Original Article

The prognostic role of thyroid transcription factor-1 in lung adenocarcinoma

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ABSTRACT

Aims: In this study, we investigated the expression of thyroid transcription factor-1 (TTF-1) in lung adenocarcinoma patients' samples and analyzed the association of TTF-1 with clinicopathological parameters, prognosis, and treatment options in patients with lung adenocarcinoma.

Subjects and Methods: This retrospective study enrolled 200 patients who were histologically confirmed lung adenocarcinoma with Stage I-IV disease, between 2008 and 2015 years. The cytological archive of these hospitals' Pathology Department was searched. The available slides and the clinical information were reviewed and correlated. All analyses were conducted by SPSS version 15.0 statistical software.

Results: Sixty-five (32.5%) of the patients showed TTF-1 negativity and 135 (67.5%) of them showed TTF-1 positivity. The median survival for TTF-1 positive and negative patients was 19.6 and 12.2 months, respectively. We did not find any statistical significance in-between the parameters in terms of the survival data. In TTF-1-negative group, the survival time of epidermal growth factor receptor mutation positive ($P = 0.049$), cytokeratin 7 (CK7) positive ($P = 0.009$) patients and those who had received curative radiotherapy ($P = 0.028$) was significantly better as compared to TTF-1-positive group. We also analyzed the relation between TTF-1 and survival outcome or chemotherapy selection in Stage IV disease. We could not identify any correlation between TTF-1 and survival outcome or treatment selection.

Conclusions: This study suggests that TTF-1 is not a favorable prognostic factor in lung adenocarcinoma patients. The prognostic role of CK7 and relationship between TFF-1 expression in lung adenocarcinoma and predictive role of TTF-1 expression for the selection of first-line treatment in Stage IV lung adenocarcinoma should be validated in prospective and randomized studies.

KEY WORDS: Cytokeratin 7, lung adenocarcinoma, prognostic factor, thyroid transcription factor-1

INTRODUCTION

Lung adenocarcinoma is one of the leading causes of cancer death and accounted for nearly 40% of all lung cancers.[1] This type of lung cancer has been increasing gradually in recent decades, in many countries. Nowadays, conventional chemotherapy and radiotherapy (RT) options have limited efficiency in the treatment of lung cancer. This situation has led to the consideration of new therapeutic approaches such as inhibitors of the epidermal growth factor receptor (EGFR) and the echinoderm microtubule-associated protein like 4-anaplastic lymphoma kinase (ALK) fusion protein.[2] However, very few number of patients are suitable for such targeted treatments. In this case, predictor markers may be helpful for the clinician in the selection of chemotherapeutics or other personalized drugs.

Thyroid transcription factor-1 (TTF-1), also known as Nkx2.1, is a 38-kDa transcription factor that is normally expressed in adult thyroid tissue and Type II pneumocytes in the adult lung. TTF-1 is also expressed in nearly 75% of nonmucinous lung adenocarcinomas and is commonly used as a marker for the diagnosis of lung adenocarcinomas.[3] Recent studies also recommended that it is a lineage-specific protooncogene for lung cancer.[4]

The prognostic significance of TTF-1 was investigated with several studies in nonsmall cell

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lung cancer particularly in lung adenocarcinoma. The results of these studies reporting the prognostic significance of TTF-1 are conflicting. Most of them recommended that TTF-1 was a positive prognostic factor for survival in adenocarcinomas and was significantly associated with female gender, never-smoking status and presence of EGFR mutations. In this study, we investigated the expression of TTF-1 in lung adenocarcinoma patients' samples and analyzed the association of TTF-1 with clinicopathological parameters, prognosis and treatment options in patients with lung adenocarcinoma.

SUBJECTS AND METHODS

Patient selection

This retrospective study enrolled 200 patients with histologically confirmed primary lung adenocarcinoma who underwent lung cancer treatment at Medical Oncology Departments of four hospitals (9 Eylul University Hospital, Adnan Menderes University Hospital, Aydın Ataturk Government Hospital, and Mugla Sıtkı Kocman University Hospital) in-between 2008 and 2015. Clinical information on each patient was obtained from the hospitals' medical records databases. This study was approved by the hospital's Institutional Review Board. The clinicopathological characteristics of the patients are summarized in Table 1. The cytological archive of these hospitals' pathology departments was searched. The available slides and the clinical information were reviewed and correlated. All study cases were annotated with available clinical information in a manner that protected patient privacy.

