Original paper

Low LATS2 expression is associated with poor prognosis in non-small cell lung carcinoma

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Large tumor suppressor kinase 2 (LATS2) is a core component in the Hippo signaling pathway, and it functions as a tumor suppressor associated with tumor cell proliferation and apoptosis. The purpose of this study is to explore LATS2 expression and its clinicopathological significance in non-small cell lung cancer (NSCLC). We examined LATS2 protein expression by immunohistochemistry in 184 resected NSCLC specimens using tissue microarrays. Low LATS2 expression was significantly related to disease recurrence ($p = 0.047$). In survival analysis, the low LATS2 expression group showed a statistically poorer overall survival (OS) ($p = 0.004$) and disease-free survival (DFS) ($p = 0.014$) than the high expression group. In multivariate analysis, downregulated LATS2 expression in NSCLC could be an independent prognostic factor of poor OS and DFS. Furthermore, we evaluated the prognostic significance of LATS2 expression in two major NSCLC subtypes, squamous cell carcinoma and adenocarcinoma. The low LATS2 expression group showed worse prognosis than the high LATS2 expression group (OS [$p = 0.144$] and DFS [$p = 0.022$] in squamous cell carcinoma and OS [$p = 0.045$] and DFS [$p = 0.271$] in adenocarcinoma). We demonstrated that downregulated LATS2 expression may predict aggressive biologic behavior and a worse prognosis in NSCLC and we also suggested the possibility of LATS2 as a therapeutic target in both squamous cell carcinoma and adenocarcinoma.

Key words: LATS2, Hippo pathway, non-small cell lung cancer, immunohistochemistry, prognosis.

Introduction

Lung cancer is the leading cause of cancer-related death worldwide, although therapeutic modalities have greatly improved in recent years [1]. Because of the aggressive biological behavior of lung cancer compared to other malignant tumors, the five-year survival rate is still low even with early detection [2, 3]. Histologically, lung carcinoma is divided into two subgroups, small-cell carcinoma and non-small cell lung cancer (NSCLC). Non-small cell lung cancer accounts for approximately 80% of lung cancers and it consists of various histological subtypes including adenocarcinoma, squamous cell carcinoma, large cell carcinoma, large cell neuroendocrine carcinoma and pleomorphic carcinoma [4].

The Hippo pathway is a crucial signaling pathway associated with cell proliferation, apoptosis, and dif-

ferentiation [5]. Among its core molecules, large tumor suppressor (LATS) is a serine/threonine protein kinase with two well-known homologs, LATS1 and LATS2, which contain an analogous C-terminal region and a dissimilar N-terminal region [6, 7]. LATS biologically functions as a tumor suppressor via the phosphorylation and inactivation of its downstream targets, yes-associated protein and transcriptional co-activator with PDZ-binding motif. LATS2 is frequently downregulated in a number of malignancies including breast, prostate, and lung cancers [8, 9, 10, 11].

A few studies of LATS2 expression in lung cancer have been reported. Low LATS2 mRNA expression led to significant differences in disease-free survival and overall survival in lung adenocarcinoma patients [12]. A previous study that used immunohistochemistry revealed that low LATS2 expression contributed to poor overall survival [9]. However, the relationship between LATS2 expression and variable clinicopathological factors in lung cancer is yet to be clarified. Furthermore, no study has explored the prognostic significance of LATS2 protein expression according to lung cancer subtypes.

Here, we examined the correlations between LATS2 expression levels and a variety of clinicopathological factors in NSCLC patients. We also attempted to establish the value of LATS2 expression as a prognostic marker in the representative lung cancer subtypes, squamous cell carcinoma and adenocarcinoma.

