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Research Article

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Correlations of cofilin1 and phosphorylation at Ser3 site with sensitivity of elderly patients with non-small cell lung cancer to radiotherapy

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Abstract

***Background**: To explore the correlations of cofilin1 (CFL1) and phosphorylation level of locus serine residue at position 3 (Ser3) with the sensitivity of elderly patients with non-small cell lung cancer (NSCLC) to radiotherapy.* ***Methods**: A total of 102 eligible patients treated from June 2013 to April 2015 were selected. The cases of complete remission and partial remission were included into radiotherapy-sensitive group (n=55), while those of stable disease and progressive disease were enrolled into radiotherapy-resistant group (n=47). Before treatment, tissues were collected to detect the expressions of CFL1 and CFL1 (phospho S3) by immunohistochemistry. The survival time and rate were recorded during follow-up.* ***Results**: Compared with the radiotherapy-sensitive group, the radiotherapy-resistant group had advanced tumor-node-metastasis (TNM) stage and higher lymph node metastasis rate (P=0.000, 0.000). Compared with the tissues with negative CFL1 expression, the tissues with positive CFL1 expression had advanced TNM stage and higher lymph node metastasis rate (P=0.013, 0.000). The positive expression rate of CFL1 in the radiotherapy-resistant group was higher than that of the radiotherapy-sensitive group, whereas the positive expression rate of CFL1 (phospho S3) in the former was lower (P=0.000, 0.000). Lymph node metastasis, high CFL1 expression, and low CFL1 (phospho S3) expression were independent predictors for resistance to radiotherapy (P=0.001, 0.006, 0.003). In the radiotherapy-sensitive group, the patients with negative CFL1 expression and positive CFL1 (phospho S3) expression had long progression-free survival and high 5-year survival rate (P=0.000, 0.000).* ***Conclusion**: The sensitivity to radiotherapy of elderly NSCLC patients is correlated negatively with CFL1 and positively with phosphorylation at locus Ser3. CFL1 and phosphorylation at locus Ser3 are independent predictors for sensitivity to radiotherapy.*

***Keywords**: elderly, non-small cell lung cancer, radiotherapy, sensitivity, cofilin*

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Introduction

Lung cancer is a malignant tumor with high incidence rate worldwide, and about 85% are non-small cell lung cancer (NSCLC) cases. Although radiotherapy has been widely applied, local recurrence or metastasis easily occurs, so the mortality rate of patients remains high. The resistance to radiotherapy is considered as the main cause for local relapse or metastasis (1), and the sensitivity of tumor cells to radiotherapy is related to many factors. Cofilin1 (CFL1) is highly expressed in lung cancer tissues and closely associated with tumor invasion and metastasis (2). The protein expression of CFL1 in glioma and astrocytoma tissues with resistance to radiotherapy increases (3). The serine residue at position 3 (Ser3) at the N terminal of CFL1 can be phosphorylated, and its autophosphorylation and dephosphorylation determine the activity of CFL1 (4). CFL1 is highly expressed in esophageal cancer and associated with lymph node metastasis and clinical stage, as an important target for the diagnosis and prognostic evaluation of esophageal cancer (5). Zhang et al. found that paclitaxel modulated the growth and invasiveness of breast cancer cells by down-regulating Aurora kinase-mediated CFL1 activity, suggesting that Aurora kinase-mediated CFL1 was a potential target for the treatment of breast cancer (6).

To date, the correlations of CFL1 and the phosphorylation at its locus Ser3 with the sensitivity to radiotherapy of elderly patients with NSCLC have not been reported. Therefore, the aim of this study was to explore the correlations by detecting the expression levels of CFL1 and the phosphorylated protein at its locus Ser3 [CFL1 (phospho S3)].

Materials and Methods

Subjects

A total of 102 NSCLC patients who underwent surgical resection and received postoperative radiotherapy in our hospital from June 2013 to April 2015 were selected as the subjects. Inclusion criteria: 1) NSCLC patients who were pathologically diagnosed and could not receive surgery; 2) patients planning to undergo radiotherapy; 3) with measurable lesions before treatment; 4) patients receiving radiotherapy for the first time; 5) ≥60 years old; 6) with complete clinical and follow-up data. Exclusion criteria: 1) With surgical indications; 2) complication with other malignant tumors; 3) patients receiving anticancer therapy before.

