The prognostic value of serum epidermal growth factor receptor level in patients with non-small cell lung cancer

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ÖZET

Küçük hücreli dışı akciğer kanseri olan hastalarda serum "epidermal growth factor receptor" düzeyinin prognostik önemi

"Epidermal growth factor receptor (EGFR)"ün, aşırı ekspresyonunun sıklıkla saptandığı küçük hücreli dışı akciğer kanseri (KHDAK)'nde, tümör progresyonunu belirleyen bir faktör olduğu bildirilmiştir. KHDAK'lı hastalarda serum EGFR düzeyinin klinik kullanılabilirliği tartışmalıdır. Bu çalışmada, KHDAK'lı hastalarda serum EGFR düzeylerinin ölçümü, serum EGFR düzeyi ile hastalık evresi, histolojik tip ve sağkalım süresi arasındaki ilişkinin belirlenmesi amaçlanmıştır. Serum EGFR düzeyi ELISA yöntemi ile ölçüldü. Çalışmaya 43 KHDAK'lı hasta ve 16 sağlıklı kişi alındı. Hastaların 29'u yassı hücreli karsinoma, 14'ü adenokarsinoma idi. Serum örnekleri tedaviden önce alındı. KHDAK'lı hastalarda ortalama serum EGFR düzeyi 17.53 ± 8.09 fmol/mL, sağlıklı grupta ise ortalama serum EGFR düzeyi 16.88 ± 7.08 fmol/mL olarak saptandı. Aradaki fark istatistiksel olarak anlamlı değildi (p= 0.912). Hastalık evresi, histolojik tip ile serum EGFR düzeyi arasında ilişki saptanmadı. Serum EGFR düzeyi ile sağkalım süresi arasında ilişki saptanmadı. Bu çalışmanın sonuçları, KHDAK'lı hastalarda serum EGFR düzeyinin bir tümör belirteci veya bir prognostik faktör olarak kullanılamayacağını göstermektedir. Bununla birlikte, bu sonuçları doğrulamak için geniş hasta gruplarında prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: *Epidermal growth factor receptor (EGFR), küçük hücreli dışı akciğer kanseri, yassı hücreli karsinoma, adenokarsinoma, evre.*

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SUMMARY

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Epidermal growth factor receptor (EGFR) has been implicated as a factor indicating tumour progression or as a prognostic factor in non-small cell lung cancer (NSCLC), in which its overexpression is often detected. The usefulness of identifying EGFR in serum from patients with NSCLC is controversial. This study was designed to identify serum EGFR levels in patients with NSCLC and to evaluate the relationship between serum EGFR levels and clinical stage, histological subtype and survival time. Serum EGFR levels were measured using quantitative enzyme-linked immunosorbent assay. The study included 43 patients with NSCLC and 16 healthy controls. The histological classification was 29 squamous carcinomas and 14 adenocarcinomas. Serum samples were collected before treatment.There was no difference between serum EGFR levels in patients with NSCLC (17.53 ± 8.09 fmol/mL) in comparison with those healthy controls (16.88 ± 7.08 fmol/mL; p= 0.912). There was also no difference in serum EGFR levels according to clinical stage or histological subtype. There was no relationship between serum EGFR levels and survival time in patients with NSCLC. The study's results suggest that, the utility of serum EGFR levels in patients with NSCLC as a tumour marker or as a prognostic factor is limited. However, further prospective studies on a large number of patients will be necessary to confirm this study's results.

Key Words: *Epidermal growth factor receptor (EGFR), non-small cell lung cancer, squamous cell cancer, adenocancer, stage.*

Lung cancer is the most common cause of death by malignancy in industrialized countries and < 15% of patients can be cured for long term survival. This poor prognosis can be modulated by characteristics related to the patients or the tumour. These prognostic factors can be used for different purposes, such as a better understanding of the natural history of the disease, the identification of homogeneous patient populations with a similar outcome profile and the prediction of response (or not) to treatment. In non-small cell lung cancer (NSCLC), age, performance status and disease stage have been shown to consistently predict outcome (1).

Recent developments in cytogenetic and molecular biology have provided new ways to analyze prognosis. Growth factors and their receptors are known to play an important role in normal cell proliferation and in neoplastic growth. The epidermal growth factor receptor (EGFR), form one of the best defined autocrine growth loops in human tumours.

