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ORIGINAL RESEARCH

High CEP55 expression is associated with poor prognosis in non-small-cell lung cancer

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Objectives: Lung cancer is the most common and lethal malignancy worldwide. CEP55 was found to be overexpressed in multiple types of cancer. However, the expression pattern of CEP55 and its clinical significance in non-small-cell lung carcinoma (NSCLC) have not been investigated by immunohistochemistry.

Materials and methods: In this study, we analyzed 203 primary NSCLC specimens from Sun Yat-Sen University Cancer Center to investigate the clinical role of CEP55 in lung cancer. Tissue microarray was successfully generated for immunohistochemical evaluation. The correlation between CEP55 expression and clinical characteristics and survival was analyzed statistically. The predictive effect of CEP55 and APOBEC3B (AP3B) coexpression in lung cancer patients' prognosis was evaluated.

Results: We found that the CEP55 expression was commonly elevated in NSCLC tissues and overexpression of CEP55 was correlated with unfavorable prognosis in the patients with NSCLC. Furthermore, the combination of CEP55 and AP3B expression was significantly predictive of clinical outcome in all NSCLC patients.

Conclusion: CEP55 may act as a useful and novel prognostic biomarker for NSCLC. Further studies into the mechanism of CEP55 are warranted.

Keywords: CEP55, non-small-cell lung cancer, immunohistochemistry, prognosis

Introduction

Lung cancer is the most lethal type of cancer in the United States and worldwide. In the United States, it is predicted that 222,500 new lung cancer patients will be diagnosed, and 155,870 people will die of lung cancer in 2018.[1] The death rate from lung cancer is 25%, the highest among all types of cancer. Smoking and being exposed to certain toxins are currently known direct reasons of lung cancer; however, many lung cancer cases occur without clear reasons. The recent discovery of several key driver gene mutations, including *EGFR*, *k-ras*, and *ALK*, opened a new era of understanding lung cancer and prompted the development of targeted therapies.[2] However, most lung cancers have no symptoms at initial stages and are advanced when diagnosed, resulting in poor prognosis. Many biomarkers critical for the diagnosis and treatment of lung cancer are emerging.

CEP55, also known as c10orf3 and FLJ10540, is encoded by the *CEP55* gene. It is widely expressed in different types of tissue, especially in proliferative tissues. It locates to the centrosomes at interphase and forms homodimers to assist cytokinesis.[3] Recently, CEP55 was found to be involved in the regulations of PI3K/AKT pathway and cancer cell stemness.[4–6] Clinically, CEP55 has been found overexpressed in multiple types of cancer, such as breast, prostate, renal, and thyroid cancers.[7–10] It has been included as a gene highly associated with prognosis in several patented mRNA

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microarrays used to screen for cancer diagnosis.[11,12] However, the association of its protein level with prognosis of lung cancer patients has never been determined before. In this study, we used immunohistochemistry (IHC) and online datasets to determine the expression level of CEP55 in lung cancer patients and investigated its correlation with clinical parameters and prognosis.

Materials and methods

Patient selection

This study was approved by the medical ethics committee of Sun Yat-Sen University Cancer Center. A total of 203 primary lung cancer specimens were obtained from primary surgery from October 2000 to April 2007. The selective criteria are as previously described.[13] To avoid confusion in data analysis, neoadjuvant chemotherapy patients were excluded. The histologic grade and clinical stage of the tumors were defined as previously described.[13] The final survival status of patients was confirmed in December 2013. Patients whose tissues and medical records were used for this study had provided written informed consent.

IHC staining

IHC staining was performed to detect CEP55 expression according to the protocol previously described,[13] with minor changes. Tissue sections were deparaffinized with dimethylbenzene and then rehydrated through 100%, 95%, 90%, 80%, and 70% ethanol for 3 minutes each. After the PBS wash step, the slides were boiled for 15 minutes in citric acid in a microwave oven, followed by endogenous peroxidase blocking with 3% hydrogen peroxide. To retrieve antigen, the slides were then boiled in tris(hydroxymethyl) aminomethane-EDTA buffer (pH 8.0) in a microwave for 30 minutes. Nonspecific antigen binding was inhibited by incubation in 10% normal goat serum for 20 minutes. CEP55 antibody (1:1,000 dilution, Abgent, Rabbit Ig, San Diego, CA, USA) was incubated with slides overnight at 4°C in a moist chamber. For negative controls, slides were incubated with normal goat serum instead of the primary antibody. After the overnight incubation, the slides were sequentially incubated with biotinylated goat anti-rabbit antibody, streptavidin–peroxidase conjugate, and 3,3′-diaminobenzidine. Normal alveolar and bronchial epithelial mucosa were utilized as negative controls.

Immunoreactivity score (IRS) assessment

Two independent pathologists (Shanshan Lyu and Shumei Yan) who were blinded to the clinicopathological information performed the IRS assessment for CEP55 expression. The scoring criteria are as described previously.[13] The staining results were scored based on the 2 criteria: 1) the percentage of positive tumor cells in the tissue: 0 (0%), 1 (1%–10%), 2 (11%–50%), 3 (51%–75%), and 4 (76%–100%) and 2) the intensity of staining: 0, absent; 1, weak; 2, moderate and 3, strong. IRS was calculated by multiplying (1) and (2) (range from 0 to 12). The specimens were rescored if the difference between the two pathologists was >3.

Statistical analysis

The CEP55 IRS cutoff value was determined by the median of the staining results of 203 specimens. The correlation between CEP55 expression and clinicopathological features was analyzed by Pearson's χ^2 test. Disease-free survival (DFS) was defined as the time from surgery to regional relapse or distant metastasis. Overall survival (OS) was defined as the time from surgery to death. DFS and OS curves in different subgroups were constructed by the Kaplan–Meier method. To test significant differences between 2 survival curves, we used HRs and their 95% CIs of covariates in the analyses of DFS or OS by Cox proportional hazards model. Multivariate analysis was performed for all of the parameters that were significant in the univariate analysis. Receiver operating characteristic (ROC) curve analysis was used to assess the predictive value of clinicopathologic features.