Material and methods

Patients and samples

We enrolled a series of 184 patients with lung cancer: 90 adenocarcinomas, 75 squamous cell carcinomas, 10 large cell neuroendocrine carcinomas, 7 pleomorphic carcinomas and 2 adenosquamous carcinomas. All diagnoses were histologically and immunohistochemically confirmed, and all patients underwent surgical resection at Soonchunhyang University Cheonan Hospital between January 2001 and December 2012. Tumor tissues were prepared through formalin-fixed and paraffin-embedded processing. We retrospectively reviewed hematoxylin-eosin (H&E) slides and pathological reports as well as other medical records to collect clinicopathological information: patient age, sex, smoking history, tumor size, pleural invasion, lymphovascular invasion, lymph node metastasis and distant metastasis, American Joint Committee on Cancer (AJCC) stage, epidermal growth factor receptor mutation status, recurrence and survival. We restaged lung cancer according to the guidelines of the 8th edition of the AJCC's cancer staging manual and identified 96 stage I, 43 stage II, 41 stage III and 4 stage IV tumors. Of the patients, 130 were male and 54 were female. Patients were routinely followed up at regular intervals of 6 months or one year after surgery, and the median follow-up period was 39.8 months (range: 0 to 190 months). The mean age at diagnosis was 64.1 years (range: 39 to 82 years old) and the mean tumor size was 3.16 cm. This study was approved by the Institution Review Board of Soonchunhyang University Cheonan Hospital, and informed consent was waived (Institution Review Board no. 2016-07-029). This study conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Construction of tissue microarray

We constructed the tissue microarrays from formalin-fixed, paraffin-embedded blocks as previously described [13]. We also carefully reviewed the HE slides under light microscopy to select the most representative viable tumor portions. We obtained 2 mm single cores from previously marked tumor areas in donor blocks and transferred them into recipient blocks using trephine (Superbiochips Laboratories, Seoul, Korea).

Immunohistochemistry and interpretation

We purchased rabbit polyclonal anti-LATS2 antibody from Abcam (Abcam, Hong Kong, China, ab70565); we also performed immunohistochemical staining on 4 μm thick sections using the anti-LATS2 as previously described [13]. Briefly, we transferred the tissue microarray sections to adhesive-coated slides and then deparaffinized the slides by heating at 60°C for 1 hour, followed by washing slides three times in xylene. We blocked endogenous peroxidase activity using 5% hydrogen peroxide in methanol for 15 minutes at 37°C and retrieved the antigens using microwave treatment in a pH 6.0 epitope retrieval solution for 20 minutes. We also diluted the anti-LATS2 antibody 1:100 and incubated the sections overnight with the primary antibody in a humidified chamber at 4°C; we treated the secondary antibody using a bond polymer refine detection kit (Leica Biosystem, Wetzlar, Germany) and diaminobenzidine as a chromogen.

Two pathologists (Jang SH and Oh MH) independently evaluated the immunohistochemistry LATS2 results without knowledge of any of the patients' clinicopathological information. The cytoplasmic staining of tumor cells was classified as negative, weak, moderate or strong immunostaining intensity. Using the proportion results from the different tumor intensity groups, we semi-quantitively evaluated the LATS2 expression level with a H-score system as follows: H-score = 3 × percentage of strongly stained cells + 2 × percentage of moderately stained cells + percentage of weakly stained cells. We divided the cases into two groups, defining low LATS2 expression as an H-score of ≤ 100 and high expression as an H-score >100 (Fig. 1).

