An Investigation into the Role of IGF-1 and IGFBP3 in the Diagnosis and Treatment Response in Esophageal Cancer

Süleyman BADEMLER*, Merve Müge ÜÇÜNCÜ**, Murat SERİLMEZ***

Abstract

Aim: Esophageal cancer (EC) is the eighth most common cancer among all cancers worldwide. It constitutes 1.5-2% of all cancers and 5-7% of gastrointestinal cancers. Mortality reduction by early diagnosis, early treatment, and close follow-up is possible in esophageal cancer. However, reliable markers that rapidly provide results for early diagnosis are necessary in order to make such a diagnosis. In our study, it is aimed to investigate the role of IGFBP3 and IGF-1 in the early diagnosis of esophageal tumors.

Method: 37 patients with a histopathologically confirmed diagnosis of EC and 41 age- and sex-matched healthy controls were included in our study at Istanbul University Institute of Oncology. Serum IGF-1 and IGFBP-3 levels were determined using enzyme-linked immunosorbent assay (ELISA).

Findings: The mean age of the patients included in this study was 54.51±13.69 years. Based on the comparison between the groups, there was no difference in terms of gender and age ($p=0.675$ and 0.094). There was a statistically significant difference between the control group and the patient group in terms of IGF-1 and IGFBP3 levels. Both levels were higher in the control group ($p=0.006$, $p<0.001$). 22 patients had a recurrence. There was no significant difference between the IGF and IGFBP3 levels in those who had a recurrence. 32 patients died. There was no significant difference in terms of the histological subtype, T and pathologic stage of the disease, and IGF-1 and IGFBP3 levels.

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* Corresponding Author, Assist. Prof. Dr., Istanbul University, Istanbul Medical Faculty, Department of General Surgery, Istanbul, Turkey, E-mail: sbademler@gmail.com
ORCID ID https://orcid.org/0000-0002-0221-7153
** MD, Zeytinburnu Community Health Center, Istanbul, Turkey, E-mail: mugekusbeoglu@gmail.com ORCID ID https://orcid.org/0000-0001-6125-1848
*** Res. Assist., Istanbul University, Istanbul Medical Faculty, Institute of Oncology, Department of Biochemistry, Istanbul, Turkey, E-mail: serilmez55@hotmail.com
ORCID ID https://orcid.org/0000-0001-8502-2505

Conclusion: Our study showed that IGF-1 and IGFBP3 markers could be used in the diagnosis of esophageal tumors. We think that it is necessary to conduct further studies with larger series in order to draw a clear conclusion.

Keywords: Esophageal cancer, IGF-1 and IGFBP-3 levels, serum, early diagnosis, tumor marker, gastrointestinal system cancer.

IGF-1 ve IGFBP3'ün Özofagus Kanseri'nin Tanı ve Tedaviye Yanıtındaki Yerinin Araştırılması

Öz

Amaç: Özofagus kanseri dünya genelinde tüm kanserler arasında sekizinci sırada yer almaktadır. Tüm kanserlerin % 1,5–2'sini, sindirim sistemi kanserlerinin ise % 5-7'sini oluşturmaktadır**.** Bu kanser türünde erken tanı, erken tedavi ve yakın takiple mortalite azaltılabilmektedir. Ancak erken tanı konabilmesi için erken tanıda kullanılabilecek hızlı sonuç alınan, güvenilir belirteçlere ihtiyaç vardır. Çalışmamızda özofagus tümörünün erken tanısı için IGFBP3 ve IGF-1'in kullanılabilirliğini araştırmayı amaçladık.

Yöntem: Çalışmaya patolojik olarak özofagus kanseri tanısı alan ve İstanbul Üniversitesi Onkoloji Enstitüsünde takip edilen 37 özofagus kanserli hasta ve 41 kanser tanısı olmayanlar dahil edilmiştir. Serum IGF-1 ve IGFBP3 seviyeleri ELISA yöntemi ile belirlenmiştir.

Bulgular: Çalışmaya alınan hastaların yaş ortalaması 54.51±13.69 yıldır. Gruplar arasında yapılan değerlendirmede cinsiyet ve yaş arasında fark yoktur (p=0,675 ve 0,094). Çalışmaya alınan hastalardan kontrol grubu ile vaka grubu arasında IGF-1 ve IGFBP3 arasında istatistiki anlamlı fark vardır. Kontrol grubunda her iki değerde daha yüksektir (p=0,006, p<0,001). 22 hastada nüks gözlenmiştir. Nüks gelişmesinde IGF ve IGFBP3 seviyeleri arasında anlamlı fark gözlenmemiştir. 32 hasta ex olmuştur. Hastalığın histolojik alt tip, T ve patolojik evreleri arasında IGF-1 ve IGFBP3 arasında anlamlı fark bulunmamıştır.