Pathological methods

The tissue specimens were sectioned at 4 μm, deparaffinized and incubated with primary antibodies. After standard processing, the sections were stained using hematoxylin-eosin stain and immunohistochemical staining employing anti-TTF-1 (SP141) rabbit monoclonal primary antibody (anti-TTF-1) (SP141), according to the instructions. TTF-1 immunohistochemical staining was assessed by two experienced pathologists. A tumor was considered positive or negative for TTF-1 based on the percentage of positive cells. It was considered to be positive if >5% of tumor cells with an appropriate staining pattern were identified; otherwise, the tumor was considered to be negative. Nuclear staining was considered positive for TTF-1.

Statistical analysis

All analyses were conducted by SPSS for Windows (version 15.0.1, SPSS, Inc., Chicago, IL, USA). Categorical variables were described by frequencies and percentages; continuous variables were described by means and standard deviations or medians and interquartile range values. Chi-square test was used to discover the relationship between categorical variables. Mann–Whitney U-test was used to compare two independent means and median test was used to compare two independent medians. Kaplan–Meier analysis was performed with a log-rank test to compare prognostic factors. A COX regression analysis was run to understand multivariate interaction of prognostic factors. $P < 0.05$ was considered as statistically significant.

RESULTS

Patient characteristics and treatment properties

In total, 157 (78.5%) male and 43 (21.5%) female patients were included in this study. The median age was 62 years of whom 147 (74.2%) were smokers. There were 7 (3.5%) Stage I, 17 (8.5%) Stage II, 27 (13.5%) Stage IIIA, 32 (16%) Stage IIIB, and 117 (58.5%) Stage IV diseases. Sixty-five (32.5%) of the patients showed TTF-1 negativity and 135 (67.5%) of them showed TTF-1 positivity. Of the 200 lung adenocarcinoma samples, 17 (8.5%) were positive for EGFR mutations. A total of 60 patients were alive at the end of the follow-up, while 138 patients were died. The overall follow-up was 13.4 (22.1) months. Fifty-two (26%) patients had undergone surgery, 42 (21%) patients had received RT and 41 (20.5%) patients had received chemoradiotherapy (CRT). Thirty-four (17.1%) and 24 (12%) of the patients had received adjuvant and neoadjuvant chemotherapy, respectively. The characteristics of patients in-relation to their TTF-1 stainings are shown in Table 1.

Survival analysis

Male gender was found to be associated with a poor outcome (male 17.3 months vs. female 23.9 months). The median survival for TTF-1 positive and negative patients was 19.6 and 12.2 months, respectively [Figure 1]. The survival time of EGFR mutation-positive patients was longer than the negative ones (29.4 months vs. 16.9 months). Patients who had received curative RT or CRT had better survival time. However, we did not find any statistical significance between the parameters in terms of the survival data. Kaplan–Meier analysis showed that there was a significant association in-between survival time and tumor, node, and metastasis (TNM) stage, history of surgery or adjuvant treatment ($P < 0.001$) [Table 2]. A multivariate model confirmed that early Stage (II and IIIA) disease and operated patients had a significantly better prognosis (Stage II heart rate [HR] = 0.402, Stage IIIA HR = 0.330, operated patients HR = 0.429) as compared to Stage IV disease and the nonoperated patients, respectively.

