Prognostic Role of Thyroid Transcription Factor-1 (TTF-1) in Advanced and Inoperable Adenocarcinoma Subtype of Lung Cancer among Thai Patients

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Objective: *To determine the role of thyroid transcription factor-1 (TTF-1) as a prognostic factor in advanced adenocarcinoma of non-small cell lung cancer.*
Material and Method: *Retrospective cohort study among lung cancer patients with inoperable or metastases, adenocarcinoma type whose tumors were already tested for TTF-1 in Rajavithi Hospital from December 2003 to November 2011. The correlation of TTF-1 to survival period and the treatment outcomes were defined.*
Results: *Of 67 patients, 48 TTF-1 positive cases and 19 TTF-1 negative cases were included in the analysis. Median overall survival for all population was 263 days (111-415 days). No significant difference was found between TTF-1 positive and negative tumors (251 and 369 days, p-value = 0.8). The systemic treatment with chemotherapy was the only effective prognostic factor for survival of this study.*
Conclusion: *The prognostic factor of TTF-1 positive and negative in advanced adenocarcinoma subtype of NSCLC was not different in median overall survival.*

Keywords: *Thyroid transcription factor-1, Adenocarcinoma, Median overall survival*

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Thyroid transcription factor-1 (TTF-1), 38 kDa nuclear protein, is a thyroid-specific enhancer binding protein selectively regulating genetic transcription occurring in the lung, thyroid and diencephalon during embryogenesis. It has been commonly used as a marker to determine the presence of the primary lung especially in adenocarcinoma of non-small cell lung cancer or thyroid-derived tumor cells although its role in lung carcinogenesis remains unidentified.

Generally, normal pneumocyte type 2, Clara cell, follicular and parafollicular thyroid cells are positive to TTF-1. For positive staining in non-small cell lung cancer, the adenocarcinoma subtype accounted for 60 to 90% whereas that in large cell and squamous cell carcinoma subtype was 0-10%[1-5].

Correlation between TTF-1 and survival of adenocarcinoma of lung cancer has still been inconclusive. While the relationship between them was not found in some studies, other researchers reported that patients with TTF-1 positive lung cancer cells are more likely to survive than those with TTF-1 negative cells[6-21]. One possibility, according to one systematic review and meta-analysis study, shows TTF-1 to be a prognostic factor determining the survival of the adenocarcinoma subgroup of NSCLC[22]. The objective of the present study was to determine the role of TTF-1 toward the survival of advanced adenocarcinoma subtype and to detect other prognostic factors influencing their survival. The secondary objective was to determine other possible prognostic factors from the data of this population and relationships between TTF-1 and treatment outcomes.

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Material and Method

The protocol for this research was reviewed by the institutional ethics committee of Rajavithi Hospital, This research was a retrospective cohort study conducted by examining medical profiles of patients with a diagnosis of non-small cell lung cancer, adenocarcinoma and tested with TTF-1 in the Oncology Unit, Department of Medicine, Rajavithi Hospital between December 1, 2003 and November 30, 2011. All data were analyzed to study the effect of TTF-1 on survival and other possible survival prognostic factors

among this population.

Patient inclusion criteria

The patients selecting criteria included inoperable locally advanced or metastatic adenocarcinoma of non-small cell lung cancer, histologically confirmation of adenocarcinoma from either primary tumor or metastastic site(s) and TTF-1 testing conducted from block tissue biopsy or pack cytology of pleural effusion and staining with immunohistochemical (IHC) for TTF-1.

Histological subtype of the disease in all cases was categorized from the criteria of the WHO histological classification of lung cancer, 2004 and staging was based on the American Joint Committee on Cancer Staging of Lung Cancer, 7th edition, 2007.

TTF-1 immunoreactivity test was considered positive when any positive nuclear staining of malignant cells was found.

At enrollment, the clinical data from each patient was systematically collected and divided into two groups, based on TTF-1 results. The following patients' characteristics were defined: sex, age, ECOG (Eastern Cooperative Oncology Group) performance status, time to diagnosis, smoking status, histological subtype, stage of disease, comorbid illnesses, site(s) and number(s) of metastatic disease and systemic treatment and their outcomes determined using RECIST (Response Evaluation Criteria in Solid Tumors) criteria.

Statistical analysis

From the result from a previous study of Barlesi, et al[6] on one-year survival rate of patients with TTF-1, mainly expressed in adenocarcinoma of lung cancer, the combined HR was 0.53 (95% CI = 0.29-0.95). Estimated sample sizes for two-sample comparison of survivor function log-rank test were 40 patients in the TTF-1 positive arm and 20 patients in the TTF-1 negative arm to detect the difference survival with 70% power and alpha-level at 0.05.

To compare the baseline characteristic variables between two groups, Chi-square test was performed. The overall survival and time to progression were estimated using Kaplan-Meier method with Log-rank test.