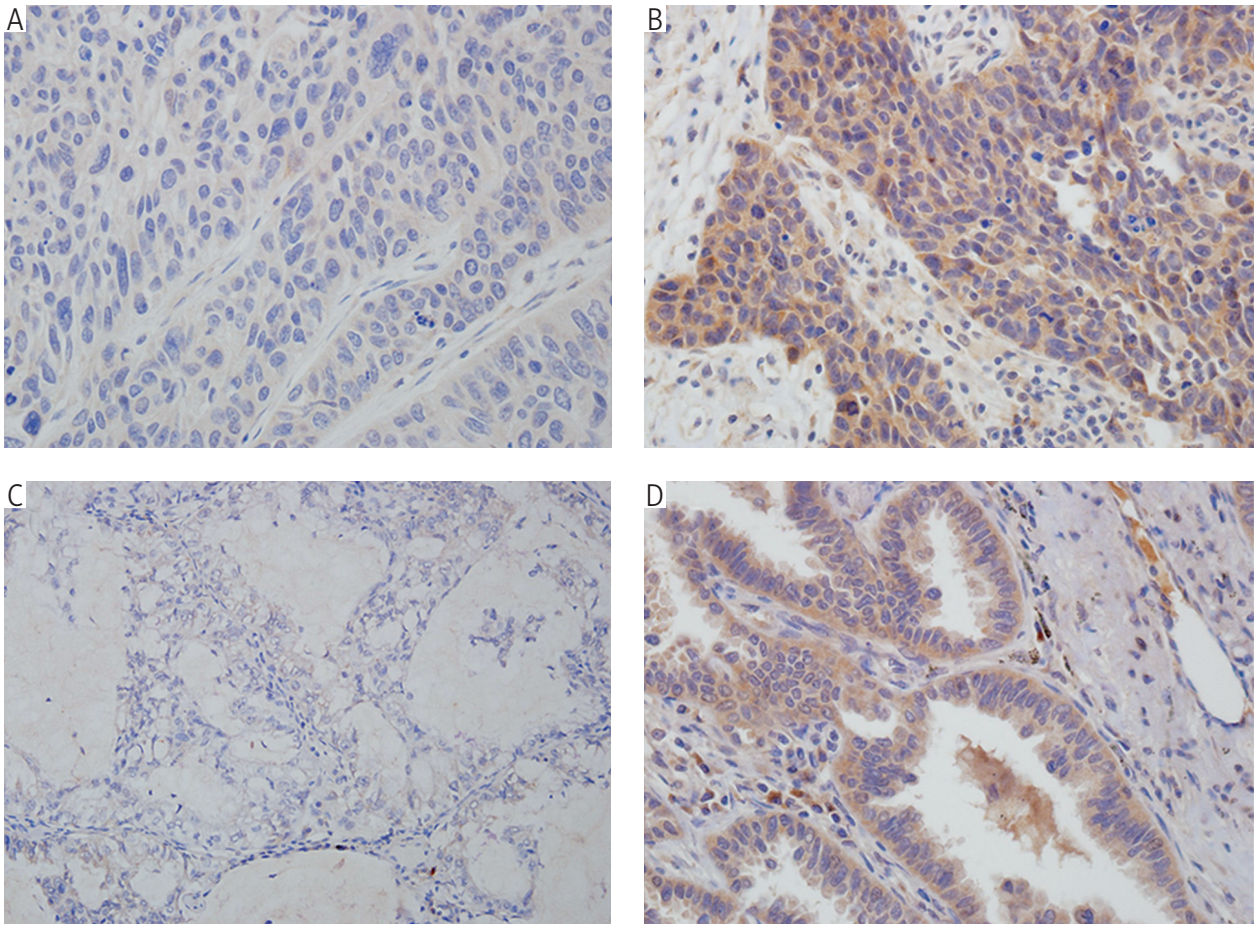

Fig. 1. Representative LATS2 immunohistochemical staining in squamous cell carcinoma and adenocarcinoma. A) Negative LATS2 staining in squamous cell carcinoma. B) Positive LATS2 staining in squamous cell carcinoma. C) Negative LATS2 staining in adenocarcinoma. D) Positive LATS2 staining in adenocarcinoma (200× original magnification)

Statistical analysis

We performed statistical analyses with SPSS version 14.0 for Windows (SPSS Inc, Chicago, IL, USA), using the χ^2 and Pearson's χ^2 tests with linear by linear trends to assess for correlations between LATS2 expression and clinicopathological parameters. We used the Kaplan-Meier method with log-rank test to analyze the overall survival (OS) and disease-free survival (DFS) curves. We also performed univariate and multivariate analyses using Cox proportional hazards regression to examine the prognostic significance of LATS2 expression. P value < 0.05 was considered to be statistically significant.

Results

Correlations between LATS2 expression and clinicopathological data

Forty (21.7%) of the 184 NSCLC specimens showed low LATS2 expression. To examine the impact of low LATS2 expression, we assessed the relationship between LATS2 expression and variable clinicopathological parameters in the 184 patients with NSCLC. There was no statistical difference between LATS2 expression and lung cancer subtypes ($p = 0.605$). Fifty-six (70.9%) of the 79 recurrent NSCLC patients showed low LATS2 expression and this low LATS2 expression was significantly correlated with disease recurrence ($p = 0.047$). We also found that low LATS2 expression tended to be correlated with adverse prognostic clinicopathological parameters including, large tumor size (> 3 cm), the presence of vascular and lymphatic invasion, and distant metastasis, although they were not statistically significant (Table I).