Data from previous publication were also utilized in this study.[13] Statistical analysis was performed using SPSS software (standard version 16.0, SPSS Inc., Chicago, IL, USA). A difference was considered statistically significance if the 2-sided probability value was less than 0.05.

Results

Patient characteristics

Fifty-four females and 149 males, aged from 30 to 79 years (median 60.0 years), were included in this study. Among them, 122 were smokers and 81 were nonsmokers. The specific clinicopathological characteristics of the 203 patients are listed in Table 1.

Expression of CEP55 in non-small-cell lung carcinoma (NSCLC) and associations with clinicopathological characteristics

In this study, the median CEP55 IRS value was <8.0. IRS scores less than this value were considered low expression, and CEP55 IRS scores, greater than this value, were considered high expression. CEP55 staining of NSCLC tissue and

Table 1 Correlation between CEP55 expression and clinicopathological variables of lung cancer cases

Variables	Cases (n=203)	CEP55 expression		*P*-value
		Low (76)	High (127)	
Age (years)				0.464
≤60	101	37	64	
>60	102	39	63	
Gender				0.623
Male	149	54	95	
Female	54	22	32	
Smoking				0.237
No	81	26	55	
Yes	122	50	72	
Tumor diameter				0.662
<3.5 cm	91	36	55	
≥3.5 cm	112	40	72	
Histology				0.880
SCC	71	26	45	
Non-SCC	132	50	82	
Histological grade				0.334
I	28	14	14	
II	84	30	54	
III	91	32	59	
Visceral pleural invasion				0.640
Absent	64	22	42	
Present	139	54	85	
Tumor status (T)				0.996
T1	39	14	25	
T2	138	52	86	
T3	18	7	11	
T4	8	3	5	
Nodal status (N)				**0.004**
N0	115	54	61	
N1	37	7	30	
N2	51	15	36	
TNM staging				0.129
I	90	40	50	
II	56	20	36	
III	57	16	41	
Adjuvant chemotherapy				0.110
No	110	47	63	
Yes	93	29	64	

Note: Statistically significant *P* value is shown in bold.
Abbreviation: SCC, squamous cell carcinoma.

normal alveolar and bronchial epithelial mucosa revealed that immunoreactivity primarily rests in the cytoplasm of tumor cells (Figure 1). Low expression of CEP55 was observed in 37.4% (76/203) of the NSCLC samples, whereas 62.6% (127/203) of NSCLC samples had high expression of CEP55 (Table 1). The expression of CEP55 correlated closely with nodal status (P=0.004). No other statistical associations were observed between CEP55 expression and age, gender, smoking, tumor diameters, histology, histology grade, visceral pleural invasion, tumor status, TNM staging, and adjuvant chemotherapy (P=0.464, P=0.623, P=0.237, P=0.662, P=0.880, P=0.334, P=0.640, P=0.996, P=0.129, and P=0.110, respectively).

CEP55 expression and patient prognosis

All patients participated for the duration of this study. About 102 (50.24%) patients were deceased, and 101 patients were still alive at the end of the duration of this study. The 5-year OS rates of the whole cohort were 53.2% (108/203). OS and DFS curves for the whole cohort are shown in Figure 2. Importantly, patients with high expression of CEP55 had a shorter OS and DFS compared with those with low expression (OS: mean of 73.04 versus 89.88 months, P=0.003; DFS: mean of 63.77 versus 84.73 months, P=0.005, Figure 2, Table 2). CEP55 can differentiate between tumors in N or TNM staging and between those which have or have not been treated, with adjuvant chemotherapy (Figure 2). High CEP55 expression was significantly associated with poor prognosis in NSCLC patients who are aged ≤60, females, nonsmokers, patients with tumor diameter >3.5 cm, G2/3, and patients who had not received without adjuvant chemotherapy (Figure 3, Table 2, DFS: P=0.006, P<0.001, P=0.027, P=0.006, P=0.014, and P=0.022; OS: P=0.005, P<0.001, P=0.018, P=0.004, P=0.008, and P=0.007).

Furthermore, univariate analysis using Cox's proportional hazard model showed that the following parameters correlated significantly with OS: tumor diameter, histological grade, tumor status, nodal status, TNM staging, AP3B expression, CEP55 expression, and adjuvant chemotherapy (Table 3). CEP55 and AP3B expression and clinicopathologic parameters that were significant in univariate analysis were further analyzed in multivariate analysis. The result demonstrated that nodal status, AP3B expression, and CEP55 expression were independent prognostic factors that affected NSCLC patients' OS (Table 3, P=0.050, P=0.003, P=0.036, respectively). High expression of CEP55 was a predictor for poor prognosis (HR, 1.617; 95% CI, 1.033–2.532; Table 3). High expression of AP3B was also a predictor for poor prognosis of NSCLC patients (HR, 1.893; 95% CI, 1.245–2.877; Table 3).

Combined increased expression of CEP55 and AP3B is correlated with poor prognosis in NSCLC

APOBEC3B, AP3B, is a newly defined DNA cytosine deaminase. Cytosine deamination resulting in cytosine to thymine (C-to-T) transition mutations, which is catalyzed by the APOBEC family, is a major source of DNA mutation in