Overall survival (OS) analyses between TTF-1 staining and other parameters showed that there was a significant association

Table 1: Characteristics of thyroid transcription factor-1 negative and positive patients

	TTF-1 negative (*n*=65)	TTF-1 positive (*n*=135)	*P*	Total patients
Age, mean (SD)	61.8 (10.1)	63.1 (10.1)	0.315	62.7 (10.1)
Sex, *n* (%)				
Male	56 (86.2)	101 (74.8)	0.068	157 (78.5)
Female	9 (13.8)	34 (25.2)		43 (21.5)
Stage, *n* (%)				
1	2 (3.1)	5 (3.7)	0.405	7 (3.5)
2	4 (6.2)	13 (9.6)		17 (8.5)
3A	13 (20.0)	14 (10.4)		27 (13.5)
3B	9 (13.8)	23 (17.0)		32 (16.0)
4	37 (56.9)	80 (59.3)		117 (58.5)
CK7, *n* (%)				
Negative	11 (16.9)	14 (10.4)	0.189	25 (12.5)
Positive	54 (83.1)	121 (89.6)		175 (87.5)
EGFR, *n* (%)				
Negative	61 (93.8)	122 (90.4)	0.409	183 (91.5)
Positive	4 (6.2)	13 (9.6)		17 (8.5)
Smoking, *n* (%)				
Absent	17 (26.2)	34 (25.2)	0.929	51 (25.8)
Present	48 (73.8)	99 (73.3)		147 (74.2)
Operation, *n* (%)				
Absent	46 (70.8)	102 (75.6)	0.470	148 (74.0)
Present	19 (29.2)	33 (24.4)		52 (26.0)
Curative RT, *n* (%)				
Absent	51 (78.5)	107 (79.3)	0.897	158 (79.0)
Present	14 (21.5)	28 (20.7)		42 (21.0)
RT + CT, *n* (%)				
Absent	50 (76.9)	109 (80.7)	0.531	159 (79.5)
Present	15 (23.1)	26 (19.3)		41 (20.5)
PFS, median (IQR)	8.4 (11.5)	7.5 (8.7)	0.365	7.9 (9.0)
Status, *n* (%)				
Alive	16 (24.6)	44 (32.6)	0.305	60 (30.3)
Ex	47 (72.3)	91 (67.4)		138 (69.7)

n=Number of patients, SD=Standard deviation, TTF-1=Thyroid transcription factor-1, CK7=Cytokeratin 7, EGFR=Epidermal growth factor receptor, RT=Radiotherapy, CT=Chemotherapy, PFS=Progression-free survival, IQR=Interquartile range, OS=Overall survival

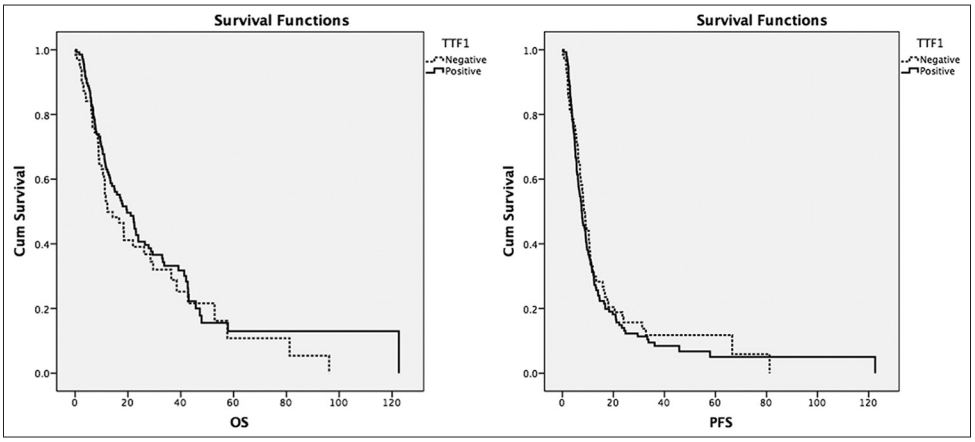

Figure 1: Survival curve according to thyroid transcription factor 1 (all patients). Cum = Cumulative, TTF-1=Thyroid transcription factor-1, PFS=Progression-free survival, OS = Overall survival

between survival time and TNM stage, history of surgery or adjuvant treatment ($P < 0.001$) [Table 3]. In TTF-1-negative group, the survival time of EGFR mutation-positive patients ($P = 0.049$), cytokeratin 7 (CK7) positive patients ($P = 0.009$), and patients who had received curative RT ($P = 0.028$) had a significantly better survival compared to TTF-1-positive group. The median survival for CRT negative and positive patients was 29.6 and 11.3 months, respectively, in TTF-1-negative group. However, the difference was not statistically significant.