The overall survival was started from the date of diagnosis until date of death as a result of any causes. The time to progression was the date of diagnosis to the date of the first evidence of lung cancer progression or documented relapse.

Multivariate analyses using Cox regression model was performed to estimate hazard ratio of death, with adjustment of the other confounding factors. A *p*-value less than 0.05 was considered statistically significant. Statistical analysis was performed with SPSS version 17.0.

Results

A total of 67 case profiles with advanced and inoperable adenocarcinoma of the lung by TTF-1 test were examined from 660 patients in the Oncology Unit, Rajavithi Hospital. TTF-1 positive and negative results were 48 (72%) and 19 (28%), respectively. Clinical characteristics of the sample population are summarized in Table 1. It can be seen that no significant difference was observed among groups in each baseline characteristics

According to the Fig. 1, the median survival period of the whole population was 263 days (111-415 days), while that of the TTF-1 positive and TTF-1 negative groups were statistically similar (251 and 369 days, *p*-value = 0.8).

Based on univariate analysis, 1) good performance status (ECOG 0-2 vs. 3-4), 2) age >65 years and 3) receiving systemic treatment were three significant prognostic factors observed (Table 2 and Fig. 2, 3). However, smoking status, presence of comorbid illnesses, sex, histological subtype of adenocarcinoma and number of organ metastases were not involved in the survival period.

The overall median survival for the patients over 65 years at the time diagnosis NSCLC was better than equal to and below 65 years, 458 (198-717 days) and 245 (125-365 days) respectively ($p = 0.026$) (Fig. 3).

The median survival time for ECOG 0-2 was 344 (277-411) days and for ECOG 3-4 was 73 (50-95) days with significant difference ($p<0.001$).

Multivariate analysis showed the systemic treatment, mostly chemotherapy, was the only prognostic factor affecting survival rate among this subgroup of patients (Table 3).

According to the Table 3-5, 37 of 67 cases (55%) received systemic first-line treatment. Among this group, 36 cases (97.3%) were given different chemotherapy regimens; 31cases (86%) received the third-generation platinum doublet, 4 cases (11%) received cisplatin or carboplatin in combination with etoposide and the others (3%) received single agent, gemcitabine. The objective response (complete or partial or stable disease) of treatment exhibited similar results (55% versus 56% for TTF-1 positive and negative, respectively). No significant difference of both

Table 1. Baseline characteristics of the patients

	TTF-1 positive (n = 48) n (%)	TTF-1 negative (n = 19) n (%)
Age (years) median (range)	54.7 (27-74)	55.3 (38-77)
Sex		
Female	24 (50)	5 (26)
Male	24 (50)	14 (74)
Smoking		
None	26 (54)	4 (21)
<20 pack-yeared	8 (17)	6 (32)
20 pack-year	14 (29)	9 (47)
ECOG		
0	2 (4)	3 (16)
1	19 (40)	5 (26)
2	14 (29)	5 (26)
3	2 (4)	5(26)
4	11 (23)	1 (5)
Staging of disease		
Stage IIIB	1 (2)	1 (5)
Stage IV	47 (98)	18 (95)
Histology		
Well differentiated	3 (6)	0
Moderately differentiated	3 (6)	1 (5)
Poorly differentiated	18 (38)	8 (42)
Undifferentiated	1 (2)	2 (11)
Other	23 (48)	8 (42)
Comorbid illness*		
Yes	36 (75)	15 (79)
No	12 (25)	4 (21)
Time to diagnosis (days) range	0-476	24-219
Median	103.5	133.5
Tissue diagnosis from		
Primary site	8 (17)	3 (16)
Metastatic site	40 (83)	16 (84)
Number of metastatic organs		
0-3	44 (92)	15 (79)
>3	4 (8)	4 (21)
Metastatic sites		
Pleura	24 (50)	8 (42)
Bone(s)	23 (48)	10 (53)
Lungs	17 (35)	5 (26)
Brain	10 (21)	2 (10.5)
Liver	9 (19)	5 (26)
Pericardium	6 (12.5)	6 (31.5)
Adrenal gland(s)	5 (10)	6 (31.5)

ECOG = eastern cooperative oncology group

* Most common comorbidity was hypertension, diabetes mellitus and dyslipidemia, which was well controlled

systemic treatments and the response to therapy was identified among both groups of patients.

Discussion

The clinical independent prognostic factors for survival of non-small cell lung cancer have previously been identified: performance status and stage of disease. To investigate other prognostic factors, the present study focused on only the advanced stage adenocarcinoma of the lung. It has

been reported that TTF-1 was not a prognostic factor in this population. The systemic treatment, mostly chemotherapy, was the only prognostic factor affecting survival rate among this subgroup of patients that shown in multivariate analysis but not in age and ECOG which decreased HR to 1.28 (may be from wide range of 95%CI). Possibly, the limited number of subjects, especially under one case estimated in TTF-1 negative tumor could be decreased the power of statistical test and the retrospective data selection approach contributed to misleading interpretation.

