

Atıla TÜRKYILMAZ<sup>1</sup>  
Atilla EROĞLU<sup>1</sup>  
Yener AYDIN<sup>1</sup>  
Nurettin KARAOĞLANOĞLU<sup>2</sup>

## The relationship of serum CEA and CA 19-9 levels to liver metastasis and pancreatic invasion in esophageal cancer

**Aim:** Previous studies have examined levels of CEA and CA 19-9 in esophageal cancer patients, but have not determined a significant relationship between CEA and CA 19-9 levels and liver metastasis and pancreatic invasion in patients with esophageal cancer. In this study, we compared the serum levels of CEA and CA 19-9 in patients with esophageal cancer with and without liver and pancreatic metastasis.

**Materials and methods:** The serum levels of CEA and CA 19-9 were measured in clinic patients between January 2007 and January 2008, including 10 patients with liver metastasis (4) and pancreas invasion (6), and 40 patients with esophageal cancer without distant organ metastasis.

**Results:** A significant relationship was found between CEA levels in patients with liver metastasis and pancreatic invasion ( $P = 0.008$  and  $P = 0.001$ , respectively). CA 19-9 levels were significantly higher in patients with pancreatic invasion compared to patients without pancreatic invasion ( $P = 0.001$ ). There was also a significant difference in CA 19-9 levels between the group with liver metastasis and the group with pancreatic invasion ( $P = 0.028$ ).

**Conclusion:** It is important to measure serum CEA and CA 19-9 levels in all subjects with esophageal cancers in order to detect possible liver metastasis and pancreatic invasion.

**Key words:** Esophageal cancer, metastasis, tumor marker, CEA, CA 19-9

### Özofagus kanserinde serum CEA ve CA 19-9 seviyelerinin karaciğer metastazı ve pankreatik invazyon ile ilişkisi

**Amaç:** Önceki çalışmalarda özofagus kanserli hastalarda serum CEA ve CA 19-9 seviyeleri incelenmiş, fakat bu kanserde CEA ve CA 19-9 seviyeleri ile karaciğer metastazı ve pankreatik invazyon arasında önemli bir ilişki tespit edilmemiştir. Bu çalışmada özofagus kanserli hastalarda CEA ve CA 19-9 seviyeleri ile karaciğer metastazı ve pankreas invazyonu arasındaki ilişkiyi araştırdık.

**Yöntem ve gereç:** Ocak 2007 ve Ocak 2008 tarihleri arasında uzak organ metastazı olmayan 40 özofagus kanserli hasta ile karaciğer metastazı ( $n = 4$ ) ve pankreas invazyonu ( $n = 6$ ) olan 10 hastada serum CEA ve CA 19-9 seviyeleri ölçüldü.

**Bulgular:** Karaciğer metastazı ve pankreas invazyonu olan hastalar ile serum CEA seviyeleri arasında önemli bir ilişki saptandı (sırasıyla;  $P = 0,008$  ve  $P = 0,001$ ). CA 19-9 seviyeleri pankreas invazyonu olmayan hastalarla karşılaştırıldığında pankreatik invazyonlu hastalarda önemli derecede yüksekti ( $P = 0,001$ ). Karaciğer metastazı ve pankreatik invazyonlu grup arasında CA 19-9 seviyelerinde önemli bir fark vardı ( $P = 0,028$ ).

**Sonuç:** Olası karaciğer metastazı ve pankreas invazyonunu saptamada serum CEA ve CA 19-9 seviyelerinin ölçülmesi önemlidir.

