

ORIGINAL RESEARCH

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Is TTF-1 a prognostic marker in non-small cell lung adenocarcinoma?

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Abstract

Thyroid transcription factor-1 (TTF-1) is first found to be a promoter of the thyroglobulin. The primary function of this protein is the regulation of nuclear transcription. TTF-1 has suggested having both oncogenic and anti-oncogenic effects on tumor biology. A total number of 1104 patient's data with lung cancers are evaluated. When the patients without adenocarcinoma histology, unknown TTF-1 status, and lost follow-up were excluded, the remaining total number of 104 patient's characteristics, chemotherapy types, treatment responses (as accommodation with Response Evaluation Criteria in Solid Tumors), progression-free survival (PFS) and overall survival (OS) were recorded and analyzed. TTF-1 positivity is significantly correlated with the female gender. The biopsy location among the groups was statistically different between the TTF-1 positive and negative groups. The EGFR mutation rate was significantly higher in the TTF-1 positive group. In the survival analysis, the TTF-1 positive patients have a significantly better OS in all study population. The statistically significant survival advantage was going on in the TTF-1 positive group when the TKI treated patients excluded. The PFS was not significantly different between the two groups. However, when the TKI treated patients excluded in both groups; the TTF-1 positive group had a significantly better PFS. In conclusion, TTF-1 positivity may be used as a positive prognostic marker for lung adenocarcinoma independent from TKI usage because of strongly correlated with a better OS.

Keywords: Lung adenocarcinoma, Prognostic marker, TTF-1

Introduction

Thyroid transcription factor-1 (TTF-1) with the other name NKX2-1 is first found to be a promoter of the thyroglobulin. The primary function of this protein is the regulation of nuclear transcription [1]. It is known to have a potential role in multiple organ development also including lung [2-4]. It has been proven to have an essential role in pneumocyte differentiation and pulmonary composition [4,5].

TTF-1 is a useful pathologic marker for the diagnosis of lung adenocarcinoma, but the biologic effects of its' positivity are still under consideration [6-8]. TTF-1 has suggested having both oncogenic and anti-oncogenic effects on tumor biology. The amplification of TTF-1 was strongly suggested to have an oncogenic function by four studies [9-12]. On the other side, TTF-1 may play a have anti-proliferative effect in cancer. The epithelial-mesenchymal transition which is induced by transforming growth down-regulate Snail and Slug transcription factors which have to induce this pathway [13-15].

Non-small cell lung carcinomas (NSCLC) are one of the most common cancer types and the leading cause of the death from the

cancer disease. The decrease in the smoking rates and alteration in smoking habits had increased the adenocarcinoma rates among the other subtypes [16,17]. TTF-1 is more frequent in small cell cancer of the lung (SCLC) than adenocarcinoma. While the positivity rate of TTF-1 is more than 90% in SCLC, this rate is approximately 70% in adenocarcinomas. However, TTF-1 over-expression is suppressing in the mucinous type of lung adenocarcinomas, but it consists of a small part of lung adenocarcinomas (5-10%) Also, mucin positive other cancers were shown to lack TTF-1.[18-20]. TTF-1 positive lung adenocarcinomas are shown to have more frequent epidermal growth factor receptor (EGFR) mutation [21,22]. The low specificity of TTF-1 in SCLC is limited its' utility to distinguish from other cancers [23-26]. The TTF-1 positivity can also be detected in squamous cell lung cancer and the different cancer types like colorectal, gynecologic and breast tumors as very rare [27,28].

The studies which investigate the prognostic effect of TTF-1 in lung cancer are limited in the literature [29-32]. In this study, we aimed to analyze the clinical prognostic effect of TTF-1 expression in patients with non-small cell lung adenocarcinomas.

Material and Methods

Study Participants

In this cross-sectional and retrospective study, we scanned archive records of single oncology center in Turkey, between 2012 and 2018

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years. A total number of 1104 patient's data with lung cancers are evaluated. When the patients without adenocarcinoma histology, unknown TTF-1 status, and lost follow-up were excluded, the remaining total number of 104 patient's characteristics, chemotherapy types, treatment responses (as accommodation with Response Evaluation Criteria in Solid Tumors), progression-free survival (PFS) and overall survival (OS) were recorded and analyzed.

Statistical analysis

The statistical analysis of the study performed with SPSS software (Statistical Package for the Social Sciences, version 22.0, SPSS Inc, Chicago, IL). The Kolmogorov-Smirnov test was used to determine whether data conformed to a normal distribution. Descriptive data are presented as either means or median for continuous variables, frequencies and percentages are reported for categorical variables. The primary endpoint of the study was OS and PFS difference between the TTF-1 positive and negative patients. Kaplan-Meier curves were used to determine the difference. The chemotherapy responses were defined from the radiologic reports. The difference between groups was tested with the Chi-square test.