Survival analysis in NSCLC patients

At the time of analyses in the present study, disease had recurred in 79 of the 184 patients (42.9%). The Kaplan-Meier DFS curves with log-rank test revealed that patients with high LATS2 expression showed significantly longer OS ($p = 0.004$) and DFS ($p = 0.014$) than those with low expression (Fig. 2A, B).

Table I. Correlations between LATS2 expression and clinicopathological parameters in 184 non-small cell lung cancer

Variables	N (%)	LATS2 expression		P value
		Low expression	High expression	
Sex				0.560
Male	130 (100)	30 (23.1)	100 (76.9)	
Female	54 (100)	10 (18.5)	44 (81.5)	
Age (year)				1.000
< 65	88 (100)	19 (21.6)	69 (78.4)	
≥ 65	96 (100)	21 (21.9)	75 (78.1)	
Tumor type				0.605
Adenocarcinoma	90 (100)	17 (18.9)	73 (81.1)	
Squamous cell carcinoma	75 (100)	19 (25.3)	56 (74.7)	
Other types	19 (100)	4 (21.1)	15 (78.9)	
Tumor size				0.212
≤ 3	91 (100)	16 (17.6)	75 (82.4)	
>3	93 (100)	24 (25.8)	69 (74.2)	
Pleural invasion				0.721
Absent	102 (100)	21 (20.6)	81 (79.4)	
Present	82 (100)	19 (23.2)	63 (76.8)	
Vascular invasion				0.087
Absent	163 (100)	32 (19.6)	131 (80.4)	
Present	21 (100)	8 (38.1)	13 (61.9)	
Lymphatic invasion				0.211
Absent	156 (100)	31 (19.9)	125 (80.1)	
Present	28 (100)	9 (32.1)	19 (67.9)	
Tumor status				0.516
T1 and T2	145 (100)	30 (20.7)	115 (79.3)	
T3 and T4	39 (100)	10 (25.6)	29 (74.4)	
Lymph node metastasis				0.248
Absent	126 (100)	24 (19.0)	102 (81.0)	
Present	58 (100)	16 (27.6)	42 (72.4)	
Metastasis				0.287
Absent	180 (100)	40 (22.2)	140 (77.8)	
Present	4 (100)	0 (0.0)	4 (100.0)	
Relapse				0.047
No	105 (100)	17 (16.2)	88 (83.8)	
Yes	79 (100)	23 (29.1)	56 (70.9)	
Pathologic stage				0.652
I	96 (100)	18 (18.8)	78 (81.3)	
II	43 (100)	12 (27.9)	31 (72.1)	
III	41 (100)	10 (24.4)	31 (75.6)	
IV	4 (100)	0 (0.0)	4 (100.0)	
Smoking				0.457
Non-smoker	66 (100)	17 (25.8)	49 (74.2)	
Smoker	115 (100)	23 (20.0)	92 (80.0)	

Table I. Cont.

Variables	N (%)	LATS2 expression		P value
		Low expression	High expression	
EGFR mutation				0.532
Absent	50 (100)	8 (16.0)	42 (84.0)	
Present	23 (100)	5 (21.7)	18 (78.3)	
Not performed	128			

