

## RESEARCH ARTICLE

# Stage Association of Preoperative Serum Carcinoembryonic Antigen with Gastric Adenocarcinoma in Iranian Patients

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### Abstract

**Background:** Gastric cancer is the second leading cause of cancer-related mortality and the fourth most common cancer globally. Tumor markers are needed for appropriate management and monitoring of treatment to improve quality of life. Recently, carcinoembryonic antigen (CEA) has been widely used as a tumor marker in the diagnosis and follow-up of some malignancies. The aim of this study was to evaluate the significance of CEA detection in the course of disease in gastric cancer patients at different stages. **Methods:** Seventy six cases of gastric adenocarcinoma from the Rasht Razi Hospital were studied between January 2016 and December 2016, along with a control group of 152 people. Serum CEA was measured by ELISA reader. Statistical analysis was performed using SPSS 14.0 for Windows (SPSS Inc., Chicago, USA). The two groups were also compared by cross-table analysis using Pearson's chi-square test, with P-values <0.05 considered significant. **Results:** CEA was positive in 61.8 % of patients versus 2.6% of the control group (P = 0.0001). Some 21% of patients at stages I and II (initial disease) and 40.8% at stages III and IV (advanced disease) demonstrated positive CEA. which was significantly correlated with higher N stage and poor differentiation. **Conclusions:** Our study showed that a high preoperative CEA level was not prevalent in early stage gastric cancer patients. We recommend to design other prospective studies and meta-analyses for elucidation of claims for diagnostic efficacy.

**Keywords:** Adenocarcinoma- carcinoembryonic antigen- gastric cancer

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### Introduction

Gastric cancer is the second leading cause of cancer-related mortality and the fourth most common cancer globally (Ang and Fock, 2014; Carcas, 2014; Crew and Neugut, 2006). There are, however, distinct differences in incidence rates in different countries (Ang and Fock, 2014) Gastric cancer is considered as the second most prevalent cancer in Iran (Kavousi et al., 2014). Data indicate a high occurrence rate of this cancer in northern (Caspian littoral), northwestern and some central regions of Iran, particularly in our province, Guilan (Kavousi et al., 2014; Mousavi et al., 2001; Shafaghi et al., 2012).

Gastric cancer remains a major diagnostic and therapeutic challenge and may be a major health problem by frequency, aggressiveness and low rate of cure in symptomatic stage (Patru et al., 2013). Adenocarcinoma is the main type of gastric malignancy. The mechanisms of carcinogenesis and risk factors differ depending on the location in proximal or distal part and the histological type (de Korwin, 2014).

The overall 5-year survival rate of patients with advanced resectable gastric cancer differs between

different countries and different centers, but in general, it ranges from 10% to 30 % (Cenitagoya, 1998, Dikken et al., 2012; Shiraishi et al., 2007).

The 5-year survival rate was influenced by the tumor size, gross type, serosal invasion, extragastric lymph node metastasis, liver metastasis, peritoneal dissemination, stage of disease, resection margin, and operative curability (Shiraishi et al., 2007).

Response markers are needed to monitor treatment, and to improve quality of life, reduce time until surgery in non-responders, and reduce costs (Hartgrink et al., 2009). Tumor markers such as Carcinoembryonic Antigen (CEA), carbohydrate antigen (CA) 19-9, CA72-4, and CA125 are used in gastric cancer patients, although reports have shown the value of tumor markers as prognostic factors (Chen et al., 2012; Sun, 2014).

These makers seem to play important roles in predicting recurrence and metastasis, and in evaluating prognosis (Jiexian et al., 2012). CEA, first identified as a tumor-specific antigen, is used for the evaluation of colorectal cancer patients. Recently, CEA has been widely used as a tumor marker in the diagnosis and monitoring of some other malignancies (Ren et al., 2012). Preoperative

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serum CEA levels could provide a predictive value in determining tumor stage and prognostic information for patients with potentially resectable gastric cancer during the preoperative period (Tachibana et al., 1998). In other studies, however, CEA was neither indicator of survival benefit nor of advanced stage of disease (Chen et al., 2012, Mattar et al., 2002).

The aim of this study was to evaluate the significance of CEA detection in the course of disease in gastric cancer patients with different stages and different aspects.

## Materials and Methods

Patients were 20-70 years with a diagnosis of gastric adenocarcinoma that was proven by histology. They had no history of previous gastric surgery and other treatments including radiotherapy, synchronous or metachronous cancers, uncontrolled infection and significant cardiac, renal or hepatic failure.

