RESEARCH ARTICLE

Combined Detection of CEA, CA 19-9, CA 242 and CA 50 in the Diagnosis and Prognosis of Resectable Gastric Cancer

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Abstract

Our aim was to investigate the value of combined detection of serum carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9, CA 242 and CA 50 in diagnosis and assessment of prognosis in consecutive gastric cancer patients. Clinical data including preoperative serum CEA, CA 19-9, CA 242, and CA 50 values and information on clinical pathological factors were collected and analyzed retrospectively. Univariate and multivariate survival analyses were used to explore the relationship between tumor markers and survival. Positive rates of tumor markers CEA, CA 19-9, CA 242 and CA 50 in the diagnosis of gastric cancer were 17.7, 17.1, 20.4 and 13.8%, respectively, and the positive rate for all four markers combined was 36.6%. Patients with elevated preoperative serum concentrations of CEA, CA 19-9, CA 242 and CA 50, had late clinical tumor stage and significantly poorer overall survival. Five-year survival rates in patients with elevated CEA, CA 19-9, CA 242 and CA 50 were 28.1, 25.8, 27.0 and 24.1%, respectively, compared with 55.0, 55.4, 56.4 and 54.5% in patients with these markers at normal levels ($p<0.01$). In multivariate Cox proportional hazards analyses, an elevated CA 242 level was determined to be an independent prognostic marker in gastric cancer patients. Combined detection of four tumor markers increased the positive rate for gastric cancer diagnosis. CA 242 showed higher diagnostic value and CA 50 showed lower diagnostic value. In resectable gastric carcinoma, preoperative CA 242 level was associated with disease stage, and was found to be a significant independent prognostic marker in gastric cancer patients.

Keywords: Gastric cancer - carcinoembryonic antigen - CA 242 - CA 50 - diagnosis - prognosis

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Introduction

Gastric cancer is the fourth leading cause of cancer-related death worldwide (Ferlay et al., 2010). The incidence of gastric cancer has decreased alongside improving economic development over recent years. However, because gastric cancer is concealed and early symptoms are not obvious, there is often a delay in receiving treatment and the 5-year survival rate is very low. Therefore, early detection plays an important role in the optimal treatment for gastric cancer patients. Currently, endoscopy and ultrasonic and imaging technology have led to great progress in the diagnosis of gastric cancer. Additionally, the early detection of blood tumor markers has great advantages compared with other screening programs. When used in isolation, most blood tumor markers have poor specificity and sensitivity, but the combined detection of tumor markers can effectively increase the diagnostic and prognostic accuracy in gastric cancer. Many studies have examined the use of tumor markers such as CEA and CA 19-9 in gastric cancer patients. Sisik et al (2013) found that there was significant correlation of CEA and CA 19-9 values with advanced stage in gastric cancer patients. CEA and CA 19-9 are still valuable markers for the prognosis of gastric cancer patients. But few have studied the relationship between CA 242, CA 50 and gastric cancer. This paper explores the diagnostic value of the combined detection of serum CEA, CA 19-9 CA 242 and CA 50 in patients with resectable gastric cancer, and evaluates the association between levels of these markers, clinicopathologic features and prognostic information.

Materials and Methods

The study group comprised consecutive gastric cancer patients with complete recording of clinical findings and no other preoperative treatment who were admitted to Peking Union Medical College Hospital between January 2002 and December 2009. Patients who died of causes other than gastric cancer were excluded from the study. The 7th AJCC (American Joint Committee on

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Cancer) Gastric Cancer TNM Staging System was used to assess pathological stage. A control group comprised patients with gastric stromal tumor in the same period of hospitalization, who also had endoscopy results and complete clinical data available.

Four serum tumor markers were measured within 1 week prior to surgery, and detected using the Roche electrochemiluminescence instrument at the clinical laboratory of Peking Union Medical College Hospital. The normal reference values of the tumor markers were as follows: CEA ≤5.0ng/ml, CA 19-9 ≤37 U/ml, CA 242 ≤20 U/ml, CA 50 ≤15 U/ml. When using combined detection, the diagnosis was regarded as positive provided there was one positive result. The positive rate of the tumor markers was calculated as the number of patients who had levels of the marker above the cut-off value divided by the total number of patients. The positive rate of the simultaneous determination tumor markers was calculated as the percentage of patients who had elevation in any of the combined markers. Patients were followed up at regular intervals after surgery until December 2013. Survival outcome (death or not) of the patients were obtained through medical records and telephone follow-up survey with the patients.