The patients and their family members were informed of this study and signed the informed consent. This research was approved by the medical ethics committee of our hospital.

Radiotherapy and evaluation of therapeutic effects

Three-dimensional conformal radiotherapy or intensity-modulated radiotherapy (2.0 Gy/time, once a day, 5 times/week, with a total dose of 60 Gy) was performed for all the patients about 3 weeks after operation. One month after radiotherapy, according to RECIST 1.1, the treatment outcomes were evaluated as follows. Complete response (CR): All the target foci vanished, and the short diameter of lymph nodes reduced to less than 10 mm. Partial response (PR): The sum of target focus diameters decreased by at least 30%. Progressive disease (PD): The sum of the maximum diameters of tumors increased by at least 20% or new foci appeared. Stable disease (SD): The increase amplitude of the target foci did not accord with the condition of PD, and the decrease amplitude did not accord with the condition of PR. According to the treatment outcomes, CR and PR cases were included as a radiotherapy-sensitive group (n=55), and SD and PD cases were included as a radiotherapy-resistant group (n=47).

Measurement of CFL1 and CFL1 (phospho S3) in NSCLC tissues

The measurement was conducted by the SP method. NSCLC tissue specimens were fixed by 4% neutral formaldehyde solution, dehydrated, transparentized and embedded with paraffin. Then the specimens were serially sliced into 5 μm-thick sections, deparaffinized with xylene, soaked in gradient concentrations of ethanol solutions for hydration and digested with 3 mol/L urea, followed by antigen retrieval with sodium citrate solution. Subsequently, the sections were incubated with 3% hydrogen peroxide at room temperature for 10 min and blocked. After the blocking solution was discarded, proper amounts of diluted anti-CFL antibody (rabbit polyclonal antibody against CFL, Item No. ab42824, Abcam) and anti-CFL (phospho S3) antibody [rabbit polyclonal antibody against CFL (phospho S3), Item No. ab12866, Abcam] were added respectively for incubation in a 4°C refrigerator overnight. Phosphate buffer solution (PBS) was utilized as the control. The next day, the sections were taken out, rewarmed, washed with PBS, and incubated with diluted goat anti-rabbit IgG H&L (HRP) (ab205718, Abcam) at room temperature for 30 min, followed by PBS washing. Next, a proper amount of DAB was added for color development (Item No. ZLI-9017, Beijing ZSGB-BIO Co., Ltd). Five minutes later, the sections were added deionized water, counterstained by hematoxylin, and differentiated with 1% hydrochloric acid-ethanol solution. Following rinsing with tap water and dehydration with gradient concentrations of ethanol solutions, the sections were transparentized in xylene, sealed after drying, and observed under a microscope.

The sections were evaluated blindly by two senior pathologists. First, the staining intensity was observed under a low-power microscope, and scored 3 points, 2 points, 1 point, and 0 point for medium brown, pale brown, light yellow, and no color, respectively. Then 5 high-power fields of view were randomly selected, in which the percentage of positive cells was calculated. >75%, 51-75%, 26-50% and <25% of positive cells were scored 4 points, 3 points, 2 points, 1 point, and 0 point, respectively. The sum of the two scores ≥3 points indicated positive expression, and that <3 points indicated negative expression.

Follow-up

After operation, the patients were followed up by hospitalization or telephone call once every 3-6 months, for a total of 6-60 months. The survival time and survival rate of patients were recorded. Overall survival (OS) is defined as the time from operation to death or the end of follow-up, and progression-free survival (PFS) is defined as the time from the end of radiotherapy to relapse.

Statistical analysis

SPSS18.0 software was used for statistical analysis. Numerical data were expressed as n (%) and detected by the χ^2 test. The influencing factors for sensitivity to radiotherapy were explored by multivariate logistic regression analysis. Besides, intergroup comparisons of the survival rate and survival time were conducted by the Log-rank (Mantel-Cox) test using GraphPad Prism software, and the survival curve was plotted by the Kaplan-Meier method. Two-tailed test was employed, and $P<0.05$ represented that the difference was statistically significant.

