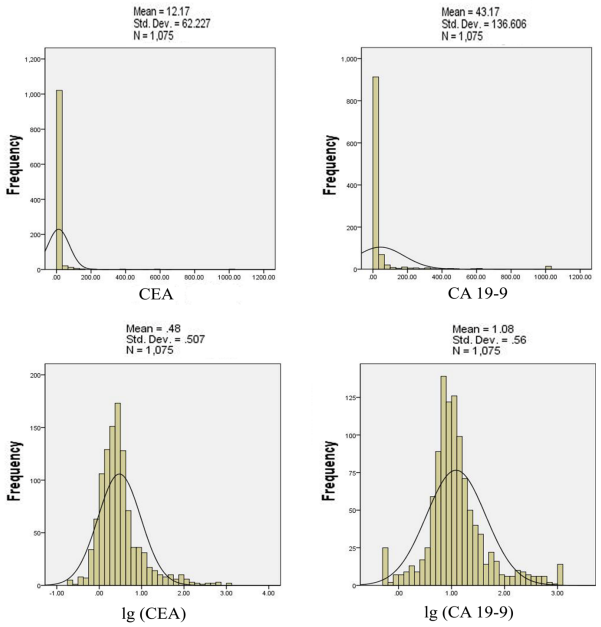

Figure 1. Distribution and Logarithm of Preoperative Serum CEA, CA19-9 levels in Patients with Gastric cancer. Logarithmic transformation was necessary because of the extreme skewness of the data

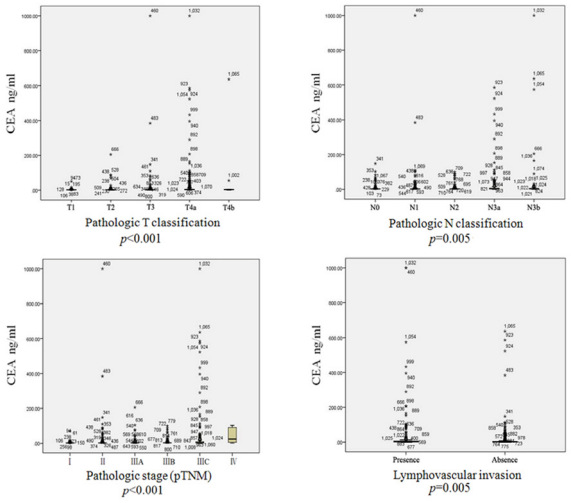

Figure 2. Preoperative CEA Levels According to Pathologic T Classification, Pathologic N Classification, Pathologic Stage (pTNM), Lymphovascular Invasion (Box and Whisker Plot). The Kruskal-Wallis test revealed a significant correlation between preoperative CEA levels and these features of gastric cancer

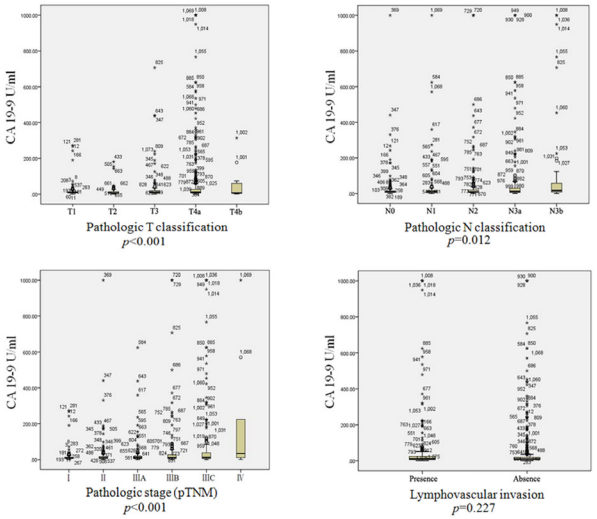

Figure 3. Preoperative CA19-9 Levels According to Pathologic T Classification, Pathologic N Classification, Pathologic Stage (pTNM), Lymphovascular Invasion (Box and Whisker Plot). The Kruskal-Wallis test revealed a significant correlation between preoperative CA19-9 levels and these features of gastric cancer, but lymphovascular invasion

Table 2. Correlation of Preoperative Serum CEA Positivity and CA19-9 Positivity in Patients with GC

	CEA(+)	CEA(-)	χ^2	P
CA19-9(+)	60	72	45.911	<0.001
CA19-9(-)	181	762		

Table 3. Age and Gender Distributions of Patients with GC

Age (y)	Male (N=764)	Female (N=311)	χ^2	P
<60	305	161	12.632	<0.001
≥60	459	150		

and lower subgroup (p=0.096). Unlike the whole patients, CA19-9 positivity did not present significant association with lymphovascular invasion in the upper third group (p=0.07), while the relationship did exist in the middle and lower group (p=0.034) (Table 5B). Other associations between CEA or CA19-9 positivity and other characteristics in patients with the upper third GC or the middle and lower third GC were consistent with that in whole patients.