We included 76 gastric cancer patients who underwent upper gastrointestinal (GI) endoscopy at Razi Educational and Therapeutic hospital, Rasht, Iran, between January 2016 and December 2016. At the same time, a control group consisted of 152 people who referred to same hospital for routine checkup due to non-GI problems, were also enrolled. They were matched on gender, age (5-year intervals), cigarette smoking and alcohol consumption on a 2:1 control: case ratio. These patients had no history of gastrointestinal diseases and family history of GI cancers. After obtaining written informed consent from all study participants, venous blood samples were obtained from cancer patients at the preoperative workup and from control group. Samples were collected and then centrifuged for 10 minutes at 3000 rpm; serum was then separated for assay. Serum CEA, was measured by Streptavidin Biotin Based Sandwich Assay by Mono-bind Kits (Sensitivity 1.0 ng/ml) using a Stat Fax 3200 (USA) ELISA reader. The patients whose serum levels of CEA were greater than 5 ng/mL were considered to be CEA positive. Patients diagnosed with gastric cancer were treated according to standardized protocol that was recently introduced

This study was approved by the Local Ethical Committee and informed consent for drawing extra blood at the time of routine venepuncture was obtained from subjects.

### Statistical analysis

Statistical analysis was performed using SPSS 14.0

Table 1. Comparison of Demographic Data in the Study Subjects

	Patients	Controls	Differences
Age (years)	62.73 + 10.42	59.89 + 10.14	N.S.
Gender (M/F)	58/18	108 /44	N.S.
BMI (Kg/M2)	22.13 + 2.84	23.21 + 2.76	0.02
Smokers	29 (38.2%)	58 (38.1%)	N.S.
Alcohol drinkers	7 (9.2%)	14 (9.2 %)	N.S.
CEA level (ng/ml)	35.18 + 75	1.59 + 1.3	0.0001

P values less than 0.05 were considered significant- NS, not significant

for Windows (SPSS Inc., Chicago, USA). The data are presented as mean ± standard deviation. The two groups were compared by cross-table analysis using Pearson's chi-square test. P-values <0.05 were significant.

## Results

The demographic data such as age, gender, Body Mass Index (BMI), Smoking and alcohol drinking habits and also CEA level in gastric cancer and healthy control groups were shown in Table 1. The mean CEA level was significantly higher in gastric cancer group than that in healthy control group.

The study included 76 patients. Their disease characteristics are presented in Table 2.

CEA was positive in 61.8 % of patients versus 2.6% in control group (P = 0.0001). It was positive in 21% of patients at stages I and II (initial disease) and in 40.8% of patients at stages III and IV (advanced disease). This difference was not significant.

CEA was positive in 67.7% of patients with lymph node metastasis and in 35.7% patients negative for lymphatic invasion (P = 0.009).

There was not significant correlation between Positive CEA and T or M stages.

Table 3 showed clinicopathologic features of 76 patients with gastric cancer according to CEA levels.

## Discussion

According to the guidelines of the American Society of Clinical Oncology, for colorectal cancer, it is recommended that carcinoembryonic antigen (CEA) be ordered preoperatively, if it would assist in staging and surgical planning (Locker et al., 2006). Postoperative CEA levels should be performed every 3 months for stage II and III disease for at least 3 years. CEA is the marker of choice for monitoring the response of metastatic colorectal cancer to systemic therapy. Data are insufficient to recommend the routine use of CEA in other gastrointestinal cancers

Table 2. Disease Characteristics of Gastric Cancer Patients

Tumor Localization	N (%)
Cardia type	19 (25)
Non-cardia type	57 (75)
Pathology	
Signet ring	15 (19.7)
Non signet ring	61 (80.3)
Tumor TNM Stage	
I	14 (18.5)
II	15 (19.7)
III	19 (25%)
IV	28 (36.8%)
Tumor Grade	
Well differentiated	24 (31.6)
Moderately differentiated	22 (28.9)
Poorly differentiated	30 (39.5)

Table 3. Clinicopathologic Features of 76 Patients with Gastric Cancer According to CEA