Results

Clinicopathological characteristics of radiotherapy-sensitive and radiotherapy-resistant groups

Among the included patients, there were 60 males and 42 females aged 65-85 years old, with a mean of (73.18 ± 7.46) years old. The pathological types (56 cases of squamous cell carcinoma and 46 cases of adenocarcinoma), tu-

mor-node-metastasis (TNM) stage (23 cases in stage I, 31 cases in stage II and 48 cases in stage III), degree of tissue differentiation (34 cases of low differentiation, 49 cases of moderate differentiation and 19 cases of high differentiation), lymph node metastasis (37 cases with lymph node metastasis and 65 cases with no lymph node metastasis), and smoking history (61 cases with a history of smoking and 41 cases with no history of smoking) were recorded. There were no significant differences in age, gender, pathological type, degree of tissue differentiation, and smoking history between radiotherapy-sensitive and radiotherapy-resistant groups (P>0.05). The TNM stage was advanced and the lymph node metastasis rate was higher in the radiotherapy-resistant group than those in the radiotherapy-sensitive group (P<0.05) (**Table 1**).

Correlations of CFL1 and CFL1 (phospho S3) with clinicopathological characteristics

The CFL1 and CFL1 (phospho S3) expressions in NSCLC tissues were detected by immunohistochemistry (**Figure 1**). Among the 102 NSCLC patients, the positive expression rates of CFL1 and CFL1 (phospho S3) were 70.59% and 80.39% respectively, and the double positivity rate was 45.10%. The expressions of CFL1 and CFL1 (phospho S3) in NSCLC tissues were not correlated with age, gender, pathological type, degree of tissue differentiation or smoking history (P>0.05). In comparison with the tissues with

Table 1. Clinicopathological characteristics of radiotherapy-sensitive and radiotherapy-resistant groups

Clinicopathological characteristic	n	Radiotherapy-sensitive group (n=55)	Radiotherapy-resistant group (n=47)	χ^2	P
Age (n)				**0.146**	**0.703**
<75 years old	52	29	23		
≥75 years old	50	26	24		
Gender (n)				0.020	0.887
Male	60	32	28		
Female	42	23	19		
Pathological type (n)				0.103	0.748
Squamous cell carcinoma	56	31	25		
Adenocarcinoma	46	24	22		
TNM stage (n)				16.056	0.000
Stage I	23	18	5		
Stage II	31	21	10		
Stage III	48	16	32		
Degree of tissue differentiation (n)				0.080	0.961
Low differentiation	34	19	15		
Moderate differentiation	49	26	23		
High differentiation	19	10	9		
Lymph node metastasis (n)				28.631	0.000
Yes	37	7	30		
No	65	48	17		
History of smoking (n)				0.002	0.965
Yes	61	33	28		
No	41	22	19		