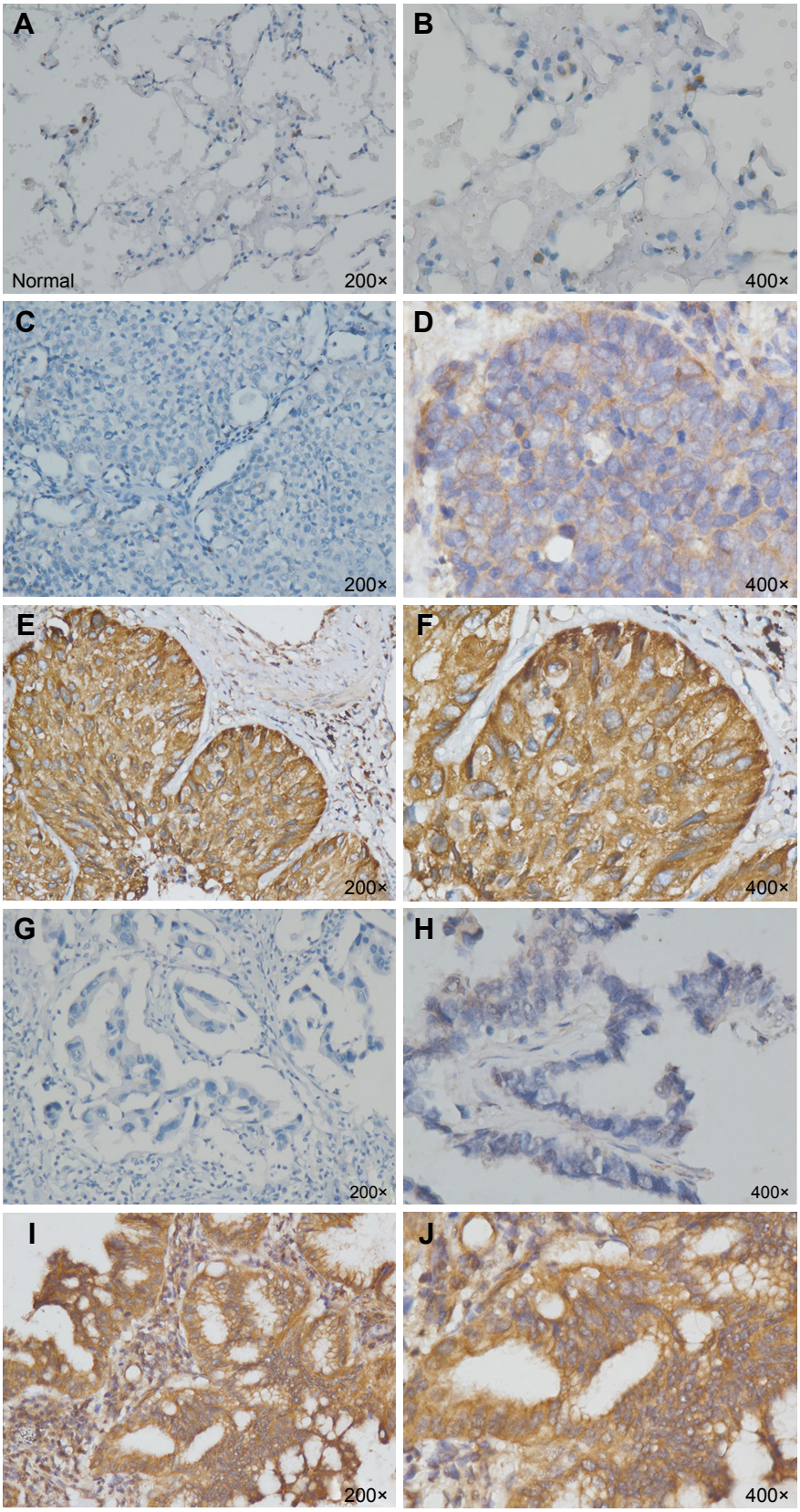

Figure 1 CEP55 expression is determined by IHC.
Notes: No or low expression of CEP55 protein in the cytoplasm of adjacent normal tissue (magnification: **A**, 200×; **B**, 400×). (**C**, **D**) Low expression level of CEP55 in epithelial NSCLC tissues (magnification: **C**, 200×; **D**, 400×). (**E**, **F**) High expression levels of CEP55 in epithelial NSCLC tissues (magnification: **E**, 200×; **F**, 400×). (**G**, **H**) Low expression level of CEP55 in adeno-NSCLC tissues (magnification: **G**, 200×; **H**, 400×). (**I**, **J**) High expression levels of CEP55 in adeno-NSCLC tissues (magnification: **I**, 200×; **J**, 400×).
Abbreviations: IHC, immunohistochemistry; NSCLC, non-small-cell lung cancer.