The EGFR is a 53 aminoacid, 170 kDa transmembrane peptid and composed of three major domains; an extracellular domain connected via a transmembrane lipophilic segment to an intracellular protein tyrosine kinase domain. The extracellular domain binds receptor specific ligands and activates the cytoplasmic domain, which then initiates a cascade of biological signals from the cytoplasm to the nucleus, ultimately resulting in mitogenesis (2,3).

EGFR and its ligands are important in normal and neoplastic epithelial cell growth. Diverse biological roles in malignancy are attributed to this autocrine growth factor loop, including the regulation of mitogenesis, cell survival or apoptosis, angiogenesis and cell motility or metastasis, making the EGFR an attractive therapeutic target (4).

The EGFR has been implicated as a factor indicating tumour progression or as a prognostic factor in NSCLC in which its overexpression is often detected (5,6).

In NSCLC, EGFR overexpression is reported in 13-80% of tumours (24-89% of squamous cell lung cancer and 23-46% of adenocarcinoma).

Numerous studies have suggested that expression of high levels of EGFR is associated with advanced or metastatic disease and a poor prognosis. In most of these studies overexpression of EGFR was evaluated by immunohistochemical staining. However, immunohistochemistry has difficulty for the quantification of the level of EGFR expression. EGFR is readily identifiable and quantifiable in serum and several reports have indicated, changes in the serum level of EGFR is associated with aggressive cancer development, including kidney, gastric and lung cancer (7-9). However, the usefulness of identifying EGFR level in serum from patients with NSCLC is controversial.

In this study, we investigated serum EGFR level in patients with NSCLC and the findings were compared with the clinical-pathologic features of disease.

MATERIALS and METHODS

This study consisted of 16 healthy controls and 43 NSCLC patients. All subjects were enrolled between January 2001 and February 2002 at Ankara University School of Medicine, Department of Chest Diseases in Ankara, Turkey. Stage grouping was made according to the TNM classification (10,11).

After collection of the venous blood samples from patients and control subjects, the samples were centrifugated at 3000 rpm for 10 min and then stored at -70°C until assay. The human Active EGF-R ELISA (Bender Medysystems Diagnostics GmbH, Rennweg 95b A-1030 Vienna, Austria) kit was used to detection of quantitative level of EGFR in serum according to the recommendation of the manufacturer.

Statistical Analysis

All statistical analyses were performed using the SPSS version 10.0. Statistical comparisons between all groups were investigated by the Mann-Whitney U test. A p value of less than 0.05 was considered as statistically significant.

RESULTS

The median age of the patient group was 62 years (range, 38-79) and that of the control group was 47 (range, 44-51). In the NSCLC patients, the mean value of the serum EGFR level was 17.53 ± 8.09 fmol/mL and was 16.88 ± 7.08 fmol/mL in healthy controls (Table 1). This difference was not statistically significant (p= 0.912). The survival graphic was shown in Figure 1. We couldn't determine a relationship between serum EGFR level and survival time. In the patients group the histological classification was 29 squamous and 14 adenocarcinomas. There was no difference for serum EGFR level in the patients according to histological subtype. The staging of the disease was made according to TNM classification. Since the patients with stage IIIB and IV were accepted as inoperable, the patients were divided into two groups. In operable group, the mean serum EGFR level was 15.70 ± 6.34 fmol/mL and was 18.32 ± 8.73 fmol/mL in inoperable group. The difference was not significant (p= 0.341). We investigated relationship between serum EGFR level and tumour status (T), nodal status (N) and distant metastasis (M). For this purpose, patients with T1-T2 and T3-T4, N0 and N1-2-3, M0 and M1 were compared. There was no difference for serum EGFR level in the patients according to T, N and M status.

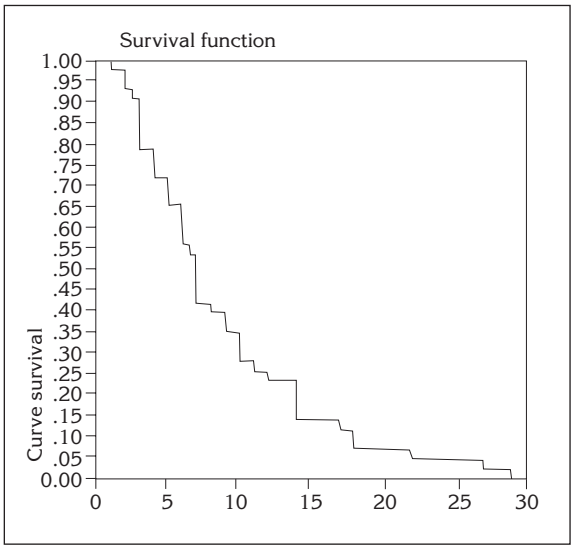

Figure 1. The survival graphic.