Sonuç: Çalışmamızda özofagus tümör tanısı için IGF-1 ve IGFBP3 markerlarının kullanılabileceğini göstermektedir. Net kanıya varmak için daha geniş örnek gruplarında çalışılması gerekliliği kanaatine varılmıştır.

Anahtar Kelimeler: Özofagus kanseri, IGF-1 seviyesi, IGFBP-3 seviyesi, erken tanı, tümör marker, sindirim sistemi kanseri.

Introduction

Globally, esophageal cancer is the eighth most common cancer among all cancers. It constitutes 1.5-2% of all cancers and 5-7% of gastrointestinal cancers[1]. In 2016, there were 16910 new cases and 15910 deaths due to esophageal cancer in the United States[2]. The 5-year survival rate for esophageal cancer ranges between 15-25%[1]. Early diagnosis, early treatment, and close follow-up can reduce the mortality of this cancer type. The most prevalent histological type is squamous cell carcinoma, followed by adenocarcinoma[3]. However, reliable markers that rapidly provide results for early diagnosis are necessary for such a diagnosis.

IGFs are markers that were used in the detection of tumor tissue in various studies. IGF levels increase in cancerous tissues[4-8]. It is stated that, among IGFs, increased IGF-1 was the most significant marker for cancers[4,9,10]. In our study, it was aimed to investigate the role of IGFBP3 and IGF-1 in the diagnosis of esophageal tumors.

Materials and Methods

37 patients that were pathologically diagnosed with esophageal cancer and were under follow-up in İstanbul University Oncology Institute between 01.01.2012 and 01.01.2016 were included in this study. The patients who previously received chemotherapy in another center, who did not prefer/confirm to participate in the study and those who did not come to their follow-ups and continued their treatment in another center were excluded from the study. Disease staging was performed based on the International Union Against Cancer TNM classification. Computed tomography (CT), magnetic resonance imaging (MRI) and/or positron emission tomography (PET/CT) were used as imaging methods. The findings of distant metastasis and the pathological features of the tumors were recorded. Clinical examinations, biochemical tests, and blood counts were evaluated before the treatment. The Control Group was recruited from healthy individuals with no findings of carcinoma who visited our center for routine screening. Individuals with a history of abdominal surgery or other malignancies, including rectal cancer, were excluded.

Blood Samples and Study Method

Blood samples were collected from the patients in the patient and control groups when they presented to our clinic and agreed to participate in the study. The serum separated from the blood samples after centrifugation were stored at -80°C until analysis. Serum IGF- 1 and IGFBP-3 levels were measured using the Immulite 2000 system (all from Siemens Healthcare Diagnostics Products Ltd., Sudbury, UK). This system is based on solid phase enzyme linked chemiluminescence (EIA) method. After the samples were diluted, serum IGF-1 and IGFBP-3 levels were automatically studied.

Statistical Analysis

$\chi 2$ test and One Way Anova test were used for the count data. The Spearman method was used for correlation analysis ($\alpha = 0.05$), and $p < 0.05$ was considered statistically significant. The differences in survival were measured using the Kaplan-Meier test. SPSS 22.0 software (SPSS, Inc., Chicago, IL, USA) was used for the statistical analyses.
The approval for this study was obtained from the Ethics Committee of Istanbul Medical Faculty.

Results

This study included 37 patients with esophageal cancer (patient group) and 41 patients without a cancer diagnosis (control group). The mean age of the patients was 54.51±13.69. There were 42 male patients. There was no statistically significant difference between the groups in terms of gender and mean age (p=0.675 and 0.094). The most prevalent histological subtype was squamous cell carcinoma (86.5%). There was a statistically significant difference between the control group and the patient group in terms of IGF-1 and IGFBP3 levels. Both levels were higher in the control group (p=0.006, p<0.001) (Table 1) (Figure 1-2).