The percentage of both positivity for CEA and negativity for CA19-9 was 16.8%, the percentage of both negativity for CEA and positivity for CA19-9 was 6.7%, the percentage of positivity for both CEA and CA19-9

Table 4A. Correlation between CEA Positivity and Clinicopathological Features of GC According to Gender

Characteristics	Male			Female		
	CEA(-) (N=574)	CEA(+) (N=190)	P	CEA(-) (N=260)	CEA(+) (N=51)	P
Tumor location			0.257			<0.001
Upper third	177	67		72	28	
Middle and lower third	397	123		188	23	
Lymphovascular invasion			0.005			0.155
Absence	442	127		198	34	
Presence	132	63		62	17	

Table 4B. Correlation between CEA Positivity and Clinicopathological Features of GC According to Gender

Characterics	Male			Female		
	CA19-9(-) (N=671)	CA19-9(+) (N=93)	P	C CA 19-9(-) (N=272)	CA 19-9(+) (N=39)	P
Tumor location			0.257			<0.001
Upper third	177	67		72	28	
Middle and lower third	397	123		188	23	
Lymphovascular invasion			0.005			0.155
Absence	442	127		198	34	
Presence	132	63		62	17	

Table 5A. Correlation between CEA Positivity and Clinicopathological Features of GC according to Tumor Locations

Factors	Upper third			Middle and lower third		
	CEA(-) (N=249)	CEA(+) (N=95)	P	CEA(-) (N=585)	CEA(+) (N=146)	P
Sex			0.919			<0.001
Male	177	67		397	123	
Female	72	28		188	23	
Lymphovascular invasion			0.997			<0.001
Absence	194	74		446	87	
Presence	55	21		139	59	

Table 5B. Correlation between CEA Positivity and Clinicopathological features of GC According to Tumor Locations

Factors	Upper third			Middle and lower third		
	CEA(-) (N=249)	CEA(+) (N=95)	P	CEA(-) (N=585)	CEA(+) (N=146)	P
Sex			0.919			<0.001
Male	177	67		397	123	
Female	72	28		188	23	
Lymphovascular invasion			0.997			<0.001
Absence	194	74		446	87	
Presence	55	21		139	59	

Table 6. Clinicopathologic Features of Patients with GC According to the Combination of CEA and CA19-9

Features	CEA(+)/CA19-9(-) (N=181)	CEA(-)/CA19-9(+) (N=72)	CEA(+)/CA19-9(+) (N=60)	P1	P2
Age(y)				0.521	0.064
<60	67	19	25		
≥60	114	53	35		
Sex				0.401	0.296
Male	145	48	45		
Female	36	24	15		
Tumor size				0.007	0.719
≥3	141	66	56		
<3	40	6	4		
Tumor location				0.615	0.365
Upper third	73	32	22		
Middle and lower third	108	40	38		
Pathologic T classification				0.006	0.022
T1	19	7	0		
T2	21	2	4		
T3	28	13	4		
T4a	111	48	50		
T4b	2	2	2		
Pathologic N classification				0.001	0.01
N0	53	18	3		
N1	30	8	8		
N2	32	18	12		
N3a	52	16	26		
N3b	14	12	11		
Pathologic stage (pTNM)				<0.001	0.002
I	31	7	0		
II	37	14	6		
IIIA	25	10	6		
IIIB	28	19	11		
IIIC	56	22	33		
IV	4	0	4		
Lymphovascular invasion				0.329	0.443
Absence	124	49	37		
Presence	57	23	23		

*P1: CEA(+)/CA19-9(-) group vs CEA(+)/CA19-9(+) group, P2: CEA(-)/CA19-9(+) group vs CEA(+)/CA19-9(+) group

accounted for 5.6%, and the remaining with negativity for both CEA and CA19-9 was 70.9%. As shown in Table 6, there was significant difference of depth of tumor invasion, lymph node involvement and pTNM stage between single positivity group for CEA or CA19-9 and double positivity group, which confirmed that preoperative serum CEA or CA19-9 positivity did relate to these clinicopathologic features. The tumor size presented remarkable difference between CEA(+)/CA19-9(-) group and CEA(+)/CA19-9(+) group, indicating that preoperative serum CA19-9 positivity may be more meaningful for tumor size.