We performed univariate and multivariate analyses for all NSCLC patients of LATS2 expression level, sex, age, tumor size, local invasion-associated factors, lymph node metastasis, tumor stage and smoking history. Low LATS2 expression ($p = 0.005$), sex ($p < 0.001$), tumor size ($p < 0.001$), pleural invasion ($p = 0.011$), vascular invasion ($p = 0.043$), lymphatic invasion ($p = 0.019$), lymph node metastasis ($p < 0.001$), tumor stage ($p < 0.001$) and smoking history ($p = 0.014$) were correlated with poor OS based on univariate analysis; low LATS2 expression ($p = 0.017$), tumor size ($p < 0.001$), pleural invasion ($p < 0.001$), lymphatic invasion ($p = 0.022$), lymph node metastasis ($p < 0.001$) and tumor stage ($p < 0.001$) were correlated with significantly poor DFS (Tables II, III). We conducted a multivariate analysis using a Cox proportional regression model to investigate whether low LATS2 expression in NSCLC could be an independent predictor of survival and disease recurrence in the patient. We determined that low LATS2 expression could be an independent predictor of OS ($p = 0.032$, HR = 1.639) and DFS ($p = 0.030$, HR = 1.745; Tables II, III).

Survival analysis in squamous cell carcinoma and adenocarcinoma patients

Next, we selected patient groups with two major NSCLC subtypes, squamous cell carcinoma ($n = 75$) and adenocarcinoma ($n = 90$), and then assessed the effect of LATS2 expression level on OS and DFS for each subtype. In the squamous cell carcinoma patients, the Kaplan-Meier curves with log-rank test also showed that high LATS2 expression was more favorable for OS ($p = 0.144$) and DFS ($p = 0.022$) compared to low LATS2 expression (Fig. 2C, D). In adenocarcinoma patients, Kaplan-Meier disease curve with log-rank test also showed that OS ($p = 0.045$) and DFS ($p = 0.271$) of patients with high LATS2 expression was better than those of patients with low LATS2 expression (Fig. 2E, F).

Discussion

LATS2 on chromosome 13q11-12 is a tumor suppressor gene that encodes a 1046 amino acid protein with a PAPA repeat [8]. In various cancer types, LATS2 is involved in a diverse range of biological functions, including regulating cell cycle, inducing apoptosis and maintaining mitosis integrity [14, 15, 16]. The representative mechanisms of LATS2 inactivation include hypermethylation of the promoter region, tumor-specific mutations and altered upstream microRNA expression, which can trigger tumor development and progression [7, 9, 10, 17]. Various cancer studies have shown a considerable range of decreased LATS2 expression, from 0% to 80% [9, 12, 18, 19, 20]. Additionally, a previous lung cancer study reported that 49.2% (31 of 63) of lung adenocarcinoma and 58.5% (86 of 147) of NSCLC cases showed decreased LATS2 expression through immunohistochemistry. In the present study, low LATS2 expression was observed in 21.7% of NSCLC patients (40 of 184 cases), which is slightly lower than in a previous study. This discordance of LATS2 expression prevalence may be due to the limited number of cases and subtypes of NSCLC enrolled in the studies. Furthermore, each study examined LATS2 expression level based on immunohistochemistry using different interpretation criteria. In the present study, we evaluated LATS2 expression using H-scores because the H-score system could reflect both quantitative and qualitative aspects of immunohistochemical staining results.

Some *in vitro* studies demonstrated that the downregulation of LATS2 can lead to promotion of cancer cell growth and migration, which is a phenomenon related to the increase of tumor aggressiveness and invasiveness [9, 12, 20, 21, 22]. Especially in NSCLC cell lines, LATS2 is one of the key molecules associated with tumor growth, epithelial mesenchymal transition and/or invasion/metastasis [9]. Compared to previous studies, we also analyzed more concrete and detailed clinicopathological factors in this study. Disease relapse, which could represent the tumor growth and invasiveness, was more frequently observed in the low LATS2 expression group than in the high LATS2 expression group. Although not statistically significant, large tumor size (> 3 cm), vascular invasion ($p = 0.087$) and lymphatic invasion ($p = 0.211$) also tended to be more frequent in the low LATS2