Table 1: Characteristics of patient and control groups

	Control	Patient	p
Number	41	37	
Gender (M/F)	23/18	19/18	0.675
Mean age	52.04±15.07	57,24±11,56	0.094
IGF 1 (ng/ml)	155.14±54.52	119.25±57.40	0.006
IGFBP3 (ng/ml)	4.51±1.35	3.37±1.34	<0.001

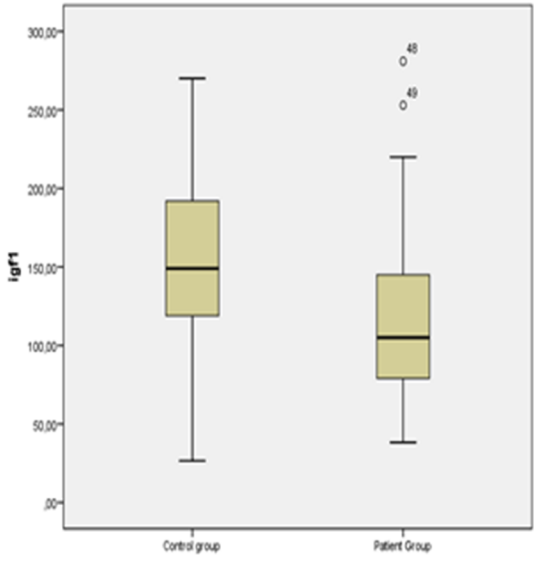

Figure 1: IGF-1 levels

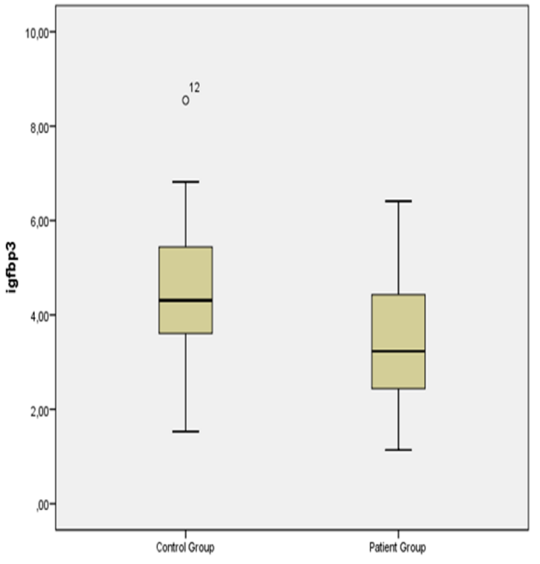

Figure 2: IGFBP- 3 levels

Based on the TNM classification of the patient group, 2 patients had T1 cancer, 7 patients had T2, 24 patients had T3 and 4 patients had T4. Considering the stage of cancer, there were 2 patients with stage 1, 7 patients with stage 2, 15 patients with stage 3 and 13 patients with stage 4 cancer. There was no statistically significant difference between the IGF1 and IGFBP3 levels of these patients (Table 2).

Table 2: Comparison of pathological datas of patient group

	IGF-1	**p**	**IGFBP-3**	**p**
Stage	0.933		0.626	
Stage 1	113.50±6.36		4.50±1.74	
Stage 2	107.77±50.27		3.10 ±1.08	
Stage 3	125.24±71.51		3.45±1.43	
Stage 4	119.25±57.40		3.26±1.39	
Histological type	0.429		0.520	
Adenocarcinoma	99,24±17,71		3,01±1,27	
SCC	122,38±60.92		3.43±1.36	
Differentiation	0.487		0.341	
Low	131.33±58.20		3.65±1.33	
Moderate	111.32±64.08		2.97 ±1.39	
Good	102,02±22,47		3,63±1,18	
pT	0.583		0.258	
T1	142.50±47.37		4.80±1.32	
T2	142.38±78.87		3.72 ±1.56	
T3	110.41±54.59		3.28±1.28	
T4	120.25±57.40		2.61±1.09	

SCC: Squamous Cell Carcinom T: Depth of İnvasion

There was a positive correlation between IGF1 and IGFBP3 levels. The Spearman correlation coefficient between IGFBP3 and IGF1 among the control subjects was 0.660 ($P < 0.0001$) (Figure 3).