Subgroup analysis of metastatic disease

We created a subgroup from our database by selecting patients who were in Stage IV at diagnosis and who became Stage IV at least 6 months after adjuvant treatment. In this subgroup, we analyzed the relation between TTF-1 and survival outcome or chemotherapy selection [Table 4]. The median survival time for TTF-1 positive and negative patients was 13.3 and 9.1 months, respectively. However, we did not find any significant relation between them [Figure 2]. We analyzed the

Table 2: Overall survival analysis

	OS				PFS			
	Median	95% CI		*P*	Median	95% CI		*P*
		Lower	Upper			Lower	Upper	
Sex								
Male	17.3	11.2	23.3	0.114	7.7	6.5	9.0	0.061
Female	23.9	11.8	36.1		9.7	6.6	12.8	
Stage								
1	122.6	.	.	<0.001	12.4	8.8	16.0	<0.001
2	43.0	33.9	52.1		21.2	15.9	26.5	
3A	52.8	38.0	67.7		24.0	14.0	33.9	
3B	22.1	8.4	35.8		8.8	5.5	12.2	
4	11.3	9.3	13.3		6.4	5.2	7.7	
TTF-1								
Negative	12.2	5.7	18.8	0.333	8.8	7.2	10.5	0.577
Positive	19.6	14.1	25.2		7.7	6.1	9.2	
CK7								
Negative	11.8	6.2	17.4	0.475	5.4	3.4	7.4	0.021
Positive	18.4	13.2	23.6		8.2	7.0	9.3	
EGFR								
Negative	16.9	12.4	21.4	0.466	7.8	6.7	9.0	0.984
Positive	29.4	21.6	37.2		9.6	6.4	12.7	
Smoking								
Absent	33.2	23.2	43.1	0.246	10.1	8.2	12.0	0.072
Present	28.4	21.4	35.4		7.5	6.5	8.6	
Operation								
Absent	11.8	10.1	13.5	<0.001	6.4	5.4	7.5	<0.001
Present	43.0	37.8	48.2		22.3	15.2	29.4	
Curative RT								
Absent	15.0	10.5	19.6	0.056	7.7	6.7	8.6	0.084
Present	33.2	17.1	49.4		10.7	7.8	13.6	
RT + CT								
Absent	15.9	10.5	21.2	0.342	7.8	6.6	9.1	0.933
Present	23.1	9.2	36.9		8.4	6.3	10.6	
Overall	18.3	12.7	23.9		8.0	6.8	9.2	

TTF-1=Thyroid transcription factor-1, CK7=Cytokeratin 7, EGFR=Epidermal growth factor receptor, RT=Radiotherapy, CT=Chemotherapy, CI=Confidence interval, PFS=Progression-free survival, OS=Overall survival

relationship between the chemotherapy regimens and TTF-1 staning in this group of patients. The OS time was longer for patients who were treated with taxanes and platinums in both TTF-1 positive and negative groups. Patients who were treated with gemcitabine and platinums had worse OS time in TTF-1-positive group (8.9 months). Pemetrexed and platinum regimens also had the shortest OS in TTF-1-negative group (6.1 months). However, this was not statistically significant [Table 5].

DISCUSSION

In the present study, we found that female gender, positive EGFR mutation, and receiving curative RT or CRT were associated with better survival in lung adenocarcinoma patients. In addition, we found that TTF-1-positive patients tended to survive longer than TTF-1 negative group, though the difference was not statistically significant. The effect of our patients' clinical parameters on survival was analyzed separately in the TTF-1 negative and positive groups. OS analyses between TTF-1 status and other parameters showed that there was a significant association between survival time and TNM stage, history of surgery or adjuvant treatment in both TTF-1 negative and positive groups. In TTF-1-negative group, EGFR mutation-positive patients, CK7 positive patients and patients who received curative RT had significantly better survival.