**Anahtar sözcükler:** Özofagus kanseri, metastaz, tümör marker, CEA, CA 19-9

### Introduction

Despite advances in surgical and medical treatments, cancer is still the second most common cause of death in the world (1). Although tumor markers are used

<sup>1</sup> Department of Thoracic Surgery,  
Faculty of Medicine,  
Atatürk University,  
Erzurum - TURKEY

<sup>2</sup> Department of Thoracic Surgery,  
Atatürk Training and  
Research Hospital for Chest  
Disease and Chest Surgery,  
Ankara - TURKEY

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### Correspondence

Atilla EROĞLU  
Department of Thoracic Surgery,  
Faculty of Medicine,  
Atatürk University,  
Yenişehir 25240,  
Erzurum - TURKEY

atilaeroglu@hotmail.com

to assist in diagnosis to determine the extent of disease, and to detect recurrences, no tumor marker currently exists that is sensitive and specific enough to be used solely for diagnosis of cancer.

Tumor markers include antigens, enzymes, specific proteins, metabolites, and oncogenes that are not expressed or expressed in very low levels in normal tissues, but are elevated during malignant transformation (2). Tumor markers such as carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA 19-9), CA 125, CA 50, and squamous cell carcinoma (SCC) antigen have been investigated for early diagnosis and treatment evaluation in esophageal cancers (3-6). In most studies, especially ones performed in the early treatment stages of esophageal cancer, these tumor markers have limited utility (3-6). CEA levels are increased in colorectal cancer patients, and are used to detect liver metastasis (7). CEA is a glycoprotein that plays a role in metastasis by virtue of its homophilic and heterophilic adhesion abilities (8). CA 19-9 is a carbohydrate detected in gastrointestinal cancer cells and in pancreatic adenocarcinomas.

Common metastases in esophageal cancer include the liver and lymph nodes, with subsequent pancreatic invasion. The aim of this study is to investigate the relationship between CEA and CA 19-9 levels and liver metastasis and pancreatic invasion in patients with esophageal cancer.

## Patients and methods

### Patient characteristics

Patients diagnosed with esophageal cancer who came to Atatürk University Medicine Faculty, Thoracic Surgery Clinic, were enrolled in the study. Esophageal cancer was diagnosed with flexible endoscopy in all patients. All patients were evaluated with abdominal ultrasonography and contrast enhanced thoracic and abdominal computed tomography. None of the patients had undergone surgical, chemotherapeutic, or radiation treatment. A total of 50 patients were enrolled, and there was no evidence of metastasis in 40 of the patients (80%). Liver metastases were present in 4 patients (8%), and peripancreatic lymph node invasion and pancreatic invasion were present in 6 patients (12%). Suspicion

of liver metastasis was raised in one patient by radiologic evaluation; this suspicion was confirmed by histopathologic evaluation during the surgical exploration of the patient. Hystopathologic evaluation revealed that the tumor had already metastasized to the liver. Furthermore, in 3 patients with radiologic suspicion of peripancreatic lymph node invasion, surgical exploration revealed unresectable infiltrated peripancreatic lymph node invasion. Among 6 other patients, preoperative radiologic evaluation revealed liver metastases and pancreatic invasion. Serum levels of CEA and CA 19-9 were compared between metastatic and non-metastatic groups.

### Evaluation of tumor markers

A total of 5 mL of blood was drawn from all patients into biochemistry tubes (Greiner Vacuette activator, gel serum separator, or plain tubes). Samples were incubated for 20 min at room temperature to coagulate. Following coagulation, samples were centrifuged for 5 min at 5000 rpm, and serum was transferred into biochemistry tubes. A chemiluminometric method was used to measure CEA (Immulite 2000 DPC-Diagnostic, USA) and CA 19-9 (Hitachi E170, Tokyo, Japan). Normal values for these markers are 0-4 ng/mL for CEA and 0-33 µg/mL for CA19-9.

### Statistical analysis

The SPSS statistics program was used to evaluate the results. Means ( $\pm$ ), standard deviation ( $X \pm SD$ ), and standard error ( $X \pm SE$ ) were determined.  $P < 0.05$  was considered to be statistically significant. A one-way ANOVA test was used to determine the significance between groups. The Pearson correlation test was used to analyze relations. The least significant difference (LSD) test was used when the comparisons were at 5% significant levels.