Table 1. Control group and patients characteristics and serum EGFR levels.

		No	Serum EGFR level (fmol/mL)	p
Control group		16		
	Male/female	13/3	16.88 ± 7.08	0.912
	Age	47 ± 2.1		
Patient group		43		
	Male/female	38/5	17.53± 8.09	0.912
	Age	62 ± 11.5		
Pathological subtype	Squamous cell cancer	29	18.38 ± 8.19	0.204
	Adenocancer	14	15.75 ± 7.88	
Tumour status (T)	T1-T2	16	17.24 ± 8.88	0.505
	T3-T4	27	18.01 ± 6.81	
Nodal status (N)	N0	10	17.28 ± 6.33	0.698
	N1-N2-N3	33	17.60 ± 8.64	
Metastasis status (M)	M0	28	16.11± 6.54	0.157
	M1	15	20.18 ± 10.13	
Operability	Operable	13	15.07 ± 6.34	0.341
	Inoperable	30	18.32 ± 8.70	

DISCUSSION

The over expression of EGFR is a common trait in human tumours, which has been observed in NSCLC (5,12,13). In NSCLC, EGFR over expression is reported 13-80% of tumours (24-89%) of squamous cell lung cancer and 23-46% of adenocarcinoma) and also it was reported that, expression of high levels of EGFR can be associated with advanced or metastatic disease and a poor prognosis. Veale et al., reported that patients with high EGFR concentration have a poor prognosis (14). Tateishi and colleagues showed that the five year survival rates of patients with high EGF or TGF-α levels were significantly worse only in the EGFR positive cases (15). However other studies couldn't show a relationship between EGFR and prognosis in patients with lung cancer.

Immunohistochemical staining of cancer tissue is the most commonly applied method to evaluate the overexpression of EGFR. However, immunohistochemistry has difficulty in the quantification of the level of EGFR expression (16). As used in the current study, ELISA allows easy quantification of the EGFR level, especially in serum (17). The serum assay for oncoprotein using ELISA can be easily and frequently performed because of its minimal invasiveness compared with surgically obtained tissue material. Using ELISA in breast, ovary, lung and pancreatic carcinoma, several investigators have reported an elevated serum level of c-erbB-2, which is highly homologus to EGFR, and suggested its possible role as a useful tumour marker (18-21). The usefulness of identifying EGFR in serum from patients with lung cancer or other malignancies is still unknown. Choi et al. reported that the mean serum level for EGFR in the gastric carcinoma patients was significantly elevated compared with that of healthy controls but no significant association was noted between positivity of EGFR and gender, age, stage and tumour differentiation (9). There are limited studies that evaluating the usefulness of serum EGFR in lung cancer. Jacot et al., investigated the prognostic feature of serum EGFR and HER-2 levels and reported that neit-

her HER-2 nor EGFR levels were associated with a partıcular prognosis of NSCLC (22). Schneider et al., reported that serum EGFR level were not elevated in patients with lung cancer compared with that of healthy controls and there was also no difference in EGFR serum concentrations as a function of histological subtype (23). In the current study there was no difference for serum EGFR level in patients with NSCLC in comparison with those healthy controls. Sasaki et al., reported that serum EGFR level were higher in the lung cancer patients with lymph node metastasis than in the patients without lymph node metastasis but, there was no difference in serum EGFR level according to clinical stage or histological subtype and also there was no difference between serum EGFR levels in patients with lung cancer in comparison with those in nonmalignant disease controls (7). In our study, there was no difference for serum EGFR level according to histological subtype consistent with previous studies and also there was no relationship between serum EGFR level and T, N and M status. We compared inoperable patients with operable patients and no significant difference was observed between two groups for serum EGFR level.

The immunohistochemical over-expression of EGFR is a common trait in human tumours. Although it has been reported that, the overexpression of EGFR is a poor prognostic factor and associates with advanced disease in NSCLC, in our study serum EGFR level were not elevated in patients with NSCLC and there was no relationship between serum EGFR level and survival time and also no difference for serum EGFR level according to histological subtype and disease stage was observed.

In summary, the current study's results suggest that the utility of serum EGFR level in patients with NSCLC, as a tumor marker or as a factor indicating tumour progression is limited. However further prospective studies on a large number of patients will be necessary to confirm this study's results. We also have suggested that evaluating overexpression of EGFR at cancer tissue with quantitative detection by immunohistochemical methods can be more useful than serum assessment.

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