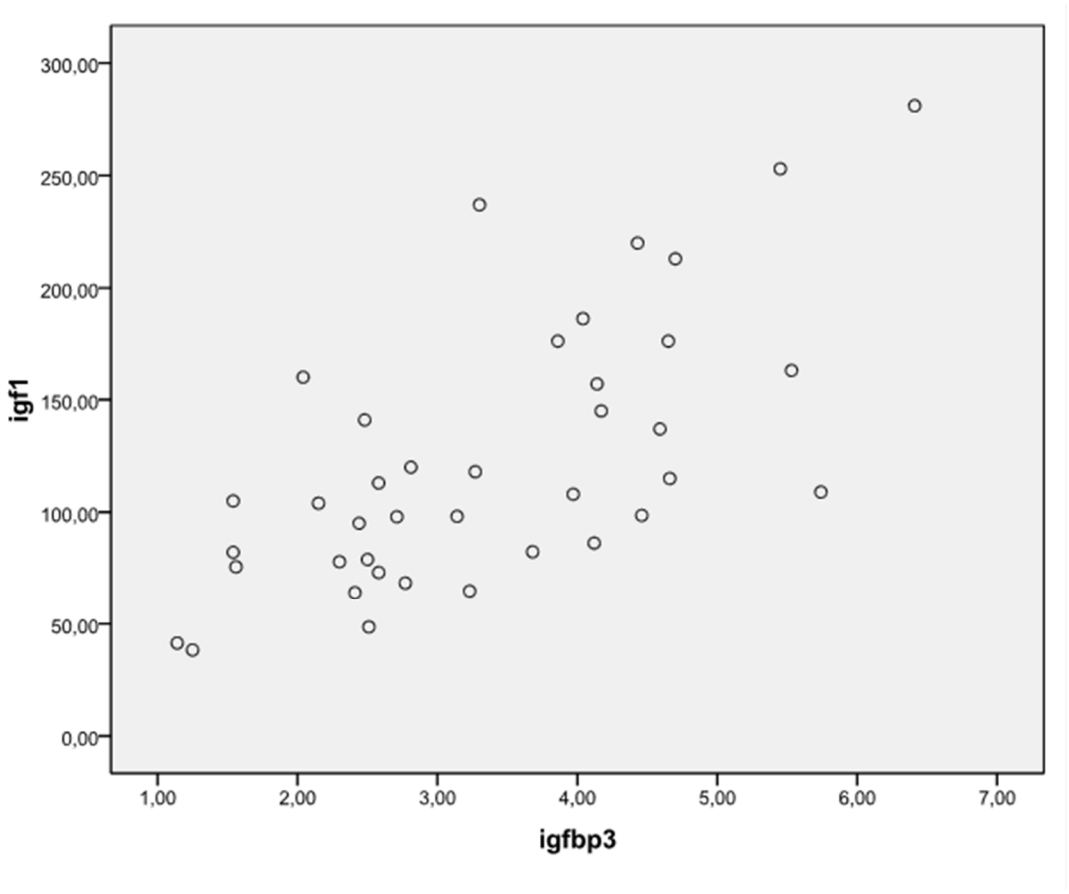

Figure 3: Correlation diagram between IGF1 and IGFBP3

Only 7 patients (18.9%) were operated. There was no statistically significant difference between the operated and non-operated patients in terms of IGF-1 and IGFBP3 levels (p=0.242 and p=0.741). The median follow-up period was 12 months (1-85). 22 patients had a recurrence. There was no significant difference between the IGF and IGFBP3 levels in those who had a recurrence. 32 patients died. 1-year survival rate was 48.8%, whereas 5-year survival rate was 15.1% (Figure 4).