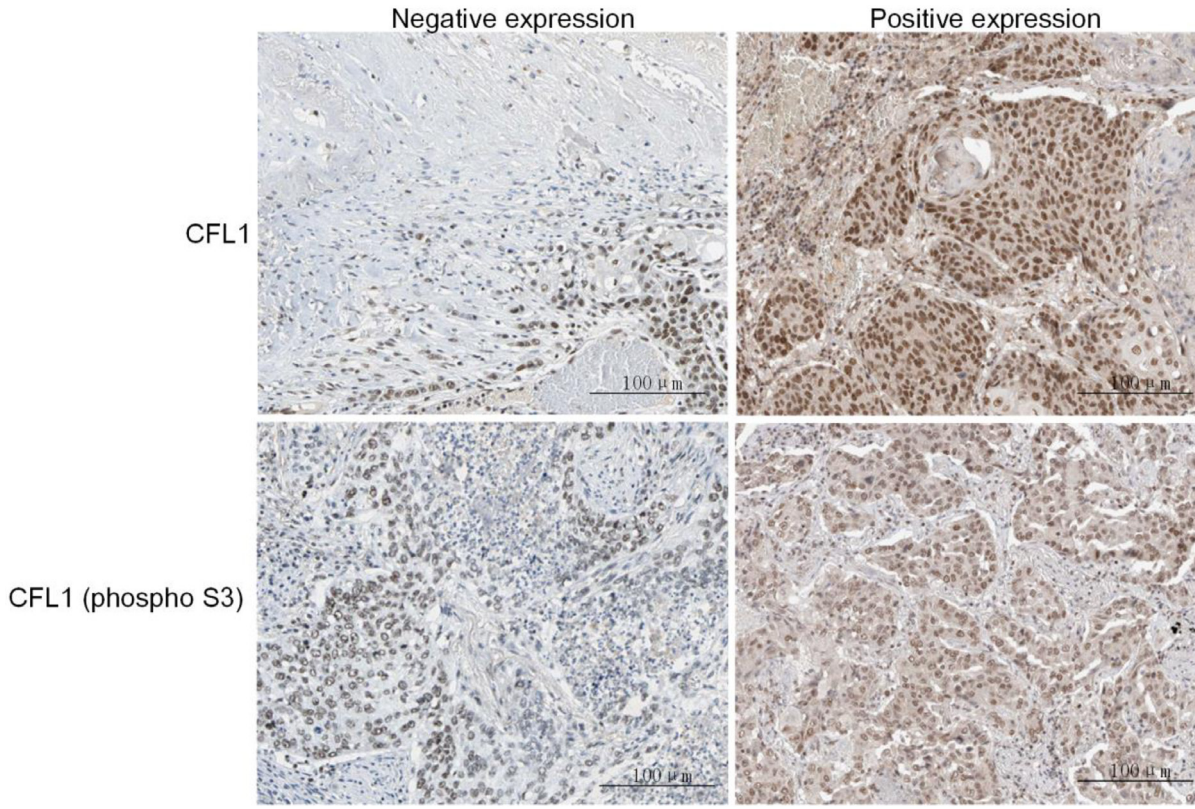

Fig. 1. CFL1 and CFL1 (phospho S3) expressions in NSCLC tissues detected by immunohistochemistry.

negative CFL1 expression, the tissues with positive CFL1 expression had advanced TNM stage and higher lymph node metastasis rate, while those with positive CFL1 (phospho S3) expression had earlier TNM stage and lower lymph node metastasis rate (P<0.05) (**Table 2**).

Expressions of CFL1 and CFL1 (phospho S3) in NSCLC tissues of radiotherapy-sensitive and radiotherapy-resistant groups

The positive expression rates of CFL1 in radiotherapy-sensitive and radiotherapy-resistant groups were 26.64% and 85.11%, respectively, and those of CFL1 (phospho S3) were 81.82% and 48.94%, respectively, with significant differences (P<0.05) (**Table 3**). The double positivity rates of CFL1 and CFL1 (phospho S3) in radiotherapy-sensitive and radiotherapy-resistant groups were 12.75% and 22.55%, respectively, which were significantly different (χ^2=6.110, P=0.013).

Influencing factors for sensitivity to radiotherapy

With all clinicopathological characteristics as the independent variables and resistance to radiotherapy (insensitivity) as the dependent variable, multivariate logistic regression analysis showed that lymph node metastasis, high expression of CFL1 and low expression of CFL1 (phospho S3) were independent predictors for resistance to radiotherapy (P<0.05) (**Table 4**).

Prognostic values of CFL1 and CFL1 (phospho S3) for NSCLC patients

PFS was 20.5 months in the radiotherapy-sensitive group and 3 months in the radiothera-

Table 2. Correlations of CFL1 and CFL1 (phospho S3) with clinicopathological characteristics

Clinicopathological characteristic	n	CFL1				CFL1 (phospho S3)			
		- (n=49)	+ (n=53)	χ2	P	- (n=34)	+ (n=68)	χ2	P
Age (n)				2.490	0.115			0.079	0.779
<75 years old	52	21	31			18	34		
≥75 years old	50	28	22			16	34		
Gender (n)				0.539	0.463			0.182	0.670
Male	60	27	33			21	39		
Female	42	22	20			13	29		
Pathological type (n)				0.698	0.403			0.020	0.888
Squamous cell carcinoma	56	29	27			19	37		
Adenocarcinoma	46	20	26			15	31		
TNM stage (n)				27.470	0.000			8.711	0.013
Stage I	23	18	5			5	18		
Stage II	31	21	10			6	25		
Stage III	48	10	38			23	25		
Degree of tissue differentiation (n)				1.816	0.403			0.521	0.771
Low differentiation	34	19	15			12	22		
Moderate differentiation	49	23	26			17	32		
High differentiation	19	7	12			5	14		
Lymph node metastasis (n)				23.556	0.000			53.015	0.000
Yes	37	6	31			29	8		
No	65	43	22			5	60		
History of smoking (n)				0.079	0.778			0.510	0.475
Yes	61	30	31			22	39		
No	41	19	22			12	29		