Our results were similar to five previous studies that revealed no survival difference between TTF-1 positive and TTF-1 negative tumors[17-21]. The data supported that TTF-1 positive correlated with good survival was still limited to the early stage of lung cancer[7-9].

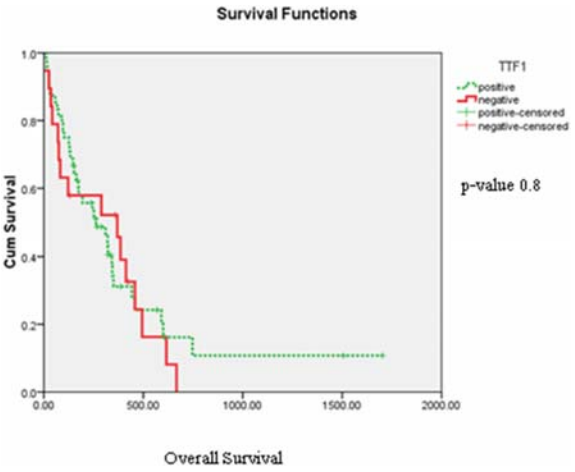

Fig. 1 Kaplan-Meier curves of overall survival; TTF-1 expression and overall survival analysis.

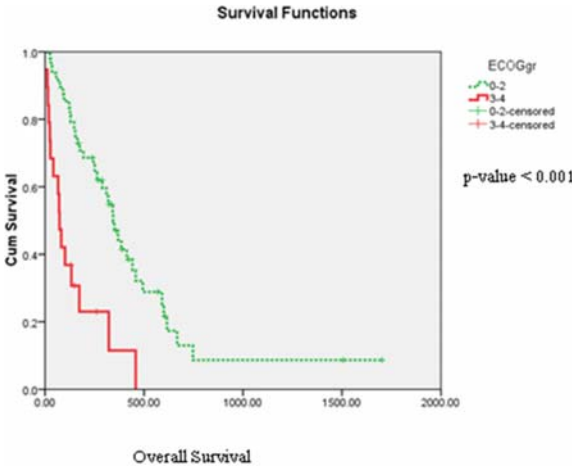

Fig. 2 Kaplan-Meier curves of overall survival; good performance status (0-2) versus poor performance status (3-4).

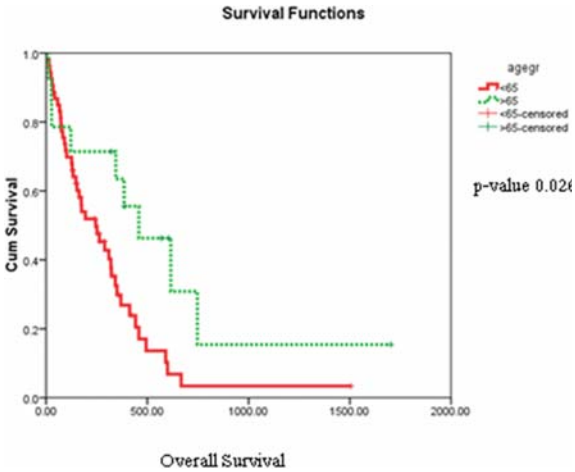

Fig. 3 Kaplan-Meier curves of overall survival; subgroup analysis for age group ≤65 vs. >65.

Table 2. Univariate overall survival analyses of possible prognostic factors

Factors	n (%)	Median survivale timedays (range)	*p*-value	HR	95% CI
Overall	67 (100)	263 (111-415)			
Age					
≤65 years	53 (79)	245 (125-365)		1	
>65 years	14 (21)	458 (198-718)	0.026	0.44	0.21-0.92
ECOG PS					
PS 0-2	48 (72)	344 (277-411)		1	
PS 3-4	19 (28)	73 (50-95)	<0.001	3.64	1.93-6.88
Received systemic treatment					
No	22 (33)	73 (22-124)		1	
Yes	45 (67)	385 (273-497)	<0.001	0.36	0.25-0.52

The actual carcinogenesis role of TTF-1 has been progressively investigated. One study concluded that both TTF-1 positive and EGFR mutation with EGFR-TKI treatment could prolong the survival, compared with those with TTF-1 negative and EGFR mutant tumors[23]. As a result, TTF-1 would be the predictive factor rather than the prognostic factor.

Patients receiving systemic treatment (mostly chemotherapy) had a significantly longer survival period than those receiving only supportive treatment. The much shorter survival time of the nonsystemic treatment group could be derived from their poor performance status.