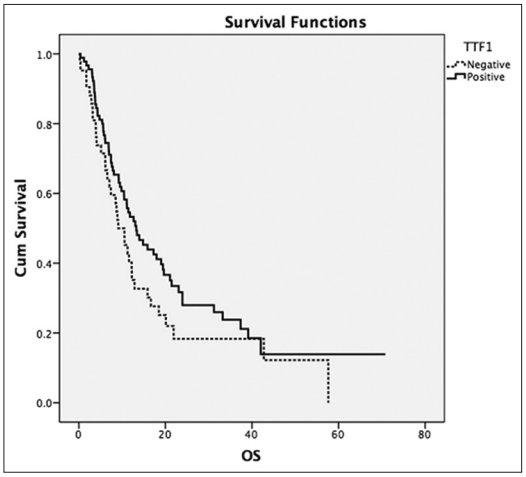

Figure 2: Survival curve according to thyroid transcription factor 1 (subgroup metastatic patients). Cum=Cumulative, TTF-1=Thyroid transcription factor-1, OS=Overall survival

Table 3: Survival analyses between thyroid transcription factor-1 staining and other parameters

	TTF-1 negative				TTF-1 positive			
	Median (months)	95% CI		*P*	Median (months)	95% CI		*P*
		Lower	Upper			Lower	Upper	
Sex								
Male	12.2	5.3	19.1	0.188	19.6	12.2	27.1	0.302
Female	26.1	3.0	49.2		23.1	12.5	33.6	
Stage								
1	14.2	.	.		122.6	.	.	
2	38.5	9.2	67.7	<0.001	43.0	25.4	60.6	<0.001
3A	52.8	18.9	86.8		45.7	28.2	63.2	
3B	28.5	.	.		22.1	8.8	35.3	
4	8.9	7.0	10.8		13.4	8.8	18.0	
CK7								
Negative	6.6	0.3	12.8	0.009	23.1	0.4	45.7	0.457
Positive	18.4	7.9	28.9		19.4	13.1	25.8	
EGFR								
Negative	11.6	8.0	15.2	0.049	19.4	13.0	25.9	0.879
Positive	26.1	.	.		29.4	25.1	33.7	
Operation								
Absent	10.6	8.4	12.7	<0.001	13.4	9.7	17.2	<0.001
Present	52.8	26.0	79.6		43.0	40.3	45.7	
Smoking								
Absent	29.6	4.6	54.5	0.232	19.6	5.6	33.7	0.494
Present	11.6	8.1	15.1		21.1	14.6	27.5	
Curative RT								
Absent	11.3	9.0	13.5	0.028	17.7	10.3	25.1	0.400
Present	38.5	23.8	53.2		26.4	7.9	44.9	
RT + CT								
Absent	11.3	4.8	17.7	0.518	18.0	10.0	26.0	0.473
Present	29.6	4.2	55.0		23.1	14.4	31.7	
Treatment								
Palliative	11.3	8.0	14.5	0.007	14.8	9.7	20.0	0.001
Neo-adjuvant	28.5	1.1	55.9		22.1	6.4	37.8	
Adjuvant	52.8	30.9	74.8		45.7	41.3	50.1	

TTF-1=Thyroid transcription factor-1, CK7=Cytokeratin 7, EGFR=Epidermal growth factor receptor, RT=Radiotherapy, CT=Chemotherapy, CI=Confidence interval

Table 4: Stage IV patients and their treatment details

	Total (*n*=134)	TTF-1		*P*
		Negative (*n*=43)	Positive (*n*=91)	
Age, mean (SD)	62.0 (9.3)	61.6 (9.8)	62.3 (9.2)	0.689
Gender, *n* (%)				
Female	23 (17.2)	3 (7.0)	20 (22.0)	0.032
Male	111 (82.8)	40 (93.0)	71 (78.0)	
Treatment, *n* (%)				
Platinum + gemcitabine	39 (29.1)	15 (34.9)	24 (26.4)	0.243
Platinum + pemetrexed	30 (22.4)	6 (14.0)	24 (26.4)	
Platinum + taxane	65 (48.5)	22 (51.2)	43 (47.3)	
OS, median (IQR)	10.6 (14.1)	9.8 (14.7)	11.1 (15.0)	0.617
PFS, median (IQR)	6.1 (6.2)	6.2 (6.6)	6.1 (7.4)	>0.999

n=Number of patients, SD=Standard deviation, TTF-1=Thyroid transcription factor-1, PFS=Progression-free survival, IQR=Interquartile range, OS=Overall survival