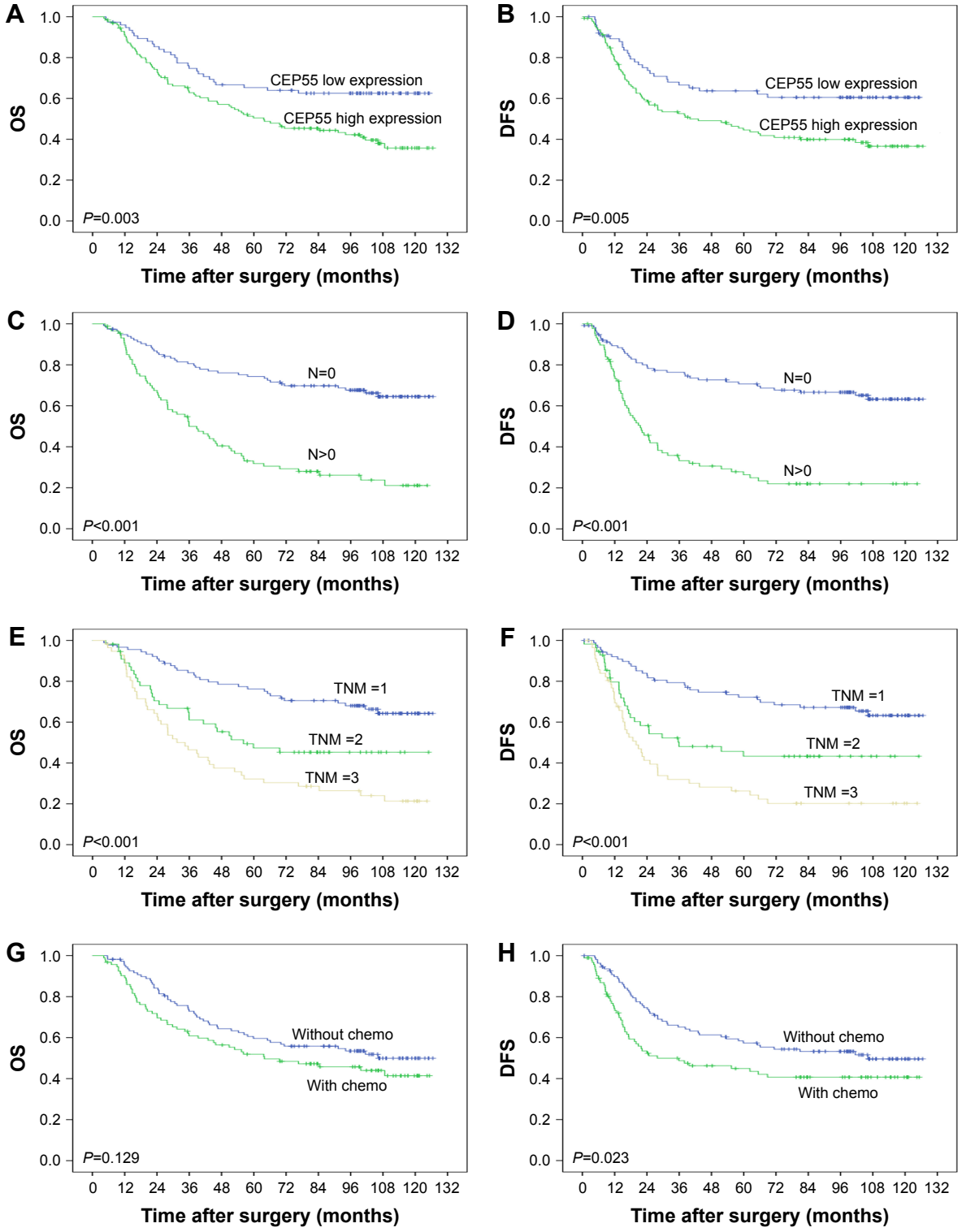

Figure 2 OS curve and DFS curve of 203 NSCLC patients based on different clinicopathological characteristics and CEP55 expression.
Notes: (**A**, **B**) OS curve and DFS curve in NSCLC patients with high and low levels of CEP55 expression. (**C**, **D**) OS curve and DFS curve in NSCLC patients with N=0 or N>0. (**E**, **F**) OS curve and DFS curve in NSCLC patients with different TNM staging. (**G**, **H**) OS curve and DFS curve in NSCLC patients with or without chemotherapy.
Abbreviations: DFS, disease-free survival; NSCLC, non-small-cell lung cancer; OS, overall survival.

many different tumors. We retrieved data from 203 patients analyzed for a previous study[13] to analyze whether CEP55 and AP3B coexpression affects NSCLC prognosis. As shown in Figure 4, when all NSCLC patients were stratified by AP3B expression, we found that the prognosis of patients with low CEP55 had significantly higher DFS and OS ($P<0.05$, Figure 4A and B). However, in patients with high AP3P expression, patients with low expression of CEP55 had

Table 2 CEP55 expression in lung cancer patients by Kaplan–Meier 5-year survival analysis (log-rank test)

Variables	Case	DFS (months)			OS (months)		
		Mean	Median	*P*-value	Mean	Median	*P*-value
Total							
Low expression	76	84.73	NR	**0.005**	89.876	NR	**0.003**
High expression	127	63.736	39.970		73.040	66.100	
Age categories							
≤60				**0.006**			**0.005**
Low expression	37	89.181	NR		94.079	NR	
High expression	64	56.286	24.670		65.503	55.430	
>60				0.276			0.203
Low expression	39	80.168	NR		85.459	NR	
High expression	63	69.473	59.870		75.327	71.330	
Gender categories							
Male				0.281			0.253
Low expression	54	76.011	NR		82.397	NR	
High expression	95	66.121	51.600		74.113	70.030	
Female				**<0.001**			**<0.001**
Low expression	22	104.230	NR		106.665	NR	
High expression	32	55.996	27.870		61.395	42.970	
Smoking categories							
Yes				0.064			0.059
Low expression	50	80.846	NR		86.482	NR	
High expression	72	62.201	38.270		70.829	69.600	
No				**0.027**			**0.018**
Low expression	26	91.148			95.294		
High expression	55	64.230	43.070		70.925	56.170	
Tumor diameters							
≤3.5 cm				0.270			0.265
Low expression	36	85.021	NR		90.339	NR	
High expression	55	75.385	66.100		84.851	99.770	
>3.5 cm				**0.006**			**0.004**
Low expression	40	83.342	NR		88.281	NR	
High expression	72	54.457	22.870		60.395	35.900	
Histologic grade							
G1				0.386			0.405
Low expression	14	94.726	NR		95.631	NR	
High expression	14	84.551	101.530		88.402	NR	
G2/3				**0.014**			**0.008**
Low expression	62	82.081	NR		88.297	NR	
High expression	113	60.662	37.930		68.750	56.170	
N categories							
N=0				0.216			0.197
Low expression	54	95.888	NR		98.706	NR	
High expression	61	88.314	NR		93.458	NR	
N=1/2				0.137			0.106
Low expression	22	55.003	35.870		66.833	45.070	
High expression	66	40.343	17.300		49.892	29.800	
Adjuvant chemotherapy							
Yes				0.183			0.210
Low expression	47	84.579	NR		87.670	NR	
High expression	63	74.523	71.330		79.894	91.370	
No				**0.022**			**0.007**
Low expression	29	84.761	NR		93.100	NR	
High expression	64	52.872	19.930		62.255	50.830	

Note: Statistically significant *P* values are shown in bold.
Abbreviations: DFS, disease-free survival; NR, not reached; OS, overall survival.

significantly higher OS ($P<0.05$, Figure 4C), but showed no difference in DFS ($P=0.065$, Figure 4D).

