NDRG2 combined with EGFR improved its prognostic value for lung adenocarcinoma

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Abstract

Background N-Myc downstream-regulated gene2 (NDRG2) plays an important role in lung adenocarcinoma (LUAD). Epidermal growth factor receptor (EGFR) mutation has significantly improved prognosis in patients with adenocarcinoma. We aimed to elucidate the clinical value of NDRG2/EGFR as a prediction of prognosis in patients with lung adenocarcinoma.

Materials and Methods Immunohistochemistry and western blot analysis were conducted to detect the expression of NDRG2 protein. Association between NDRG2/EGFR expression and clinicopathological parameters of the patients were examined. Serum Carcinoembryonic antigen (CEA) level was examined prior to treatment in patients with LUAD. Patients' survival rate was assessed by Kaplan–Meier. Candidates for independent prognostic biomarkers were analyzed using a COX proportional hazard model.

Results NDRG2 levels were significantly decreased in patients with lung adenocarcinoma. NDRG2 levels were positively correlated with CEA and EGFR. Advanced stages were significantly associated with low expression of NDRG2. Patients with NDRG2-high combined with EGFR-positive expression had the best prognosis during the 5-year follow-up period. Meanwhile, COX regression analysis showed that the conjoined expressions of NDRG2-low/EGFR-positive, NDRG2-high/EGFR-positive and vascular invasion were independent prognostic indicators for lung adenocarcinoma.

Conclusion NDRG2 is of more prognosis value as the biomarker for lung adenocarcinoma when analyzed combined with the EGFR expression.

Background

Lung cancer remains the leading cause of cancer-related death worldwide and in China, counting for 19.4% mortality of cancer in adults[1]. Small-cell lung cancer (approximately 15%), together with non-small cell lung cancer (NSCLC) (approximately 85%) constitute the lung cancer. The latter group includes LUAD, which is the most prevalent subtype of lung neoplasms[2]. However, only approximately 20% NSCLC patients can be potentially cure by resection and the other 80% are diagnosed in advanced stages[3]. Despite advances in early detection and standard treatment such as surgical, chemotherapy, radiotherapy, and iodine-125 (^{125}I) brachytherapy, the overall prognosis of NSCLC remains poor[4].

Targeted therapy has recently emerged as a new therapeutic method for patients with advanced NSCLC, especially in lung adenocarcinoma harbour EGFR mutations and showed better progression-free survival than squamous cell carcinoma treated with the molecular targeted drugs such as tyrosine kinase inhibitors (TKIs)[5,6]. However, more and more patients after surgical resection eventually developed incapable survival due to inevitable drug resistance, and patients lacking driver oncogene aberrations are still treated with traditional regimens which will cause great suffering[7].

NDRG2 is one of four members of the NDRG family[8]. Previous studies have shown that NDRG2 exerts important functions in various tissues. Decreased expression of NDRG2 has been found in many kinds of human cancer, such as lung cancer, bladder cancer, colon cancer, pancreatic cancer, thyroid cancer, glioblastoma, melanoma and meningioma[9]. Although previous analysis showed that NDRG2 might serve as a novel prognostic marker in human lung cancer, its prognostic value remains to be determined in LUAD. Additionally, the association between NDRG2 expression and EGFR mutation is unclear.

Accordingly, the identification of novel LUAD prognosis markers is urgently needed. This study confirmed the prognosis value of the combined detection of NDRG2 /EGFR in LUAD.

Methods

Patients

The study protocol was approved by the Ethics Committee of the Tianjin First Central Hospital of Nankai University (Tianjin, China; approval no. 2018N054KY). Written informed consent was obtained from all enrolled patients. All patients' data were treated in accordance with the local privacy regulations.