Ethical considerations

All participants gave written informed consent. Ethical approval was provided by Peking Union Medical College Hospital.

Statistical methods

The χ^2 and the Fisher exact probabilities tests were used for categorical variables and the T-test method used to analyze the statistical significance for continuous variables. Kaplan-Meier survival curves were generated and compared with the log rank test. A multivariate Cox proportional hazards regression model was used to select significant predictors of 5-year survival. *P*-values of <0.05 were considered statistically significant. All statistical analyses were performed using SPSS® software version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

The study group comprised 181 gastric cancer patients (121 males and 60 females; average age 59.5 years), and 48 control patients (30 males and 18 females; mean age 58.6 years) with gastric stromal tumors.

Comparison of serum CEA, CA 19-9, CA 242 and CA 50 levels between study group and control group

Tumor marker values are presented as median (range) in table 1. The median values of serum CEA, CA 19-9, CA 242 and CA 50 in the gastric cancer group were higher than those in the control group ($p<0.05$).

Diagnostic significance of combination and single detection tumor markers in gastric cancer patients

The positives rates of CEA, CA 19-9, CA 242 and CA 50 measured individually were 17.67, 17.12, 20.44 and 13.81%, respectively. When evaluating two tumor markers combined, the highest positive rate was for the combination of CEA+CA 242 (30.39%). When three tumor markers were combined, the highest was the combination of CEA+CA 19-9+CA 242 (35.59%). The positive rate for all four tumor markers combined was 36.57% (Table 2).

Tumor markers, clinical pathological features and gastric cancer staging

Table 3 reports the relationship between positive serum markers and different clinical pathological variables. Positive rates of CEA, CA 19-9 and CA 242 were significantly higher when there was deep invasion in the gastric wall, lymph node involvement and more advanced tumor stage (All $p<0.05$). However, there was no correlation with deep invasion of the gastric wall and CA 50. Positive rates of CA 50 were only associated with lymph node metastasis and tumor stage. No correlation was documented between histopathologic type and any of the tumor markers (All $p>0.05$).

Relationship between clinical factors and prognosis of gastric cancer

As shown in Table 4, of the 181 patients were followed up for 5 years, univariate analysis revealed that elevated preoperative levels of four tumor markers and neutrophil-lymphocyte ratio (NLR) were all associated with poor survival rate. No association was found between older age, Lauren's classification, smoking and overall survival. Preoperative NLR value also correlated with lower 5-year

Table 2. Diagnostic significance of combination and single tumor markers

Variable	Sensitivity (%)	Combination (%)		
		CA 19-9	CA 242	CA 50
CEA	17.67	27.62	30.39	23.2
CA 19-9	17.12		24.31	25.97
CA 242	20.44			29.28
CA 50	13.81			
CEA+CA 19-9+CA 242	35.59			
CEA+CA 242+CA 50	32.04			
CEA+CA 19-9+CA 50	33.7			
CA 19-9+CA 242+CA 50	28.73			
CEA+CA 19-9+CA 242+CA 50	36.57			

Table 1. Comparison of Serum CEA, CA 19-9, CA 242 and CA 50 Levels Between The Study Group And Control Group a

Group	N	CEA	CA 19-9	CA 242	CA 50
GC	181	3.01 (0.01-1000.00)*	10.31 (0-3745.02)*	7.00 (0-538.40) *	3.81 (0-259.00)*
Con	48	2.20 (0.01-6.46)	6.26 (0-32.60)	4.30 (0-19.60)	3.19 (0.69-21.00)

*$p<0.05$, statistically significant in comparison with controls; a: Values are presented as median (range); GC: Gastric Cancer; Con: Control; CA=carbohydrate antigen; CEA=carcinoembryonic antigen

Table 3. Relationship Between CEA, CA 19-9, CA 242, CA 50 and Clinical Pathological Characteristics