## Results

CEA levels in patients with liver metastasis and pancreatic invasion were significantly different compared to the non-invasion group ( $P = 0.008$  and  $p = 0.001$ , respectively). CEA levels were not significantly different ( $P = 0.93$ ) when the group with liver metastasis was compared to the pancreatic invasion group. Although serum CA 19-9 levels were

higher in all patients with liver metastasis, there was no significant difference compared to the non-invasion group ( $P = 0.53$ ). Serum CA 19-9 levels were significantly different between the patient group with pancreatic invasion and the patient group without invasion ( $P = 0.001$ ). There was a significant difference in CA 19-9 levels between the group with liver metastasis and the group with pancreatic invasion ( $P = 0.028$ ). A relationship was determined between serum CEA and CA 19-9 levels using the Pearson correlation test. While only 1 of the 4 patients with liver metastasis had histopathologically diagnosed adenocarcinoma, 5 out of 6 patients with pancreatic invasion had adenocarcinoma. Demographic characteristics of esophagus cancer patients, and serum levels of CEA and ca 19-9 in patients with non-metastatic disease, with liver

metastasis, and with pancreatic invasion are given in the Table and presented graphically in Figures 1 and 2.

### Discussion

Esophageal cancer comprises 5%-7% of all gastrointestinal system cancers. Currently, the only potentially curative treatment is surgical removal of the tumor. However, most patients are ineligible for surgery at diagnosis due to lymph node metastasis or distant organ metastasis (9).

Serum CEA and CA19-9 levels are high in many gastrointestinal cancers. Due to their low specificity and sensitivity, they are only used for diagnosis and detection of recurrences. The sensitivity and specificity of CA 19-9 is 80%-90% for pancreatic

Table. Demographic characteristics and serum CEA and CA 19-9 levels of esophagus cancer patients with non-metastatic disease, with liver metastasis and with pancreatic invasion.

	Non-metastatic	Liver metastasis	Pancreatic invasion
Cases (n)	40	4	6
Age (mean)	55.8	61.8	62.5
Female / Male	21/19	3/1	5/1
SCC/Adenocarcinoma	31/9	3/1	1/5
CEA	$1.6 \pm 1.0$	$22 \pm 41.4$	$22.8 \pm 28.5$
CA 19-9	$12.3 \pm 10.6$	$389 \pm 434$	$2074.7 \pm 3518.6$

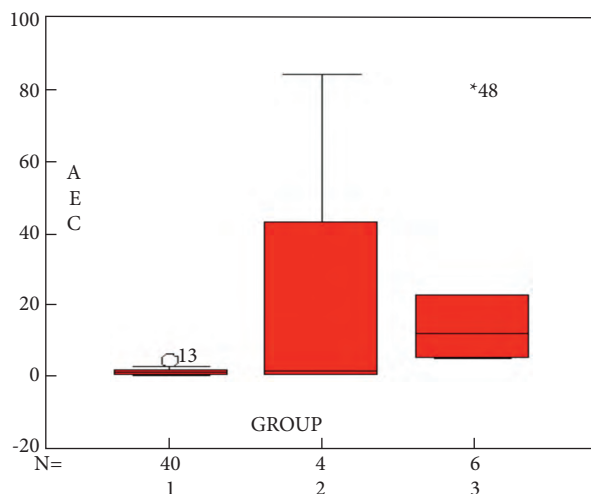


Figure 1. Serum CEA levels in non-metastatic patients (group 1), patients with liver metastasis (group 2), and patients with pancreatic invasion (group 3).