py-resistant group, showing a statistically significant difference (χ^2=13.267, P=0.000). PFS of the patients with positive CFL1 expression was 3.5 months, and that of the patients with negative CFL1 expression was 18 months, with a statistically significant difference (χ^2=15.458, P=0.000). Moreover, PFS of the patients with positive CFL1 (phospho S3) expression was 19 months, while that of the patients with negative CFL1 (phospho S3) expression was 3 months, which were significantly different (χ^2=23.617, P=0.000). In the radiotherapy-sensitive group, the patients with positive CFL1 expression had 12-month PFS, whereas those with negative CFL1 expression had 23-month PFS, with a statistically significant difference (χ^2=10.593,

Table 3. Expressions of CFL1 and CFL1 (phospho S3) in NSCLC tissues of radiotherapy-sensitive and radiotherapy-resistant groups

Group	CFL1		CFL1 (phospho S3)	
	- (n=49)	+ (n=53)	- (n=34)	+ (n=68)
Radiotherapy-sensitive group (n=55)	42 (76.36)	13 (26.64)	10 (18.18)	45 (81.82)
Radiotherapy-resistant group (n=47)	7 (14.89)	40 (85.11)	24 (51.06)	23 (48.94)
χ2	38.363		12.331	
P	0.000		0.000	

Table 4. Influencing factors for sensitivity to radiotherapy

Factor	β	SE	Wald value	P	OR value (95%CI)
Age	0.583	0.416	2.749	0.125	2.054 (0.638~3.425)
Gender	0.695	0.573	3.286	0.078	1.432 (0.501~2.167)
History of smoking	2.152	0.968	2.371	0.083	1.025 (0.826~1.574)
Pathological type	1.237	0.849	3.658	0.314	0.761 (0.249~1.352)
Degree of tissue differentiation	0.846	0.735	4.192	0.267	3.538 (0.975~4.093)
TNM stage	0.738	0.657	1.469	0.136	1.657 (0.759~2.861)
Lymph node metastasis	1.145	0.892	1.738	0.001	3.182 (1.614~4.739)
CFL1 expression	2.834	0.687	6.459	0.006	2.356 (1.769~3.841)
CFL1 (phospho S3) expression	-1.453	0.632	4.725	0.003	0.345 (0.163~0.739)

Independent variable assignment: age: ≥ 75 years old =1 and < 75 years old = 0, gender: male = 1 and female = 0, pathological types: squamous cell carcinoma = 1 and adenocarcinoma = 0, degree of tissue differentiation: low differentiation = 1, moderate and high differentiation = 0, smoking history: yes = 1, no = 0, TNM stage: stage II+III = 1 and stage I = 0, lymph node metastasis: yes =1 and no = 0, CFL1 expression: high expression = 1 and low expression = 0, and CFL1 (phospho S3) expression: high expression = 1 and low expression = 0.

P=0.000). There was no significant difference in PFS between the patients with positive and negative CFL1 expressions in the radiotherapy-resistant group (1.5 months *vs.* 4 months) (χ^2=0.286, P=0.735). In the radiotherapy-sensitive group, PFS of the patients with positive CFL1 (phospho S3) expression was 20 months, while that of the patients with negative CFL1 (phospho S3) expression was 3.5 months (χ^2=26.843, P=0.000). In the radiotherapy-resistant group, PFS of the patients with positive CFL1 (phospho S3) expression was 5 months, whereas that of the patients with negative CFL1 (phospho S3) expression was 2 months (χ^2=0.724, P=0.319).