In conclusion, no implication of TTF-1 was observed toward the advanced adenocarcinoma subtype of NSCLC from the present study. On the other hand, systemic treatment still played an important role to prolong the survival period of the population in this study.

Table 3. Multivariate analysis of prognostic factors and survival time by Cox proportional hazard model

Factors	HR (95% CI)	*p*-value
ECOG		
0-2	1	
3-4	1.28 (0.62-2.61)	0.51
Age		
≤65	1	
>65	0.68 (0.31-1.53)	0.35
Received systemic treatment		
No	1	
Yes	0.41 (0.27-0.62)	<0.001

ECOG = eastern cooperative oncology group

Potential conflicts of interest

None.

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Table 4. Systemic treatment of the study population

Treatment	TTF-1 positive (n = 48) n (%)	TTF-1 negative (n = 19) n (%)
First-line treatment	26 (54)	11 (58)
Chemotherapy	25 (52)	11 (58)
EGFR-TKI	1 (2)	0
Second-line treatment	16 (33)	6 (32)
Chemotherapy	13 (27)	6 (32)
EGFR-TKI	3 (6)	0
Third-line treatment	5 (10.4)	3 (15.8)
Chemotherapy	3 (6.2)	3 (15.8)
EGFR-TKI	2 (4.2)	0
More than three-lines of treatment	2 (4.2)	0

EGFR-TKI = Epidermal growth factor receptor-tyrosine kinase inhibitors

Table 5. Treatment outcomes

	TTF-1 positive (n = 48) n (%)	TTF-1 negative (n = 19) n (%)
First-line chemotherapy	n = 25	n = 11
CR	0	0
PR	5 (20)	4 (36.4)
SD	9 (36)	2 (18.2)
PD	9 (36)	3 (27.2)
Unknown*	2 (8)	2 (18.2)
Median time to progression (days)	265 (65-504)	229.5 (174-314)
Second-line chemotherapy	n = 13	n = 6
CR	0	0
PR	2 (15.4)	1 (16.7)
SD	5 (38.5)	3 (50)
PD	5 (38.5)	2 (33.3)
Unknown**	1 (7.6)	0
Median time to progression (days)	63 (23-267)	119 (77-126)
Third-line chemotherapy	n = 3	n = 3
CR	0	0
PR	0	1 (33.3)
SD	2 (66.7)	0
PD	1 (33.3)	2 (66.7)
Median time to progression (days)	217 (100-328)	80.5 (49-112)

* unknown = the treatment just started and then the patient was lost follow-up
** unknown =At the evaluated time, the patient received only one cycle of second line treatment
CR = complete response; PR = partial response; SD = stable disease; PD = disease progression

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บทบาท Thyroid Transcription Factor-1 (TTF-1) ในการพยากรณ์มะเร็งปอดระยะลุกลามชนิด Adenocarcinoma ในประเทศไทย

เจษฎา มณีชวขจร, ดวงนภา เบญจวงศ์เสถียร

วัตถุประสงค์: *เพื่อศึกษาบทบาท Thyroid transcription factor-1 (TTF-1) ที่จะนำมาช่วยทำนายการมีชีวิตรอดของผู้ป่วยมะเร็งปอดที่ไม่ใช่เซลล์ขนาดเล็กชนิด adenocarcinoma*

วัสดุและวิธีการ: *ได้ทำการเก็บข้อมูลย้อนหลังของผู้ป่วยมะเร็งปอดระยะลุกลามที่ผ่าตัดไม่ได้หรือมีโรคกระจายชนิด adenocarcinoma ที่ได้รับการตรวจตัวรับ TTF-1 ในโรงพยาบาลราชวิถีตั้งแต่ เดือนธันวาคม พ.ศ. 2546 ถึง เดือนพฤศจิกายน พ.ศ. 2554 และนำมาหาความสัมพันธ์ระหว่าง TTF-1 กับการรอดชีพรวมถึงผลการรักษา*

ผลการศึกษา: *มีผู้ป่วยจำนวน 67 รายที่ทราบผลการตรวจ TTF-1 เป็นผลบวก 48 ราย ผลลบ 19 ราย พบว่าค่าเฉลี่ย median การรอดชีพ 263 วัน (111-415 วัน) พบว่าไม่มีความแตกต่างทางสถิติในระยะเวลารอดชีพ (251 และ 369 วันตามลำดับ p-value = 0.8) และพบว่ากลุ่มที่ได้รับการรักษาจะมีการพยากรณ์การรอดชีพดีกว่า*

สรุป: *การพยากรณ์โรคมะเร็งปอดชนิด adenocarcinoma ระยะลุกลามด้วยการใช้ TTF-1 ที่เป็นบวกหรือลบ ไม่มีความแตกต่างในการรอดชีพของผู้ป่วย*