Ethics

The study was approved by the local ethics committee of the Afyon Sağlık Bilimleri University, and the trial was conducted in accordance with the Declaration of Helsinki Principles.

Results

A totally one hundred and four patient enrolled in the study. TTF-1 positivity is significantly correlated with the female gender. The median age between TTF-1 positive and negative group was 63 and 62 years, respectively. The smoking status and smoking periods were not differentiated between the two groups. The biopsy location among the groups was statistically different between the TTF-1 positive and negative groups. More patients in the TTF-1 negative group had diagnosed with the metastatic tissue biopsy. The metastatic sites were not different between the groups. The EGFR mutation rate was significantly higher in the TTF-1 positive group. The tyrosine kinase inhibitory (TKI) treatment was not significantly different among the two groups, but there was a trend of more treatment in TTF-1 positive patients. The treatment types, treatment modalities, and chemotherapeutic agents were not different between groups. The patients' characteristics are shown on the Table-1.

Table 1. The patients' characteristics with lung adenocarcinoma

Gender	TTF-1 negative patients(n:19)			TTF-1 positive patients (n:85)			P value=
	Male	Female		Male	Female		
Age	17	2		35	50		
Smoking	Positive 14	62* Negative 5		Positive 50	63* Negative 33		0.74
Biopsy Location	Primary	Lymph node	Metastatic Tissue	Primary	Lymph node	Metastatic Tissue	
Stage	11 1-2	1 3	7 4	69 (12)a 1-2	7 3	8 4	0.011
Lung met**	Positive 3	Negative 16	13	Positive 16	Negative 66	67	0.30
Liver met**	Positive 3	Negative 16		Positive 10	Negative 75		0.75
Brain met**	Positive 4	Negative 15		Positive 19	Negative 66		0.70
Bone met**	Positive 9	Negative 10		Positive 29	Negative 56		0.92
Adrenal met**	Positive 2	Negative 17		Positive 12	Negative 73		0.31
Other met**	Positive 1	Negative 18		Positive 19	Negative 66		0.50
EGFR mut***	Positive 1	Negative 18		Positive 17	Negative 48		0.11
ALK mut***	Positive	Negative		Positive	Negative		0.05
Surgery	Positive 1	Negative 18		Positive 10	Negative 73		0.39
Chemotherapy	Positive 17	Negative 2		Positive 70	Negative 13		0.73
Radiation Txb	Positive 8	Negative 11		Positive 40	Negative 43		0.60
RT Type	Definitive 4	Palliative 4		Definitive 8	Palliative 32		0.17
TxbType	Neoadjuvant 2	Adjuvant 1	Palliative 14	Neoadjuvant 3	Adjuvant 10	Palliative 57	0.35
Platinum	Cisplatin 12	Carboplatin 5		Cisplatin 55	Carboplatin 16		0.55
First-line chemo response	PD 5	SD 1	PR 8	PD 26	SD 9	PR 27	0.59
TKI Txb	Positive 2	Negative 16		Positive 28	Negative 54		0.08

In the survival analysis, the TTF-1 positive patients have a significantly better OS in all study population ($p=0.007$). (Figure-1) The statistically significant survival advantage was going on in the TTF-1 positive group when the TKI treated patients excluded ($p=0.018$). (Figure-2) The PFS was not significantly different between the two groups ($p=0.34$). However, when the TKI treated patients excluded in both groups; only the TTF-1 positive group had a significantly better PFS ($p=0.04$).

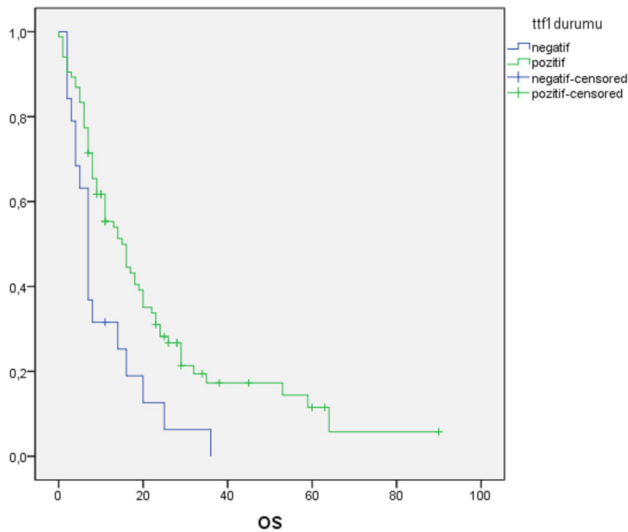


Figure 1. Comparing overall survival (OS) times in TTF-1 positive and negative groups