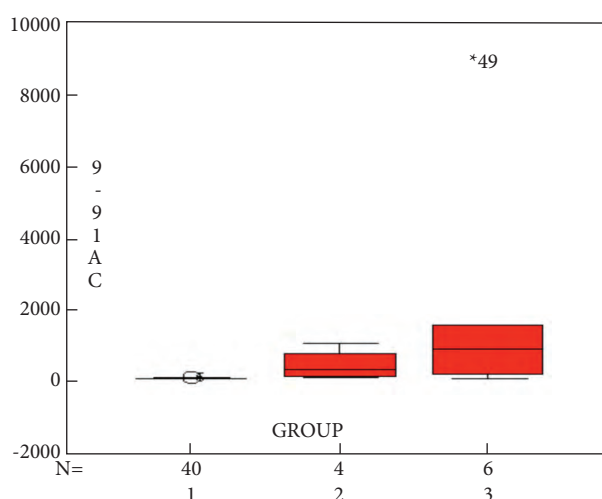


Figure 2. Serum CA 19-9 levels in non-metastatic patients (group 1), patients with liver metastasis (group 2), and patients with pancreatic invasion (group 3).

cancers and 60%-70% for biliary tract cancers. When CA 19-9 levels are high in patients with a suspected tumor, pancreatic adenocarcinoma and cholangiocarcinoma are suspected. There is no relationship between tumor mass and CA 19-9 levels. CA 19-9 is increased not only in malignant conditions but also in benign conditions such as acute pancreatitis, chronic pancreatitis, cholangitis, chronic liver disease and cirrhosis (10).

CEA levels are increased in patients with colorectal cancers, and very high preoperative levels indicate a poor prognosis. Nevertheless, CEA levels are important for determining postoperative disease recurrence. Elevated CEA levels are also seen in breast, lung, thyroid, pancreas, bladder, ovarian, prostate, and liver cancers. In addition to these malignant conditions, CEA levels are also elevated in response to benign conditions such as peptic gastritis, diverticulitis, bronchitis, liver abscess, cirrhosis, aging, and smoking. CEA is a useful tumor marker for digestive organ cancers, and, in particular, CEA and CA 19-9 are very good indicators for gastric cancer (11). When used together, CA 19-9 and CEA have 94% sensitivity for detection of the recurrence of stomach cancer (11). In other gastrointestinal cancers, increased CEA and/or CA 19-9 levels are useful for prognosis, especially in predicting metastasis. The sensitivities of serum CEA and CA 19-9 are especially high in gastric adenocarcinomas with diffuse lymph node metastasis (12). Positive preoperative CEA, CA 19-9 and CA 72-4 are a risk factor for liver metastasis after radical surgery for stomach cancer (13). Previous studies have found that levels of serum CEA increase in esophageal cancer as distant organ metastasis occurs (3,4,14). Indeed, high levels of serum CEA

were detected in approximately 50% of patients with tumor spread to lymph nodes and 75% of patients with distant organ metastasis (7).

Serum levels of CA 19-9 greater than 1000 µg/mL may be indicative of metastatic disease(15). In studies of pancreatic adenocarcinomas, high levels of biliary and serum CA 19-9 were present in patients with liver metastasis (16,17). In addition, elevated CA 19-9 in colorectal cancer patients is indicative of liver metastasis (18). High levels of CEA and CA 19-9 were present in one subject with submucosal esophageal cancer with multiple liver metastases (19). Furthermore, elevated levels of serum CEA and CA 19-9 have been observed in colorectal cancers and gastric cancers with lymph node metastasis (20-22).

In our study, we observed increased levels of serum CEA and CA 19-9 in 10 patients with metastatic esophageal cancer, 4 of whom had liver metastases and 6 of whom had pancreatic invasion due to peripancreatic lymph node involvement. We detected the presence of metastasis in 1 patient with liver metastasis and 3 patients with pancreatic metastasis during surgical exploration in which preoperative ultrasonography and computerized tomography had not clearly detected presence of the metastasis; in addition, their CEA and CA 19-9 levels were found to be high. Only negligible increases were seen in the serum CEA and/or CA 19-9 levels in patients with non-metastatic cancer. We think that it is clinically prudent to monitor progressive increases in these markers in esophageal cancer patients to predict liver metastasis and pancreatic invasion. However, further studies are needed to determine the absolute utility of these measures.

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