Table 5: Survival analysis of thyroid transcription factor-1 negative and positive metastatic patients

	TTF-1 negative (95% CI)					TTF-1 positive (95% CI)				
	Median (months)	SE	Lower	Upper	*P*	Median (months)	SE	Lower	Upper	*P*
Platinum + gemcitabine	8.9	2.2	4.5	13.3	0.73	9.2	2.3	4.7	13.7	0.37
Platinum + pemetrexed	6.1	2.1	1.9	1.03		11.4	3.3	5.1	17.8	
Platinum + taxane	11.3	2.4	6.6	16.0		15.9	3.0	10.0	21.7	

TTF-1=Thyroid transcription factor-1, SE=Standard error, CI=Confidence interval

TTF-1 is a homeodomain-containing transcription factor that is essential for morphogenesis and differentiation of the lungs. It is expressed in nearly 75% of nonmucinous lung adenocarcinomas and is most commonly used to distinguish primary lung adenocarcinoma from other metastatic tumors.[5] Although the role of TTF-1 in the diagnosis of

lung adenocarcinoma has been well understood, its role in carcinogenesis remains unclear. The prognostic impact of TTF-1 was assessed with several studies in non-small cell lung cancer especially in lung adenocarcinoma[6-23] and eleven of the studies included only adenocarcinoma histology[5,8,12,14-22] while others had nonsmall-cell lung carcinoma (NSCLC) histology.[7,9-11,13,20,23] Most of these studies showed that TTF-1 is a positive prognostic factor for survival in lung adenocarcinoma. In general, these studies were retrospective analysis with small number of patients, several important prognostic parameters were not taken into consideration, and there is a high heterogeneity within these studies [Table 6]. Anagnostou *et al*. found a positive relation only in Stage 1 patients' survival and TTF-1 staining, and there was not any association in other stages.[16] Among these studies, many analyzed the data by selecting specific patient subgroups. In the study conducted by Chung *et al*., patients who were under TKI treatment were evaluated. More than 300 TTF-1-positive patients (*n*: 345) were compared only with 43 TTF-1 negative patients.[22] In another study, TTF-1-positive patients' survival was statistically significantly improved in nonsolid pattern type. No impact was seen in solid patern.[5] Sun *et al*. investigated the relationship between TTF-1 staining pattern and pemetrexed treatment.[20] Berghmans *et al*. found better survival outcome in early-stage NSCLC patients with TTF-1 expression and another recent meta-analysis suggested that TTF-1 was a favorable prognostic factor in Stage I and Stage IIIb–IV NSCLC and lung adenocancer patients.[6,24] However, there is a high heterogeneity between the compiled studies in both meta-analysis and some prognostic parameters were not taken into consideration. Besides, there is only one study showing a negative prognostic impact of TTF-1 in lung adenocarcinoma patients[7] while five studies showed no impact on survival.[8,11,13,16,23] Because of the conflicting results of these studies, it is hard to say that TTF-1 overexpression is associated with a favorable prognosis in patients with lung adenocancer.

CK7 is a basic CK found on many glandular and transitional epithelia. In daily practice, it is commonly used in the diagnosis of lung cancer. The specificity and sensitivity of CK7 is high in the differential diagnosis, and its positivity confirms the diagnosis of lung adenocarcinoma.[25,26] In our study, CK7 expression was measured in the lung adenocancer tissue with IHC, and we analyzed the relationship between the TTF-1 and CK7. CK7-positive and TTF-1-negative patients had a significantly better survival than CK7-negative and TTF-1-negative patients. In TTF-1-positive group, CK7-negative patients lived longer than CK7 positive ones, but it was not statistically significant. To the best of our knowledge, CK7 and TTF-1 interaction has not been reported previously. Further studies are necessary to demonstrate any relationship between them.