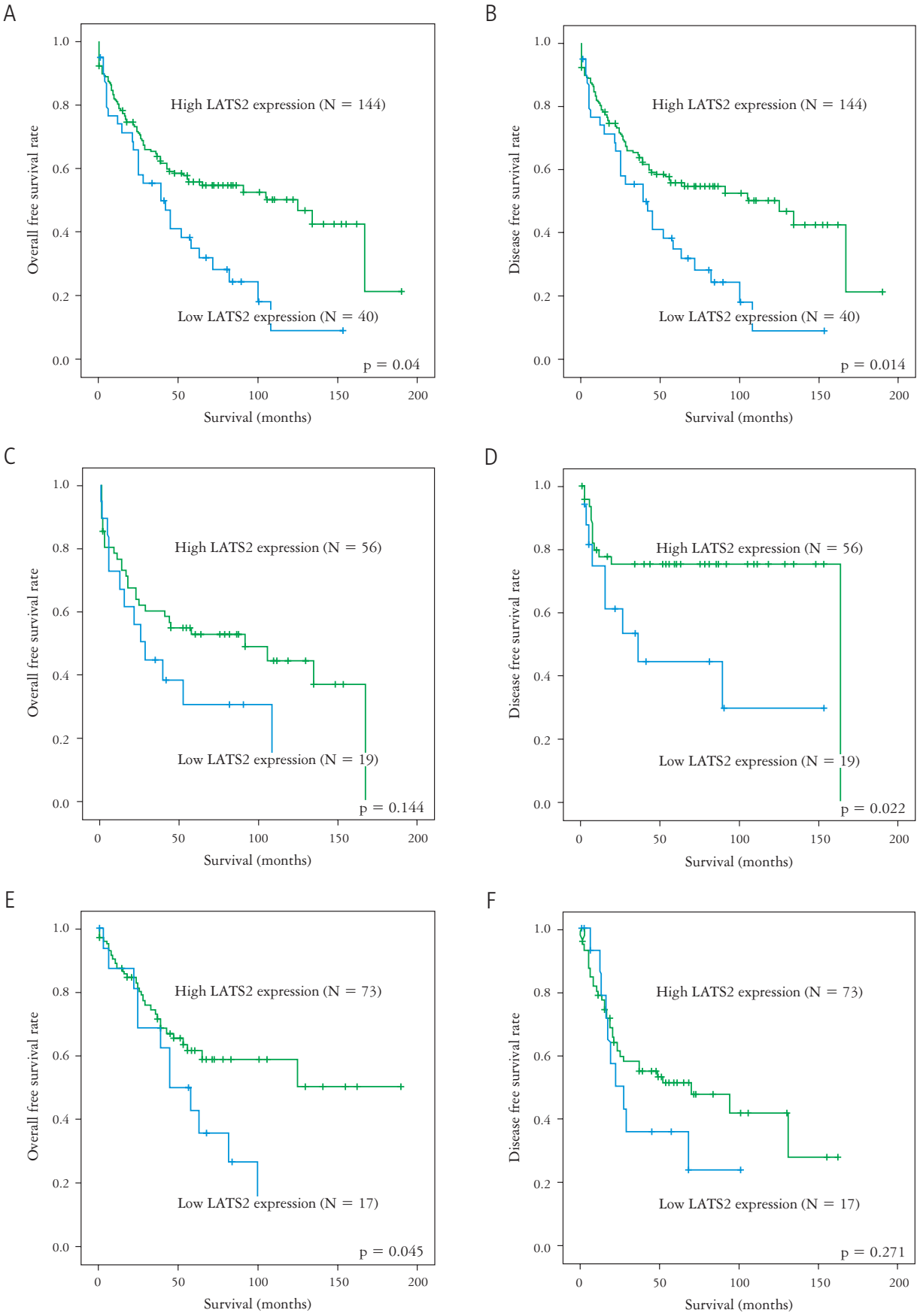

Fig. 2. Kaplan-Meier survival curve with log-rank test of LATS2 expression level for 184 NSCLC samples (A and B), 75 squamous cell carcinoma samples (C and D) and 90 adenocarcinoma samples (E and F)

Table II. Univariate and multivariate analyses of overall survival in 184 patients with non-small cell lung cancer

Variables	Univariate analyses (p value)	Multivariate analyses (p value)	Hazard ratio	95% Confidence interval
Low LATS2 expression	0.005	0.032	1.639	1.044-2.571
Sex (female vs. male)	< 0.001	0.001	0.324	0.169-0.621
Age (≥ 65 vs. < 65)	0.052			
Tumor size (> 3 cm vs. ≤ 3)	< 0.001	0.974		
Pleural invasion	0.011	0.204		
Vascular invasion	0.043	0.723		
Lymphatic invasion	0.019	0.438		
Lymph node metastasis	< 0.001	0.033	1.815	1.048-3.144
Stage (III, IV vs. I, II)	0.001	0.250		
Smoking	0.014	0.232		