A total of 89 LUAD patients were prospectively enrolled from the Tianjin First Central Hospital of Nankai University between June, 2013 and June, 2014 (52 men and 37 women, mean age 65.6; range 38 to 86 years). None of the patients had received any chemotherapy, radiotherapy and/or immunotherapy before sampling. The clinical and pathologic characteristics of LUAD patients are listed in Table 1. Those individuals smoking at least 1 cigarette per day for over 1 year were defined as smokers. The criteria used for tumor staging and grading were determined according to TNM classification system of malignant tumors published by the 8th edition of Union for International Cancer Control and World Health Organization classifications, respectively. Histodiagnosis of the haematoxylin and eosin-stained slides of the specimens was performed and verified by two board-certified pathologists with crosschecked diagnosis. Among these, 34 patients underwent curative-intent surgery resection. 55 advanced LUAD patients treated with iodine-125 (^{125}I) brachytherapy. Patients' preoperative work-flow (including PET/CT, lung function and cardiac ultrasonography) was examined to exclude those with secondary lung cancer and those with systemic disease.

Immunohistochemistry
Four-micrometre-thick formalin-fixed, paraffin-embedded sections were used for detecting NDRG2 protein expression. Tissue sections were dewaxed, rehydrated, antigen retrieved and cooled to room temperature. The slides were incubated with mouse monoclonal anti-NDRG2 antibody (Abcam, United Kingdom) at 4℃ overnight, rinsed with phosphate buffer saline (PBS) and incubated with horseradish peroxidase-labeled goat anti-mouse secondary antibody for 60 min. NDRG2 localization was revealed using diaminobenzidine (DAB) as the chromogen. Negative control was performed by replacing the primary antibody with normal mouse serum. The brown or yellow staining was identified as positive expression. The total staining score of 0–12 was

scored in a semiquantitative manner and stratified as follows: negative (-, score 0–1), weak (+, score 2–4), moderate (++, score 5–8), or strong (+++, score 9–12). We divided all of the tumor specimens into the low-expression group (score 0–4) and the high-expression group (score 5–12).

Western blots

Total protein concentration was determined by the BCA protein assay. Then, the protein was separated by 10% sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) gel and transferred onto polyvinylidene fluoride (PVDF) membranes. The membranes were incubated with mouse anti-human NDRG2 antibody at 4°C overnight after being blocked with 5% non-fat milk for 1 h. β-actin was used as the internal control. Then membranes were washed and incubated with horseradish peroxidase (HRP)-conjugated secondary antibody (Santa Cruz Biotechnology, Santa Cruz, CA, USA). The blots were visualized using enhanced chemiluminescence kit (Amersham Pharmacia Biotech, Arlington Heights, IL, USA) according to manufacturer's instructions. Each experiment was performed in triplicate.

Measurements of parameters

Blood samples were collected before treatment initiation. Patient blood type was examined by measuring the serum concentrations. Carcinoembryonic antigen (CEA) was also evaluated.

Statistical analysis

Data from categorical variables are expressed as frequencies or percentages. Continuous variables are presented as mean ± standard deviation (SD). Differences between categorical groups were investigated by Pearson's chi-square test or Fisher's exact test. The differences in mean values between the groups were analyzed using the Mann-Whitney U test or Student's t-test. Associations between the two variables were quantified using Spearman's rank correlation coefficient. Overall survival rate was evaluated using the Kaplan-Meier method and differences between the groups were assessed using the log-rank test. Multivariate analysis was conducted using Cox's proportional hazards regression model to investigate the effects of patients' characteristics on overall survival. All statistical tests were two-sided, $P < 0.05$ was considered as statistically significant.

Results

NDRG2 is downregulated in primary lung adenocarcinoma patients compared with healthy controls

To investigate whether NDRG2 was detectable and altered in LUAD patients compared with healthy controls, we performed immunohistochemistry (Figure 1 A-C) and western blotting (Figure 1 D-E) to detect the expression levels of NDRG2. The results showed that the expression of NDRG2 in LUAD was significantly decreased compared with healthy controls (Figure 1 A-E).

Relationship between NDRG2 expression level and clinicopathological features of patients with LUAD

As shown in Figure 2, the expression level of NDRG2 were significantly correlated with CEA ($P < 0.001$).