Variable	Depth of invasion			Lymph node metastasis			Lauren histotype			Tumor stage		
	T1+T2 (64)	T3+T4 (117)	*P*-value	Yes (106)	No (75)	*P*-value	Intestinal (83)	Diffuse-mixed (98)	*P*-value	I+II (99)	III+IV (82)	*P*-value
CEA			0.005			0.002			0.8			0.002
≥5 ng/ml (32)	4	28		27	5		16	16		9	23	
<5 ng/ml (149)	60	89		79	70		68	81		90	59	
CA 19-9			0.002			0.003			0.66			<0.001
≥37 U/ml (31)	3	28		26	5		16	15		7	24	
<37 U/ml (150)	61	89		80	70		68	82		92	58	
CA 242			0.031			0.029			0.389			0.013
≥20 U/ml (37)	7	30		28	9		20	17		13	24	
<20 U/ml (144)	57	87		78	66		64	80		86	58	
CA 50			0.051			0.01			0.634			0.002
≥15 U/ml (25)	4	21		21	4		10	15		6	19	
<15 U/ml (156)	60	96		85	71		74	82		93	63	

Table 5. Cumulative 5-Year Survival in Gastric Cancer Patients

	No. cases	5-year cumulative survival (%)	*P*-value
CEA (ng/ml)			0.001
≥5	32	28.1	
<5	149	55	
CA 19-9 (U/ml)			<0.001
≥37	31	25.8	
<37	150	55.3	
CA 242 (U/ml)			<0.001
≥20	37	27	
<20	144	56.3	
CA 50 (U/ml)			<0.001
≥15	25	24	
<15	156	54.5	
Tumor stage			<0.001
I and II	99	70.7	
III and IV	82	25.6	
Lymphatic invasion			<0.001
No	75	76	
Yes	106	32.1	
Depth of invasion			<0.001
T1+T2	64	81.3	
T3+T4	117	33.3	

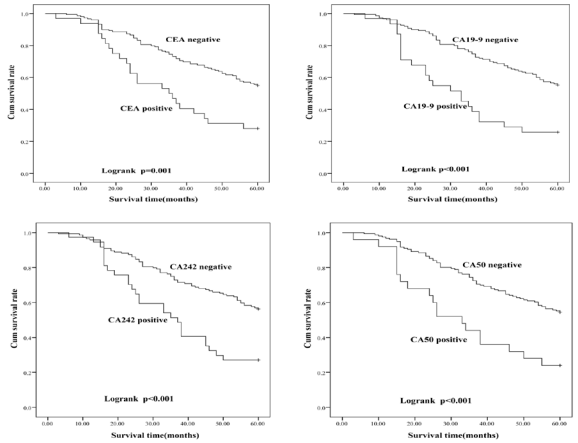

Figure 1. Survival Outcomes for Tumor Markers CEA, CA 19-9, CA 242 and CA 50. Statistical significance was measured by the logrank test. CA=carbohydrate antigen; CEA=carcinoembryonic antigen

Table 4. Relationship Between Clinical Factors and Gastric Cancer Prognosis in the Univariate and Multivariate Analyses

Variable	Univariate			Multivariate		
	OR	95%CI	*P*-value	OR	95%CI	*P*-value
Age (years)						
≥65	1.41	0.93-2.14	0.11			
<65						
Smoking						
Yes	1.35	0.90-2.04	0.16			
No						
Lauren type						
Intestinal	1.04	0.68-1.57	0.87			
Diffuse						
CEA (ng/ml)						
≥5	2.25	1.40-3.61	0.001	0.27		
<5						
CA 19-9 (U/ml)						
≥37	2.58	1.60-4.16	<0.001	0.88		
<37						
CA 242 (U/ml)						
≥20	2.31	1.47-3.65	<0.001	1.78	1.13-2.82	0.01
<20						
CA 50 (U/ml)						
≥15	2.5	1.50-4.15	<0.001			0.19
<15						
N/R						
≥2.5	1.68	1.11-2.55	0.015			0.06
<2.5						
Tumor stage						
I and II						
III and IV	4.76	3.04-7.45	<0.001	2.39	1.49-3.84	<0.001
Lymphatic invasion						
No						
Yes	4.59	2.73-7.72	<0.001	3.01	1.75-5.17	<0.001
Depth of invasion						
T1+T2						
T3+T4	5.48	2.98-10.07	<0.001	3.57	1.89-6.74	<0.001

*CA, carbohydrate antigen; CEA, carcinoembryonic antigen; CI, confidence interval; NLR, neutrophil/lymphocyte ratio; OR, odds ratio

survival rate with single factor analysis.