To determine whether coexpression of CEP55 and AP3B influence survival, patients were divided into 4 groups: 1 (CEP55–/AP3B–), 2 (CEP55+/AP3B–), 3 (CEP55–/AP3B+), and 4 (CEP55+/AP3B+). Group 1 patients had the best survival rate, and group 4 patients had the worst survival rate (mean OS: 99.82 vs 58.12 months; mean DFS: 97.41

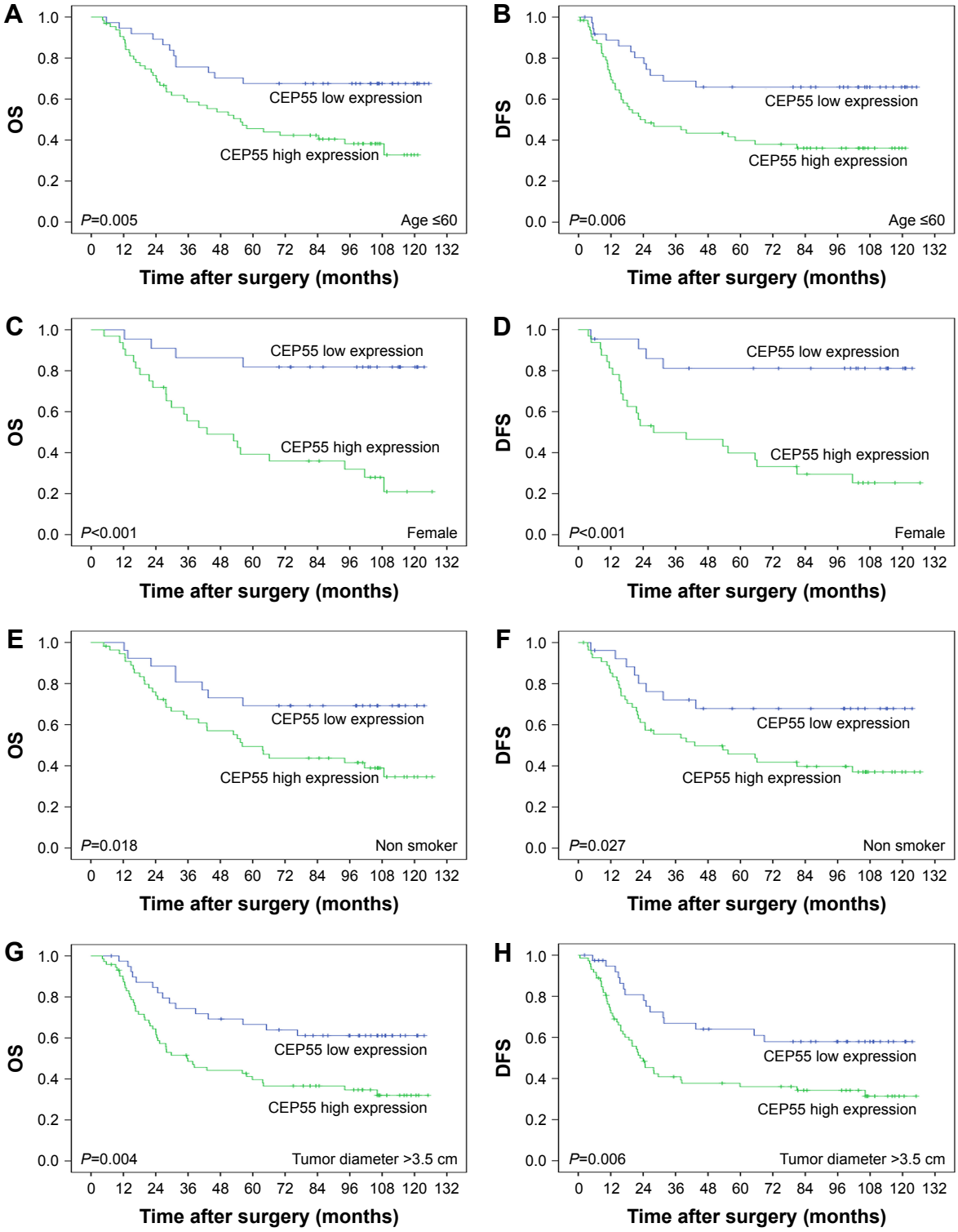

Figure 3 (*Continued*)