Table III. Univariate and multivariate analyses of disease-free survival in 184 patients with non-small cell lung cancer

Variables	Univariate analyses (p value)	Multivariate analyses (p value)	Hazard ratio	95% Confidence interval
Low LATS2 expression	0.017	0.030	1.745	1.057-2.882
Sex (female vs. male)	0.941			
Age (≥ 65 vs. < 65)	0.880			
Tumor size (> 3 cm vs. ≤ 3)	< 0.001	0.299		
Pleural invasion	< 0.001	0.108		
Vascular invasion	0.106			
Lymphatic invasion	0.022	0.657		
Lymph node metastasis	< 0.001	0.089		
Stage (III, IV versus I, II)	< 0.001	0.019	1.986	1.119-3.526
Smoking	0.342			

expression group than in the high LATS2 expression group.

Low LATS2 expression is usually correlated with unfavorable outcomes in a variety of malignancies, such as leukemia, nasopharyngeal cancer, lung cancer and breast cancer [9, 10, 12, 18, 23]. Although some limited reports have been published, the prognostic meaning of LATS2 down-regulation in NSLCL and its major subtypes, especially in squamous cell carcinomas, is not yet clearly established. Previous human lung cancer studies described that in lung adenocarcinomas, the low LATS2 mRNA expression group showed shorter OS and DFS than the high expression group [12], and another recent study demonstrated that low LATS2 immunoreactivity was associated with poor OS in NSCLC [9]. In our study, among all NSCLC cases, those with low LATS2 expression had significantly poorer OS and DFS compared to the high expression group (Tables II, III, Fig. 2A, B). Notably, low LATS2 expression could be considered as an independent prognostic factor in OS and DFS based on multivariate analyses ($p = 0.032$ and $p = 0.030$, respectively)

We also analyzed OS and DFS rates for each major NSCLC subtype (squamous cell carcinoma and adenocarcinoma) by LATS2 expression. To further advance the previous clinical study, we included a larger number of variable NSCLC subtypes. Notably, in squamous cell carcinoma, the Kaplan-Meier curve with log-rank test revealed that LATS2 expression was negatively correlated with OS and DFS (Fig. 2C, D). We first demonstrated the prognostic significance of LATS2 expression in lung squamous cell carcinoma. Although there were limitations in the number of samples, statistically significant differences were observed in OS. The survival curve for adenocarcinoma patients also showed that low LATS2 expression was correlated with poor OS and DFS ($p = 0.045$ and $p = 0.271$, respectively), which is similar to results of previous studies.

LATS2 is considered to be one of the promising therapeutic targets for malignancy via Hippo pathway modulation. Different methods for generating active LATS variants have been used to enhance LATS kinase activity as a tumor suppressor [24, 25]. Prognosis-predicting and therapeutic-targeting molecules in lung cancer have been mainly identified in adenocarcinomas [26, 27]. In this aspect, discovering novel key molecules involved in tumorigenesis and the progression of lung squamous cell carcinoma would be valuable [28]. LATS2 acts as a novel modulator of therapeutic response in various types of cancers and a potential inducer of apoptosis in a lung cancer cell line [29, 30, 31]. Our data suggest that LATS2 may serve as a potential therapeutic target in both squamous cell carcinoma and adenocarcinoma of the lung.

In conclusion, our findings demonstrated that low LATS2 expression was associated with aggressive clinicopathological features of high NSCLC recurrence rate, tumor growth and invasiveness. Low LATS2 expression was also associated with poor OS and DFS, and was found to be an independent predictor in NSCLC. Furthermore, LATS2 should be considered as a key molecule of tumor development and progression, and it is necessary to assess the possibility of LATS2 as an attractive therapeutic target in NSCLC in both lung squamous cell carcinoma and lung adenocarcinoma.

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The authors declare no conflict of interest.

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