	CEA + N: 47 (61.8%)	CEA - N: 29 (38.2%)	P value
Gender			
Male	38 (81)	20 (69)	N.S.
Female	9 (19)	9 (31)	
Age			
< 50	8 (17)	4 (13.8)	N.S.
>50	39 (83)	25 (86.2)	
Nodal involvement			
N0	5 (10.6)	9 (31)	0.009
N+	42 (89.4)	20 (69)	
TNM stage			
I	6 (12.7)	8 (27.5)	N.S.
II	10 (21.3)	5 (17.3)	
III	9 (19.2)	10 (34.5)	
IV	22 (46.8)	6 (20.7)	
Histology			
Signet ring	11 (23.4)	4 (13.8)	N.S.
Non signet ring	36 (76.6)	25 (86.2)	
Tumor localization			
Cardia	12 (25.5)	7 (24.1)	N.S.
Non-cardia	35 (74.5)	22 (75.9)	
Tumor Differentiation			
Well	10 (21.3)	14 (48.3)	0.04
Moderate	15 (31.9)	7 (24.1)	
Poor	22 (46.8)	8 (27.6)	

P values less than 0.05 were considered significant- NS, not significant

including gastric cancer thus its usefulness is still controversial.

In the present study, we examined whether the serum CEA level could be recommended for detection of higher stages of gastric cancer before surgery.

In gastric cancer patients, the overall positive rates for CEA were 16-68 % (Shimada et al., 2014). In our study 61.8% of gastric cancer patients were CEA positive versus 2.6 % in control group. Pre-operative CEA positivity was correlated with higher N stages of tumor as shown by some of the other studies (Ishigami et al., 2001; Jiexian et al., 2012; Shimada et al., 2014). Positive CEA was not correlated with T or M stage and also TNM stage in our study. It could not differentiate initial disease from advanced. It was positive in 40.8% of patients with advanced disease. Matter et al showed similar results and CEA was positive in 30% of patients with stage III and IV (Mattar et al., 2002). Positive CEA was not correlated with higher TNM stage despite that has been recently mentioned by some other studies (Jing et al., 2014; Sisik et al., 2013). In one study, however, CEA was neither indicator of lymph node involvement nor of advanced disease. Sample size of that study was lower than our study population. They showed that CA 72-4 was a better marker for advanced gastric cancer than both CA19-9 and CEA (Mattar et al., 2002).

It has been reported that serum CEA is not associated with the location of the primary cancer (Tachibana et al., 1998). There was no significant correlation between positive CEA and tumor location in our study, however, in another study, tumors located in distal part of the stomach had significantly higher positive rate of serum CEA than those located in proximal part (Park et al., 2008).

Nishida (1983) reported that the expression of CEA was more frequent and stronger in the more differentiated cancers, and CEA was localized in luminal border, cytoplasm and glandular lumen in more differentiated cancers, and only in cytoplasm in less differentiated cancers.

Although some reports showed that elevated CEA was significantly associated with differentiated tumor types (Fan and Xiong, 2010), some other reports similar to our study indicated an association with poorly differentiated types of tumors and patients with preoperative serum CEA levels >10.0 ng/mL had more poorly differentiated than did the patients with preoperative serum CEA levels <5.0 ng/mL (Kim et al., 2000), however, in another study, tissue CEA expression was not correlated with the degree of differentiation (Park et al., 2008).

In the current study, serum levels of tumor marker showed no correlation to the histology of the tumor (signet ring or non-signet ring type). Some authors have tried to explain the low sensitivity of tumor markers in their studies in terms of the histology of the tumor. However, this correlation is still controversial (Horie et al., 1996).

Clinically useful tumor markers in gastric cancer were not still available. CEA is an oncofetal protein involved in cell adhesion and the inhibition of apoptosis (Han et al., 2014). As mentioned above, CEA was used as an alternative tumor marker in stomach cancer. This marker can be readily analyzed by using blood samples and relatively inexpensive and easy methods.

To be of clinical value, tumor markers should be detected in the early stages of the disease, when curative treatment modalities including operation are possible. Our study showed that the preoperative high CEA level was not so prevalent in gastric cancer patients, but it may have a prognostic value (higher N stage and also poor differentiated) and may be clinically useful in selecting patients for neo-adjuvant and/or adjuvant treatment. In post-operative setting, however, CEA usually detect advanced gastric cancer, which only palliative therapy is feasible. As the recurrence of gastric cancer is mainly incurable, checking of CEA values seems to be ineffective for follow up of gastric cancer patients who underwent surgery. The search for more specific and sensitive tumor markers for gastric cancer, along with available methods, is still under way. We recommend designing other prospective studies and meta-analysis to elucidate this claim.

#### Disclosure of conflict of interest

The authors have nothing to disclose.

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