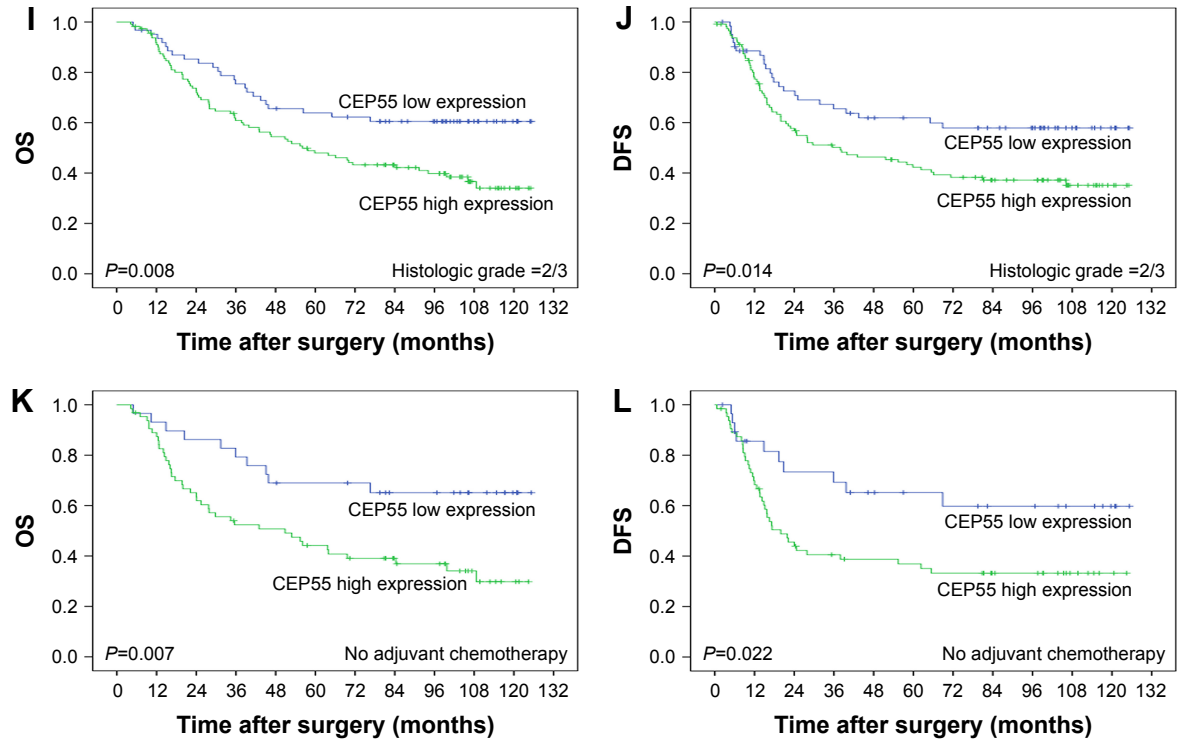

Figure 3 Subgroup analysis of patients with NSCLC based on their CEP55 expression.
Notes: (**A**, **B**) OS curve and DFS curve: patients aged ≤60 with high and low levels of CEP55 expression. (**C**, **D**) OS curve and DFS curve: female patients with high and low levels of CEP55 expression. (**E**, **F**) OS curve and DFS curve: nonsmoker patients with high and low levels of CEP55 expression. (**G**, **H**) OS curve and DFS curve: patients with tumor diameters >3.5 cm with high and low levels of CEP55 expression. (**I**, **J**) OS curve and DFS curve: patients with histological grade 2 or 3 and high and low levels of CEP55 expression. (**K**, **L**) OS curve and DFS curve: patients who underwent no chemotherapy with high and low levels of CEP55 expression.
Abbreviations: DFS, disease-free survival; NSCSC, non-small-cell lung cancer; OS, overall survival.

vs 49.42 months). Group 2 and group 3 had moderate survivals rates.

ROC curves were plotted to evaluate the patients' survival status to assess prognostic values of CEP55, AP3B, or combined expression in NSCLC. ROC curve analysis showed promising predictive significance of CEP55 combined with AP3B expression in all NSCLC patients (area under the curve =0.665, $P<0.001$, Figure 4G). ROC curves of CEP55 and AP3B showed area under the curve of 0.600 and 0.616, which is also predictively significant ($P=0.013$ and $P=0.004$, respectively, Figure 4G).

Discussion

In this study, we showed that high expression of CEP55 is predictive of worse prognosis in lung cancer patients. Nodal status, AP3B expression, and CEP55 expression

Table 3 Univariate and multivariate analyses of OS of lung cancer patients

Variables	Univariate analyses			Multivariate analyses		
	HR	(95% CI)	*P*-value	HR	(95% CI)	*P*-value
Age (years) (≤58 vs >58)	1.022	0.693–1.507	0.912			
Gender (male vs female)	1.074	0.692–1.668	0.750			
Smoking (yes vs no)	1.038	0.698–1.542	0.855			
Tumor diameter (≤3.5 vs >3.5 cm)	1.508	1.015–2.424	**0.042**	1.048	0.658–1.669	0.843
Histological grade (III/II/I)	1.353	1.012–1.808	**0.041**	1.216	0.862–1.715	0.265
Tumor status (T4/T3/T2/T1)	1.496	1.121–1.997	**0.006**	1.116	0.758–1.645	0.577
Nodal status (N>0/N0)	3.398	2.260–5.109	**<0.001**	2.210	0.958–4.957	**0.050**
TNM staging (III/II/I)	1.889	1.502–2.376	**<0.001**	1.230	0.756–1.999	0.405
AP3B expression (high/low)	2.066	1.383–3.806	**<0.001**	1.893	1.245–2.877	**0.003**
CEP55 expression (high/low)	1.895	1.226–2.920	**0.004**	1.617	1.033–2.532	**0.036**
Adjuvant chemotherapy (yes vs no)	0.639	0.433–0.942	**0.024**	1.080	0.711–1.640	0.719

Note: Statistically significant *P* values are shown in bold.
Abbreviation: OS, overall survival.

were independent prognostic factors that affected prognosis. Patients with low CEP55 and AP3B expression had the best survival rate, and patients with high CEP55 and AP3B expression had the worse survival rate. Previously, CEP55 had been shown to be a useful biomarker in breast, prostate, renal, and thyroid cancers.[7–10] However, its predictive value in lung cancer had not been reported.

CEP55 is a 55 kD centrosome- and midbody-associated protein. It contains 464 amino and was initially discovered as a key regulator of cytokinesis.[14,15] Cytokinesis is a short and final step of the cell cycle during which the cytoplasmic division of a cell occurs and two daughter cells form. CEP55 localizes on the centrosome throughout the cell cycle and is recruited to the mitotic spindle and midbody during mitosis to recruit downstream machinery to it, which is critical for the correct assembly of the midbody. Consistently, CEP55 depletion in cells led to an increase in multinucleated cells and cells arrested at the midbody stage, which demonstrated the critical role of CEP55 in cytokinesis.[16,17]

Apart from the cell cycle, CEP55 and the midbody are also associated with cell stemness. Stem cells and cancer cells accumulate more midbodies by evading autophagy, while differentiated cells possess high autophagic activity and do not accumulate midbodies.[6] Interestingly, our clinical analysis showed some similar results. We found that patients with higher histologic grade and TNM stages had a high ratio of positive CEP55 staining compared to those with well-differentiated tumors and lower TNM stages. Additionally, patients with lymph node metastasis demonstrated a higher ratio of positive CEP55 staining than those without lymph node metastasis. These clinical observations suggest that high expression of CEP55 correlates with cancer cell stemness, which is consistent with previous studies.