The 5-year OS rate of the 102 patients was 36.27%, among which the 5-year survival rate was 61.82% in the radiotherapy-sensitive group and 6.38% in the radiotherapy-resistant group (χ^2=7.908, P=0.005). The 5-year survival rate of the patients with positive CFL1 expression was 11.32%, and that of the patients with negative CFL1 expression was 63.27% (χ^2=9.869, P=0.002). In addition, the 5-year survival rate of the patients with positive CFL1 (phospho S3) expression was 45.59%, while that of the patients with negative CFL1 (phospho S3) expression was 17.65% (χ^2=4.314, P=0.038). The 5-year survival rate of the patients with negative CFL1 expression was highest (69.05%) in the radiotherapy-sensitive group, and that of the patients with positive CFL1 expression was lowest (2.50%), showing a statistically significant difference (χ^2=39.108, P=0.000). Additionally, the 5-year survival rate of the patients with positive CFL1 expression was 38.46% in the radiotherapy-sensitive group, and that of the patients with negative CFL1 expression was 28.57% in the radiotherapy-resistant group. Moreover, the 5-year survival rate of the patients with positive CFL1 (phospho S3) expression was highest (64.44%) in the radiotherapy-sensitive group, and that of the patients with negative CFL1 (phospho S3) expression was lowest (4.17%), with a statistically significant difference. Besides, the 5-year survival rate of the patients with negative CFL1 (phospho S3) expression was 50.00% in the radiotherapy-sensitive group, and that of the patients with negative CFL1 (phospho S3) expression was 8.70% in the radiotherapy-resistant group (**Figure 2**).

Discussion

Radiation-induced DNA damage, cell cycle redistribution, cell number repopulation, and cell

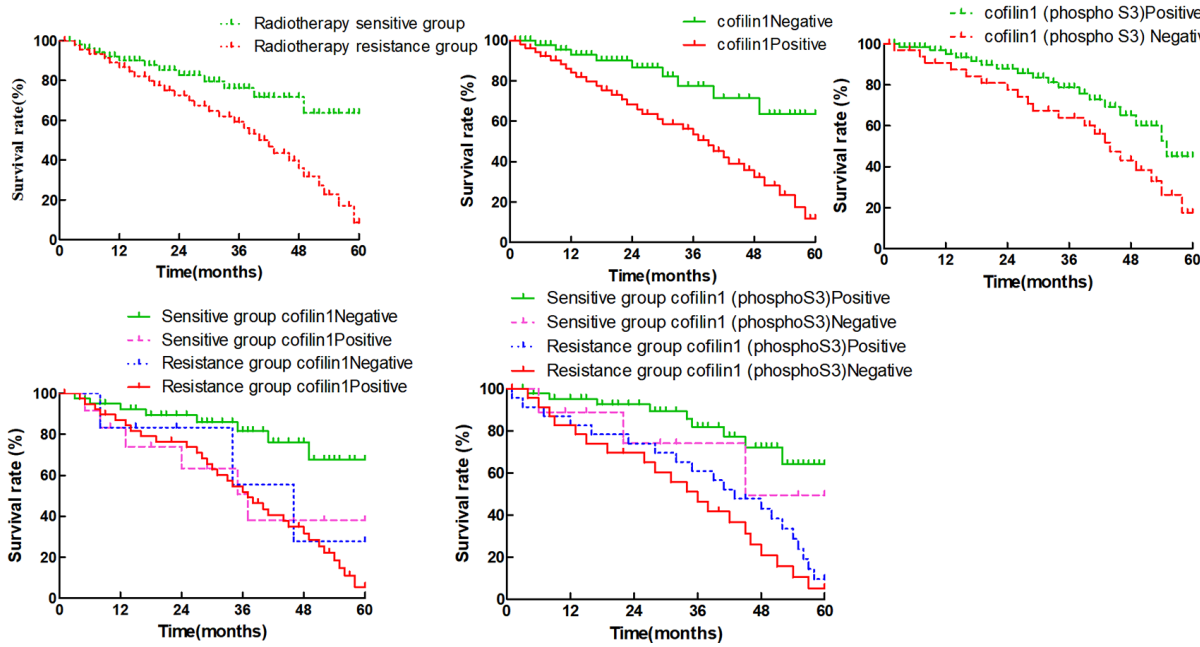

Fig. 2. Prognostic values of CFL1 and CFL1 (phospho S3) for NSCLC patients.

reoxidation are vital factors that determine the efficacy of radiotherapy (6). In this study, the TNM stage was advanced and the lymph node metastasis rate was higher in the radiotherapy-resistant group than those in the radiotherapy-sensitive group, which is consistent with a previous study on the influencing factors for the sensitivity of tumors to radiotherapy (8). The TNM stage of NSCLC patients is primarily associated with tumor diameter, lymph node metastasis and distant **metastasis** (9). Therefore, the results of this study may be attributed to the following reasons. On one hand, DNA of tumor cells is damaged under the induction of radiotherapy, which activates DNA damage repair, suppresses apoptosis and causes cell proliferation again, thereby augmenting the radiotherapy resistance. On the other hand, epithelial-mesenchymal transition greatly enhances the mobility of tumor cells, keeps them in a hypoxic microenvironment, and enables them to acquire the characteristics of stem cells, all of which increase the resistance of tumor cells to radiotherapy.