Discussion

Tumor markers (TMs) mainly arise from primary neoplasm and occasionally from other organs influenced by the cancer (Seregni et al., 2001). TMs reflect the cellular, biochemical, molecular, and genetic alterations caused by cancer, and they are widely used in early diagnosis, disease monitoring and the assessment of treatment effects (Duffy, 2007; Sikaroodi et al., 2010; Shimada et al., 2014). CEA is an oncofetal protein involved in cell adhesion and the inhibition of apoptosis, which was first detected by Gold and Freedman in 1965 (Gold and Freedman, 1965). Inflammatory bowel disease, pancreatitis, liver cirrhosis, and chronic obstructive pulmonary disease can cause borderline CEA elevation. For cancer, the main clinical use of CEA is in colorectal cancer patients (Basbug et al., 2011). CA19-9 is a mucin-type glycoprotein, and its clinical use is in pancreatic cancer patients. CA19-9 is also elevated in conditions such as benign biliary tract disease and pancreatitis (Humphris et al., 2012). A few studies had been conducted to investigate the clinical significance of CEA, CA19-9 and other TMs in GC, however, their positive rates varied widely from different studies and their prognostic values were still controversial or even conflicting (Ikeda et al., 1995; Victorzon et al., 1995; Marrelli et al., 1999; Mattar et al., 2002; Ucar et al., 2008; Dilege et al., 2010; Polat et al., 2014; Xiao et al., 2014). We speculate that relatively small volume of patients and too long study interval may result in this variance (Sakamoto et al., 1996; Marrelli et al., 1999; Marrelli et al., 2001; Mattar et al., 2002; Dilege et al., 2010; Lee et al., 2013; Li et al., 2013; Han et al., 2014; Polat et al., 2014). In this present study, we reevaluated the correlation of preoperative serum CEA and CA19-9 with clinicopathologic features in large volume of patients with resectable GC in a single tertiary hospital in recent two years.

There were 1075 patients with resectable GC enrolled

in this study. The positive rates were 22.4% for CEA and 12.3% for CA19-9. The CEA positivity was consistent with that in a system review (Shimada et al., 2014), but CA19-9 positivity was relatively lower. In this study, we reconfirmed that the preoperative serum CEA level or CA19-9 level was not normal distribution. In accord with Han's report (Han et al., 2014), serum CEA positivity was significantly correlated with serum CA19-9 positivity in patients with resectable GC.

We investigated the correlation of preoperative CEA or CA19-9 with clinicopathologic features of GC through quantitative and qualitative analyses. The CEA or CA19-9 level related respectively to depth of tumor invasion, lymph node involvement, and pTNM stage significantly. The CEA or CA19-9 positivity was associated remarkably with depth of tumor invasion, lymph node involvement, pTNM stage and lymphovascular invasion respectively. However, unlike the results of quantitative analysis, the CA19-9 positivity correlated to lymphovascular invasion, which may be due to the cut-off level of CA19-9. When doubling the threshold level of serum positivity for CA19-9 to 78 U/ml, there was no significant association of CA19-9 positivity with lymphovascular invasion (p=0.280). In this study, serum CEA positivity was found to have significant associations with tumor size, which was consistent with Marrelli's reports (Marrelli et al., 1999; Marrelli et al., 2001), while CA19-9 positivity was demonstrated for the first time to have the similar association. These results indicate that preoperative serum CEA and CA19-9 correlate with advanced stage and disease progress of GC.

Interestingly, we found the significant associations of serum CEA or CA19-9 positivity with age, gender of patients and tumor location. Park et al (Park et al., 2008) had demonstrated that the positive rate of serum CEA in GC correlated with patient gender, age and tumor location in whole patients with GC. Liu et al (Liu et al., 2012) investigated the prognostic significance of tumor markers in T4a gastric cancer, and found serum CEA was associated with gender and tumor location, CA19-9 with age and tumor location. However, the present study observed a good correlation between serum CEA and gender (p=0.003) or tumor location (p=0.005), rather than age (p=0.066). Moreover, serum CA19-9 presented association with age (p=0.013) and tumor location (p=0.019) rather than gender (p=0.868). Unlike Park's report, serum CEA or CA19-9 had more positivity in tumor located in upper third than in that in middle and lower third of the stomach respectively in this study, which was consistent with that in T4a GC (Liu et al., 2012). Furthermore, stratified analyses according to gender or tumor location showed that preoperative serum CEA or CA19-9 had different association with clinicopathologic features in different gender subgroups or location subgroups.

Many studies have examined the diagnostic value of the combinations of serum TMs, such as CEA, CA19-9, CA242, CA50 and CA724, in patients with gastric cancer (Ychou et al., 2000; Tian et al., 2014), and their inconsistent associations were reported. In this study, we conducted a correlation analysis to evaluate the clinical application of the combination of CEA and CA19-9 in gastric cancer patients, comparing with single positivity group for CEA or CA19-9. The combination of positivity for both CEA and CA19-9 exhibited significant association with depth of tumor invasion, lymph node involvement and pTNM stage, and showed remarkable statistical significance comparing the single CEA or CA19-9 positive group. The preoperative serum CA19-9 positivity may be more meaningful for tumor size rather than CEA.

Several limitations to this study should be acknowledged. First, patients with unresectable GC were not included in this study, and the positivity for CEA or CA19-9 in this study did not reflect the whole progress of GC. In addition, we could not obtain survival information of patients and recurrence of GC due to the newly cases, so information about the prognostic values of CEA and CA19-9 on overall survival and disease-free survival of patients with GC could not be provided.

In conclusion, the preoperative serum CEA and CA19-9 correlated with disease progression of GC, and may have application in aiding more accurate estimation of tumor stage, decision of treatment choice and prognosis evaluation. Prospective clinical studies should be planned to elucidate the clinical utility of these serum tumor markers or their combinations.

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