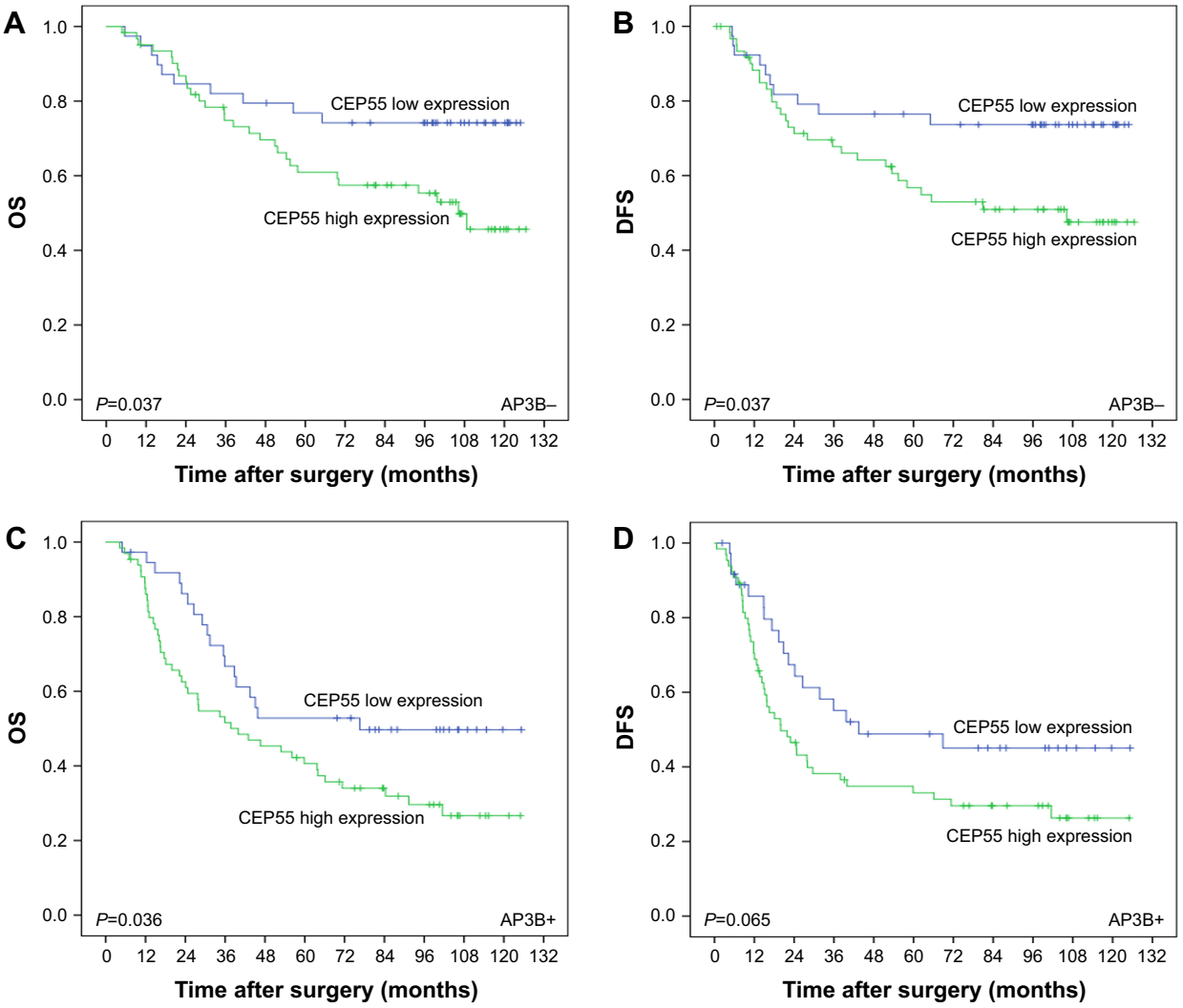

Figure 4 (*Continued*)