The prognosis for Stage IV lung adenocarcinoma patients is generally poor, conventional CT and RT options have limited effect in the treatment. Spot of patients is suitable for targeted treatment. Based on this idea, we investigated the predictive role of TTF-1 expression for the selection of first-line treatment in Stage IV lung adenocarcinoma. We created a subgroup from our database by selecting patients who were in Stage IV at diagnosis and who became Stage IV at least 6 months after adjuvant treatment. We excluded EGFR, ALK, and reactive oxygen species-1 mutations positive patients and analyzed the relationship between the chemotherapy regimens and TTF-1 staining in this group of patients. The OS time was longer for patients who were treated with taxanes and platinums in both TTF-1 positive and negative groups. Patients who were treated with gemcitabine and platinum had worse OS time in TTF-1-positive group and with pemetrexed and platinum regimens also had the shortest OS in TTF-1-negative group in which we could not find any significant difference between them. We have found three studies about the association between chemotherapy regimens and TTF-1 staining in the

Table 6: Summary of the studies investigating the prognostic impact of thyroid transcription factor-1 in lung cancer patients

First author, year	Histology	Stage	Total number patients	AC number of patients in the study	Survival results
Puglisi, 1999[7]	NSCLC	I–III	88	20	Negative
Pelosi, 2001[8]	AC	I	97	97	NS
Haque, 2002[9]	NSCLC	I–III	57	28	Positive
Tan, 2003[10]	NSCLC	I–III	126	75	Positive
Myong, 2003[11]	NSCLC	I–III	65	25	NS
Saad, 2004[12]	AC	I	100	100	Positive
Shah, 2004[13]	NSCLC	I–III	63	43	NS
Barlési, 2005[14]	AC	III–IV	106	106	Positive
Wang, 2007[15]	AC	I–III	81	81	Positive
Anagnostou, 2009[16]	AC	I–IV	98	98	NS
Anagnostou, 2009[16]	AC	I	87	87	Positive
Martins, 2009[17]	AC	IIIB–IV	51	51	Positive
Anami, 2009[18]	AC	I–III	70	70	Positive
Hiramatsu, 2010[19]	AC	I–IV	193	193	Positive
Sun, 2011[20]	NSCLC	IIIB–IV	284	255	Positive
Solis, 2012[5]	AC	I–IV	135	135	Positive
Li, 2012[21]	AC	I–IV	185	175	Positive
Chung, 2012[22]	AC	IIIB–IV	496	496	Positive
Elsamany, 2015[23]	NSCL	IIIB–IV	120	-	NS

NSCL=Non-small cell lung cancer, AC=Adeno cancer, NS=Not significant

literature. In the first study, high TTF-1 protein expression was significantly associated with better clinical outcomes in NSCLC patients who were treated with pemetrexed-based chemotherapy.[20] For gemcitabine-based chemotherapy, TTF-1 positivity only prolonged progression-free survival (PFS) in univariate analysis. There was no difference between the groups in terms of taxane therapy. In this study, first-line treatments were not compared with each other. First-line pemetrexed-based chemotherapy was administered only to 60 patients. Other patients had received pemetrexed as later-line treatment. In the second study, pemetrexed plus carboplatin versus gemcitabine plus carboplatin treatments were analyzed.[27] The associations between the TTF-1 and OS were similar for both chemotherapy regimens. In the third study, investigators compared pemetrexed-containing chemotherapy with other chemotherapy regimens in NSCLC patients.[23] Pemetrexed-containing first-line treatment had significantly improved PFS in multivariate analysis. However, any relationship in-between TTF-1 expression and type of first-line therapy could not be obtained. They found that TTF-1 expression status was not an independent prognostic factor for PFS or OS in multivariate analysis. As a result, predictive role of TTF-1 expression for the selection of first-line treatment in Stage IV lung adenocarcinoma is not clear.

CONCLUSIONS

This study suggests that TTF-1 is not a favorable prognostic factor in lung adenocarcinoma patients. We could not identify any correlation between TTF-1 and treatment selection or clinicopathological parameters in subgroup analyses. Interestingly, CK7-positive patients when compared to CK7 negative ones had significantly better survival in TTF-1-negative subgroup. Furthermore, the prognostic role of CK7 and relationship between TTF-1 expression in lung adenocarcinoma and predictive role of TTF-1 expression for the selection of first-line treatment in Stage IV lung adenocarcinoma should be validated in prospective and randomized studies.

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Conflicts of interest

There are no conflicts of interest.

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