In the multivariate analysis, lymph node metastasis and serosal invasion were important prognostic markers in gastric cancer patients. However, only preoperative serum CA 242 level >20 U/ml was correlated with poor survival rate (p=0.01). The Cox proportional hazards regression analysis showed that patients with elevated levels of CA 242 had a 1.78-fold (95% confidence interval 1.13–2.82) higher risk of death than patients with normal CA 242 levels.

Survival curves of patients according to CEA, CA 19-9, CA 242 and CA 50 preoperative positivity are shown in Figure 1. A significant difference in survival rates was observed for each of the four markers. Five-year survival rates in patients with elevated CEA, CA 19-9, CA 242 and CA 50 were 28.12, 25.83, 27.02 and 24.05%, respectively, compared with 55.01, 55.37, 56.36, and 54.51% in patients with these markers at normal levels ($p<0.01$). Patients with elevated levels of CEA, CA 19-9, CA 242 and CA 50 displayed poorer overall survival rates than those negative for these markers (All $p<0.01$). The 5-year survival rates were longer in patients with clinical stage I or II than in patients at stage III or IV ($p<0.001$), in patients with no serosal invasion ($p<0.001$), and in patients without lymph node metastasis ($p<0.001$) (Table 5).

Overall, the results indicate that the preoperative serum CA 242 value can serve as an independent prognostic marker for gastric cancer patients. CEA, CA 19-9 and CA 50 did not achieve statistical significance in the multivariate Cox regression model ($p>0.05$) (Table 4).

Discussion

Tumor markers are antigens and biologically active substances produced by tumor cells when oncogene expression is abnormal. Normal tissue and benign lesions produce low levels or none of these markers, reflecting the changes in related gene expression during the process of tumor progression.

Tumor markers are widely used in early diagnosis, disease monitoring and the assessment of treatment effects. Detection of tumor markers has become routine in gastric cancer. The ideal tumor marker has high sensitivity and specificity, with reliable methods for detection. Unfortunately, the ideal tumor marker to detect gastric cancer in the early period is not thus far identified. The findings of this study suggest that the combined detection of tumor markers can improve the initial positive rate for gastric cancer. Tumor markers correlated with tumor clinical pathological features such as serosal invasion and lymph node metastasis, and may also have application in aiding more accurate prognosis.

Different studies have reported that the rates of these markers vary widely, for example 11.1–44% for CEA (Marrelli et al., 2001; A.M. et al., 2006; Ucar et al., 2008; He et al., 2013), 5.6–50% for CA 19-9 (Ychou et al., 2000; Hwang et al.,2004; A.M. et al., 2006; Bagaria et al., 2013), 11.1–54.7% for CA 242 (A.M. et al., 2006; Zhu et al., 2012; Li et al., 2013; Yu et al., 2013), and 24–41% for CA 50 (Kuusela et al., 1987; Nilsson et al., 1992; Mittal et al., 2013). In the present study, we found tumor markers in these ranges.

We compared the serum levels of the four markers in the gastric cancer group and benign gastric tumor control group, finding that the serum levels of all four markers were higher in the gastric cancer group than in controls. When examining the four markers individually, CA 242 alone presented the highest positive rate (20.44%). The optimal combination of two markers was CEA and CA 242 (30.39%). When the four markers were combined, the positive rate was 36.57%, which was higher than other combinations. This indicates that the combined detection of multiple markers maybe preferable to single tumor marker in improving diagnostic accuracy.