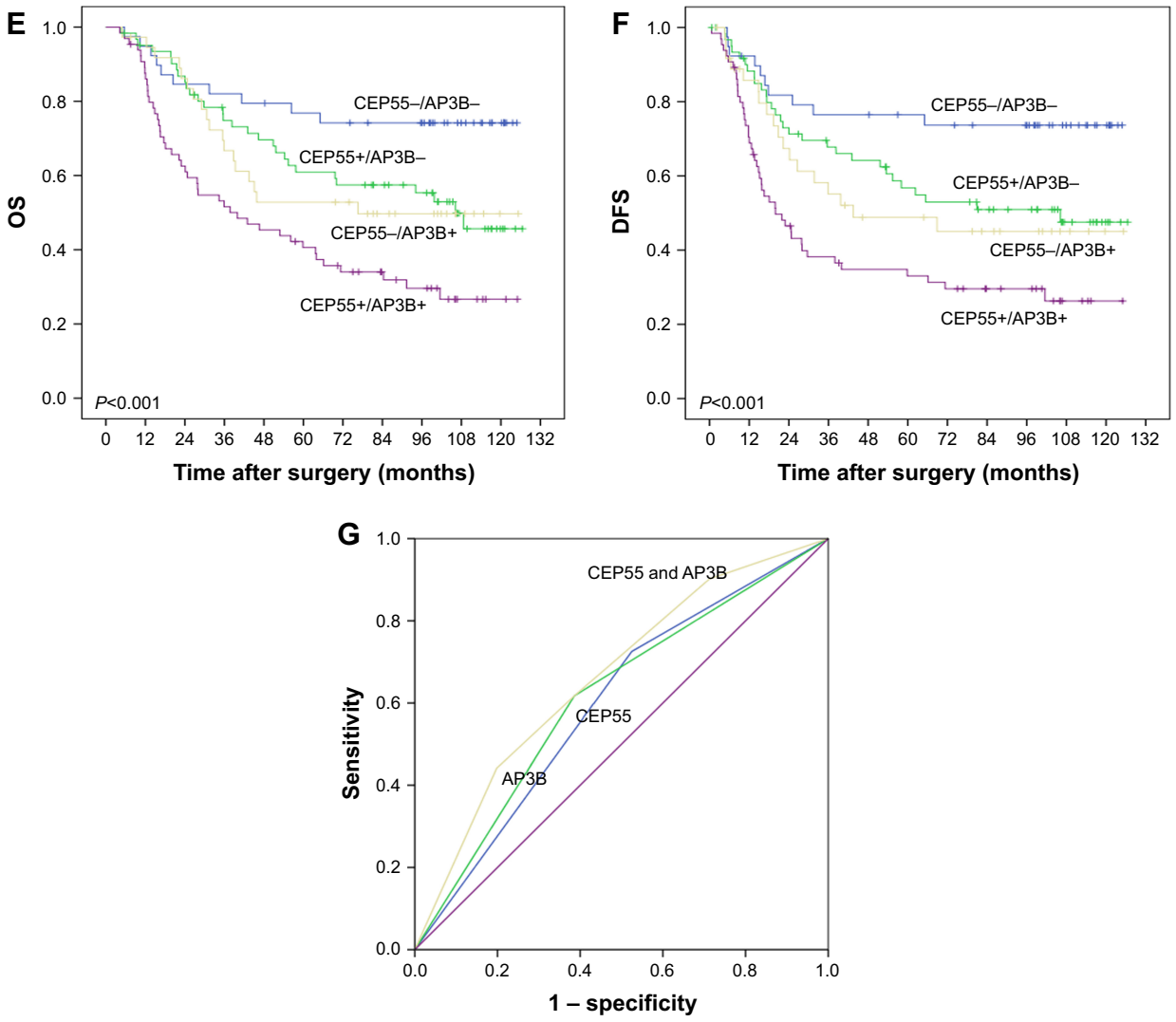

Figure 4 OS and DFS curves of patients with NSCLC based on their AP3B and CEP55 expression.
Notes: (**A**, **B**) OS curve and DFS curve: patients who have low AP3B expression levels with high and low levels of CEP55 expression. (**C**, **D**) OS curve and DFS curve: patients who have high AP3B expression levels with high and low levels of CEP55 expression. (**E**, **F**) OS curve and DFS curve of 4 groups of patients according to AP3B and CEP55 expression: CEP55–/AP3B–, CEP55+/AP3B–, CEP55–/AP3B+, and CEP55+/AP3B+. (**G**) ROC curve of CEP55 only, AP3B only, and CEP55 combined with AP3B.
Abbreviations: DFS, disease-free survival; NSCSC, non-small-cell lung cancer; OS, overall survival; ROC, receiver operating characteristic.

Another possible explanation of the high ratio of CEP55 expression in more advanced stage lung cancer patients is due to its activation of PI3K/AKT pathway, a major prosurvival pathway in cancer cells. CEP55 has been reported to bind to PIK3CA and stabilize it, leading to increased S473 phosphorylation of AKT in lung cancer.[18] In addition, the CEP55/PI3K/AKT pathway leads to increased migration and invasion of lung cancer cells.[19] Thus, the activation of AKT could be a critical oncogenic factor of these advanced stage lung cancer patients.

We conclude that CEP55 is an independent prognostic factor in lung cancers. In the Kaplan–Meier plots, lung cancer patients with high CEP55 expression have shorter survival time than those with low CEP55 expression. We also extracted Kaplan–Meier plots from SurveExpress online database and found similar results, further supporting our conclusions. As mentioned before, overexpression of CEP55 has been reported to predict poor prognosis in ovarian carcinoma, esophageal squamous cell carcinoma, bladder, breast, and thyroid cancers. Of note, in the last few decades, CEP55 has been identified as being overexpressed in mRNA microarray expression profiles of many human cancers, including gastric, hepatocellular, lung, and bladder carcinoma.[4,18,20,21] CEP55 was included in the top 70 most highly overexpressed genes in CIN 70 and in a signature in patented prognostic kits for the prediction of malignancy risk, prognosis, and therapy resistance in multiple human cancers.[22] CEP55 was also part of commercial signatures from Myriad Genetics Inc. and PAM50 for diagnosis and prognostic prediction of lung and other types of cancers.[23]

More importantly, it has been reported that CEP55 can act as a cancer vaccine target. It is not only a tumor-associated antigen but also aberrantly expressed in tumors, making it ideal for immunotherapy vaccines.[24] Previous studies have shown that CEP55 peptides were able expand and activate cytotoxic T lymphocyte clonally in vitro and in vivo.[25,26] Exciting results have been shown in the treatment of chemotherapy-resistant colon cancer cells.

Our results fill in the blank in the prognostic prediction of lung cancer patients by IHC, which strengthened the clinical significance of CEP55. All these findings demonstrate that both CEP55 RNA and protein levels can act as prognostic factors in multiple cancers and might be a good treatment target in cancer immunotherapies.

Another intriguing investigation direction is about the regulation of CEP55 by driver genes in cancers. Although it has been demonstrated that FOXM1 transactivates CEP55 and PLK1 stabilizes it, few papers cover the relationship of CEP55 with key driver mutations in lung cancer, such as ALK, EGFR, k-ras, and met.[12,27] As an important oncogenic factor, the activity of CEP55 must be strictly regulated in cells. Thus, it deserves more studies both clinically and mechanistically. We admit that this study has limitations. It was conducted only in one institution; further verifications from other independent investigators are needed. Additionally, key mutation information was not included in our data, so correlational analyses between CEP55 and other known mutations could not be performed.

Overall, our local and online analyses led to the conclusion that lung cancer patients with high CEP55 expression have shorter OS and DFS compared with those with low CEP55 expression. CEP55 might be associated with stemness of lung cancer cells, and it can be an independent predictor of survival for patients with lung cancer. Further studies are warranted.

Disclosure

The authors report no conflicts of interest in this work.

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