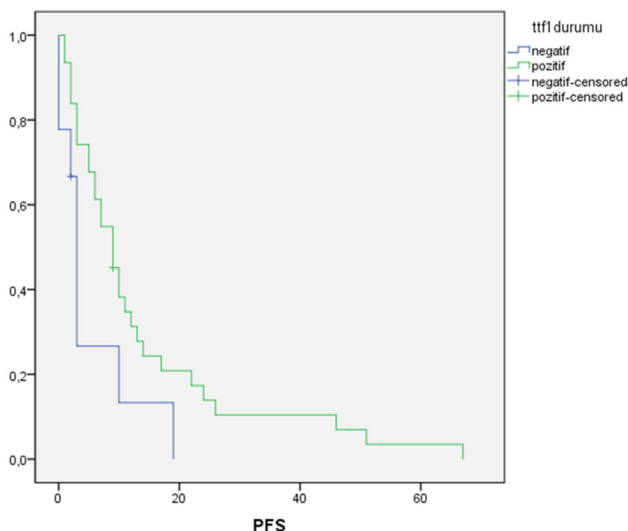


Figure 2. Comparing progression-free survival (PFS) times in TTF-1 positive and negative groups

Discussion

In this study, we found that TTF-1 positivity has a strong correlation with the overall survival and this advantage was going on even after the exclusion of TKI treated patients. This data has shown the improvement in OS and PFS might be independent of TKI agents. Also, the EGFR mutation frequency was high in the TTF-1 positive group; this data was compatible with the literature. Two preclinical studies reported the high coexistence of TTF-1 and EGFR mutation [21,22]. In correlation with this literature, a clinical found more EGFR mutation with TTF-1 over-expression

[33]. There was a statistically significant difference among gender in our study. Even though smoking status does not differentiate between TTF groups and genders, higher doses of carcinogens (tobacco, pollution, occupational exposure, etc.) which affect male gender, may cause this phenomenon.

The TTF-1 positivity was 81.7% which a correlate with the current literature. In the literature, the rates of TTF-1 expression were reported between 70 and 80 percent. Even though the higher rates of positivity were shown in the SCLC, lack of diagnostic effect made TTF-1 useless in routine practice [23–26].

In two meta-analysis, the prognostic effect of TTF-1 is confirmed. TTF-1 positive tumors had a better survival with chemotherapy. Only one of the studies had a negative result. In these studies, this effect was confirmed to be in both early and advanced stage tumors.

In a study, Doherty et al. investigated the survival difference between TTF-1 expression types in stage 4 lung adenocarcinomas. This study showed a survival difference between TTF-1 positive and negative groups. Even though there was a survival difference in this study, there were essential limitations such as low patient count and inequivalence between the arms. Also, this study only composed with the patients who received platinum and pemetrexed. The effect of the next lines and TKI use was not mentioned. In our study, independent from the chemotherapeutic agent, and the EGFR status and anti-EGFR TKI use; there was a statistically significant OS advantage and uncertain PFS advantage in favor of the TTF-1 positive group.

In an Egyptian study, which is consisting of 120 patients diagnosed with lung cancer, OS advantage had been detected in the TTF-1 positive group. The study participants had received various chemotherapeutic agents. However, In the multivariate analysis, the TTF-1 status was not an independent risk factor. Although the EGFR status of the patients was determined in this study, the TKI usage was not determined [34]. Two more studies from Norway and Brazil showed an OS advantage in TTF-1 positive tumors [35,36]. Although, some preclinical models suggested the high expression of thymidylate synthase in TTF-1 positive tumors may benefit more from pemetrexed-based chemotherapies. The current literature and our study show a higher OS independent from chemotherapeutic agents [37]. Especially, high frequency of EGFR in Asian populations the PFS of first-line chemotherapy was shown to be superior in the Asian population. The OS was not shown in this study [38]. These results suggest that the role prognostic role of the TTF-1 may be independent of ethnic diversities.

The TTF-1 may be to have a prognostic effect on KRAS mutant patients. In multivariate analysis of this study, the patients who had EGFR mutation, poor performance status and treated with monotherapeutic chemotherapy were not benefited from the prognostic effect of TTF-1 [33]. However, this area is not clearly identified because of very limited study.

Retrospective design and low patient number in the TTF-1 negative groups were study limitations of our study.

Conclusion

TTF-1 positivity can use as a positive prognostic marker for lung adenocarcinoma independent from TKI usage because of strongly correlated with a better OS.

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Competing interests

The author confirms that this article content has no conflict of interest.

Financial Disclosure

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Ethical approval

The study was approved by the local ethics committee of the Afyon Sağlık Bilimleri University.

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