The high levels of CEA, CA 19-9, CA 242 and CA 50 in gastric cancer patients suggest a more advanced tumor stage compared with controls. A strong association between tumor marker levels and tumor stage, depth and lymph node involvement has been reported previously. For example, it has been shown that CEA strongly correlates with serosal invasion, lymph node involvement and advanced stage (Kodera et al., 1996; Marrelli et al., 1999; Kim et al., 2000). Other studies have revealed that elevated CA 19-9 is associated with tumor depth, nodal involvement, and stage (Aloe et al., 2003; Mihmanli et al., 2004; Sisik et al., 2013). Ucar et al. reported that elevated CEA correlated with liver metastasis, but did not report an association with either histopathologic tumor type or tumor stage (Ucar et al., 2008). Duraker et al. (Duraker et al., 2001) reported that no correlation exists between CA 19-9 positivity and lymph node, hepatic and peritoneal metastasis, and no relationship was found between CEA positivity and tumor size, and hepatic and peritoneal metastasis. Choi et al. analyzed gastric cancer patients with and without recurrence, and found that CA 19-9 may be useful as a marker for peritoneal recurrence, whereas CEA may be a useful marker for hepatic recurrence (Choi et al., 2006). Another study conducted in Korea found that there was no significant association between CA 19-9 and depth of invation, nodal involvement and staging except metastasis, CEA did not show statistically significant relationship with nodal involvement, depth of invasion and stage (Gwak et al., 2014). In the present study, we did not find a relationship between either CEA or CA 19-9 positivity and histopathologic type. Overall, the findings in different studies on the relationship between tumor markers and clinical pathological features are inconsistent. The reason may be the variety of subjects used in these studies, with some selecting patients with resectable gastric cancer, and the others selecting patients with peritoneal metastasis.

The CA 242 tumor marker is a sialylated carbohydrate antigen, which has been shown to be co-expressed with CA 50 (Johansson et al., 1991). Some studies have reported that CA 242 has superior value in pancreatic carcinoma and colorectal carcinoma (Carpelan-Holmstrom et al., 1996; Ni et al., 2005; Yang et al., 2012), but few have examined the relationship between these two tumor markers and gastric cancer. Our study analyzed the levels of expression of CA 242 and CA 50 in gastric cancer patients, finding that serum CA 242 and CA 50 levels had a significant positive correlation with the lymph node status and tumor stage. CA 242 proved valuable in the diagnosis and estimation of prognosis in the gastric cancer patients included in our study.

The neutrophil/lymphocyte ratio (NLR) is a marker for systemic inflammatory response. It is derived from the absolute neutrophil and lymphocyte number in full blood counts. Various studies have examined the clinical use of the NLR to predict gastric cancer patient outcomes (Shimada et al., 2010; Aizawa et al., 2011; Jung et al., 2011). In our study, univariate analysis revealed that a

preoperative NLR value ≥2.5 was related with lower 5-year survival rate, but the multivariate analysis did not show the same relationship. The reason may be that the number of patients included in our study is limited. Conversely, the threshold value of 2.5 differs from that used in other studies. Further studies are required to investigate the prognostic value of this inflammatory marker in gastric cancer.

The preoperative serum CEA level has been reported as a useful marker in predicting gastric cancer prognosis (Gonzalez et al., 1996; Tachibana et al., 1998; Choi et al., 2006). However, Kodera et al (Kodera et al., 1996) revealed that serum CA 19-9 was better than CEA as a prognostic factor in multivariate analyses in gastric cancer patients. A meta-analysis performed by Xiao et al. (Xiao et al., 2014) showed that elevated serum CA 19-9 levels were associated with poorer overall survival in patients with gastric cancer. In our study, the univariate analysis indicated that there was a significant difference in 5-year survival between positive and negative cases for each of the four markers examined. Survival curves suggested that elevated CEA, CA 19-9, CA 242 and CA 50 levels were associated with poorer prognosis. However, multivariate analysis showed that only CA 242 was statistically significant. Our results may differ from those reported by others partly because of differences in the number of patients, the detection technique, cut-off values and differences in follow-up period. Furthermore, some of these studies did not consider several of the confounding factors included in our study.

This study has several limitations. First, we did not evaluate the postoperative levels of serum tumor markers in predicting survival rate, and the correlation between preoperative CEA and survival could be underestimated. In addition, preoperative CA72-4 has been shown to be an important independent factor in predicting survival (Marrelli et al., 2001; Aloe et al., 2003; Ucar et al., 2008). However, our study did not include CA72-4, so further study is required to focus on CA72-4 and other markers to further explore the findings.

In conclusion, the preoperative status of serum CEA, CA 19-9, CA 242 and CA 50 correlates with gastric cancer stage in our study, and preoperative serum CA 242 is an independent prognostic factor for 5-year survival. Elevated preoperative CA 242 values indicate a poor prognosis, and this marker may be helpful in deciding whether to use more aggressive treatment such as postoperative chemotherapy and extensive lymphadenectomy.

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