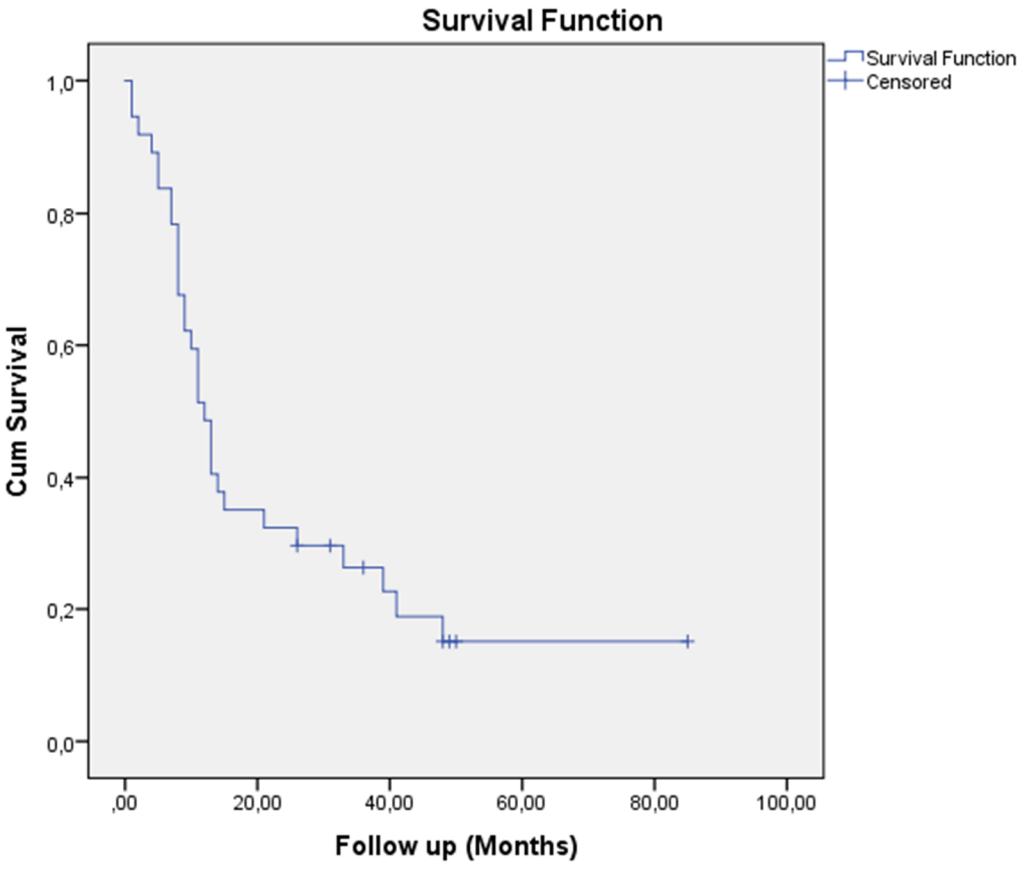

Figure 4: Overall Survival

Discussion

Esophageal cancer is the eighth most common cancer worldwide and it is the sixth leading cause of deaths due to cancer[1]. The risk factors for esophageal squamous cell carcinoma consist of a diet poor in fruits and vegetables, drinking hot beverages and poor nutrition, whereas the risk factors for the adenocarcinoma type comprise overweight, obesity and reflux disease[11].

Patients with advanced esophageal cancer generally present with dysphagia and weight loss, whereas patients usually do not have any symptoms in the early stage[3]. National Comprehensive Cancer Network (NCCN) recommends endoscopy as the first tool in the diagnosis of patients with clinical complaints[12, 13]. In addition, other diagnostic tools are

used in the staging of esophageal cancer[12,13]. A majority of the patients have advanced cancer at the time of diagnosis. Surgery, radiotherapy, chemotherapy, and combinations thereof are used in the treatment of patients[2,14-16]. For localized esophageal cancer, surgery remains to be the primary treatment[17].The 5-year survival rate in esophageal cancer ranges between 15-25% even though a surgical resection was performed[1]. In our study, 81.1% of the patients had advanced esophageal cancer and they did not undergo surgery. On the other hand, there was no significant difference between the operated and non-operated patients in terms of IGF1 and IGFBP3 levels 5-year survival rate of the patients was 15% in our study, which is consistent with the literature.

Various epidemiological studies carried out after 1990 have reported that IGF and markers associated with IGF could be used in the diagnosis and prognosis of some cancer types. IGF is an autocrine and paracrine protein that is secreted in higher amounts from the tissues that become cancerous and plays a role in the survival, growth, proliferation, and pathogenesis of cancer cells[6,18]. Six subtypes have been defined for IGF. It is stated that, among IGFs, increased IGF-1 was the most significant marker for cancers[5,18]. Moreover, it is indicated that IGFBP complex is a marker that induces apoptosis by binding IGF-1 through p53-dependent or –independent mechanisms, wherein p53 is a human tumor suppressor protein that facilitates IGF-1 transport within the blood circulation. There are three different types of IGFBP complexes. IGFBP-1 and IGFBP-2 play a role in regulating the activities of IGF-1, whereas IGFBP-3 binds IGF-1 in circulation and reduces its activity. There are findings indicating that high IGF-1 and low IGFBP3 levels are associated with an increased risk of cancer in humans[5,18]. In a study by Adachi et al. (2017), a difference was observed between the patients with esophageal cancer and the control group in terms of IGF-1 and IGFBP3 levels[19]. In this study, low IGFBP3 levels represent an important predictive marker of a high incidence of esophageal carcinoma[19]. Our study also showed that the mean IGF-1 level of the patient group was 119.25±57.40, which was lower in comparison to the control group. The difference was statistically significant. In another study; the expressions of IGFBP-3 in esophageal cancer patients is higher than normal tissue and it was closely related to tumor differentiation, depth of invasion, clinical stage, and lymph node metastasis[20]. Moreover, the mean IGFBP3 level of the patient

group was 3.37±1.34, which was also statistically significantly lower than that of the control group. In our study, there is no difference between tumor differentiation, depth of invasion, clinical stage, and lymph node metastasis.

Conclusion

Our study showed that IGF-1 and IGFBP3 markers, which were used in the diagnosis of esophageal tumors, could also be used reliably in the early diagnosis of such tumors. We are of the opinion that there is a need for further studies to benefit from these markers in assessing esophageal tumors, metastasis and survival.

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