CFL1 is expressed in various non-muscle tissues of mammals, and its main function is to speed up the dissociation of actin monomer from the end of actin microfilament and to decompose the latter, which ultimately affects the reorganization of actin skeleton involved in physiological processes such as cell growth, differentiation, cell membrane reorganization and dynamics changes (10). Ser3 of CFL1 can be phosphorylated by LIM kinases 1 and 2 and TES kinases 1 and 2, which deactivates CFL1 and prevents it from binding actin filaments, thus stabilizing F-actin. However, the dephosphorylation of Ser3 induced by phospholipases can activate CFL1 and facilitate its binding to F-actin, thus contributing to the depolymerization of actin filaments. Therefore, the phosphorylation and dephosphorylation levels of CFL1 determine its own activity (11). Sun *et al.* reported that CFL1 was highly expressed in radiotherapy-resistant glioma U251 cells and glioma patients, and closely correlated with the invasion, migration and viability enhancement of tumor cells (12). Besides, Li et al.

found that the invasion ability of breast cancer cells with CFL1 knockout was evidently weakened (13). Wang et al. confirmed that pancreatic cancer cells had stronger invasion ability after the CFL1 dephosphorylation pathway was activated (14). Consistently, this study showed that the NSCLC tissues with positive CFL1 expression had advanced TNM stage and high lymph node metastasis rate, while the tissues with negative CFL1 (phospho S3) expression had early TNM stage and low lymph node metastasis rate. In this study, CFL1 had a high positive expression rate in the radiotherapy-resistant group, while CFL1 (phospho S3) had a high positive expression rate in radiotherapy-sensitive group. Besides, lymph node metastasis, high CFL1 expression and low CFL1 (phospho S3) expression were independent predictors for resistance to radiotherapy. The high positive expression rate of CFL1 indicates its active state, and the low phosphorylation level promotes the depolymerization of actin filaments, thereby weakening cell adhesion and enhancing mobility. In addition, CFL1 suppresses angiogenesis to reduce the number of tumor microvessels, which makes the microenvironment in a low oxygen state, thus enhancing the radiotherapy resistance of NSCLC. On the contrary, the high positive expression rate of CFL1 (phospho S3) represents deactivation of CFL1, and the high phosphorylation level finally renders NSCLC more sensitive to radiotherapy.

The prognosis of NSCLC patients is obviously better than that of the patients with resistance to radiotherapy (15). CFL1 is highly expressed in malignant tumors such as oral squamous cell carcinoma, renal cancer, breast cancer and ovarian cancer, which can imply the short survival time and poor prognosis of patients (16). In the radiotherapy-sensitive group herein, the patients with negative CFL1 expression and positive CFL1 (phospho S3) expression had longer PFS and higher 5-year survival rate. The patients with negative CFL1 expression in the radiotherapy-sensitive group had the longest PFS and highest 5-year survival rate, while those with positive CFL1 expression in the radiotherapy-resistant group had the shortest PFS and lowest 5-year survival rate. Moreover, the patients with positive CFL1 (phospho S3) expression had the longest PFS and highest 5-year survival rate in the radiotherapy-sensitive group, while those with negative CFL1 (phospho S3) expression had the shortest PFS and lowest 5-year survival rate in the radiotherapy-resistant group. The results are in accordance with those of previous literature (17).

In summary, the sensitivity to radiotherapy of elderly NSCLC patients is correlated negatively with CFL1 and positively with CFL1 (phospho S3). CFL1 and CFL1 (phospho S3) are independent predictors for radiotherapy sensitivity. Nevertheless, this single-center study is limited due to small sample size which may cause bias. In the future, the signaling pathway and regulation mechanism of CFL1 and Ser3 phosphorylation involved in the sensitivity to radiotherapy of NSCLC patients will be further verified by increasing the sample size.

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Authors' contribution

FL - Study design
CZ - Data collection
YD, MW - Data analysis
QY - Writing
All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest to report regarding the present study.

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