To assess the correlation between the NDRG2 expression and clinic data, patients with LUAD characteristics were summarized in Table 2. The chi-square test revealed that the incidence of NDRG2 high group was significantly higher in LUAD tissues in stages I−II than that in stage III−IV($P<0.001$). In addition, the no vascular invasion and EGFR positive(+) was significantly higher in the patients with high NDRG2 expression than in the patients with low NDRG2 expression ($P<0.001$ and 0.001, respectively). However, there was no association between expression levels of NDRG2 and other clinicopathological features, including gender, age, smoking status, and blood type ($P>0.05$).

Regarding the operated 34 patients, NDRG2 high group was significantly higher in stages I−II than that in stage III−IV($P=0.028$). The incidence of no vascular invasion and EGFR positive(+) was significantly higher in the patients with high NDRG2 expression than in the patients with low NDRG2 expression (0.008 and 0.030, respectively).

Prognostic implications of NDRG2 and EGFR expression

Based on the grouping standard by clinicopathologic features of LUAD, NDRG2, EGFR and CEA expression status, the survival time in individual group was analyzed by Kaplan−Meier method(Figure 3 A-H). The results showed that iodine-125 radioactive seeds brachytherapy for advanced LUAD patients with NDRG2-high expression had significantly better overall survival than low expression cases ($P< 0.001$, Figure 3A), and patients with EGFR-positive and CEA<2.0 ng/ml also had better overall survival ($P < 0.001$, 0.031, Figure 3 B, C). Additionally, in operated patients with NDRG2-high expression(Fig. 3E), EGFR-positive(Figure 3F) and CEA<2.0 ng/ml(Figure 3G) cases still presented better survival ($P = 0.002$, < 0.001 and 0.013, respectively).

According to the conjoined expressions of NDRG2/EGFR, the subjects were categorized into four groups: NDRG2-low/EGFR-negative, NDRG2-low/EGFR-positive, NDRG2-high/EGFR-negative and NDRG2-high/EGFR-positive. The association between co-expression of NDRG2/EGFR and the survival rates was tested by Kaplan−Meier method. In all four groups, iodine-125 radioactive seeds brachytherapy for advanced LUAD patients with NDRG2-high/EGFR-positive subjects had the best prognosis during the 5-year follow-up period ($P< 0.001$, Figure 3D) and the same results were observed in operated patients ($P< 0.001$, Figure 3H).

Cox regression analysis

As Table 3 shown, NDRG2-low/EGFR-positive (HR=6.508, 95% confidence interval, 2.619-16.174, P<0.001), NDRG2-high/EGFR- positive (HR=3.519, 95% confidence interval, 1.384-8.949, P=0.008) and vascular invasion (HR=4.480, 95% confidence interval, 2.291-8.760, P<0.001) were independent prognostic factors of overall survival.

Discussion

To improve the prognostic and prediction of lung cancer, many tumor markers including CEA have been intensively evaluated and widely used in the prediction of lung cancer[10,11]. However, each marker has its own specificity and sensitivity, which might lead to limitation in judging the prognosis. The combined detection of tumor markers maybe of great importance in the prognostic and prediction of tumor.

MYC, originally identified as an oncoprotein, affects growth, proliferation, differentiation, and apoptosis of cells through regulating the expression of a significant number of genes[12]. In addition, MYC governs events associated with tumor progression, including genetic stability, migration, and angiogenesis[13]. N-myc downstream-regulated gene 2, together with NDRG1, NDRG3 and NDRG4, constitute the NDRG gene family, a new class of differentiation-related genes, is highly expressed in normal cells and tissues but exerts decreased expression in various tumors and tumor cell lines[14]. Previous study reported that NDRG2 was a prognostic marker in lung cancer[9,15]. Similarly, our data shown that the high expression of NDRG2 in lung adenocarcinoma tissues was significantly associated with early TNM stage and negative vascular invasion (Table 2). NDRG2 low group showed a poorer overall survival than NDRG2 high group (Figure 3). These results indicate that NDRG2 may play an important role in the development of LUAD.

CEA was first described by Gold and Freedman as an antigen present in gastrointestinal carcinoma cells[11,16]. Some studies that have demonstrated the prognostic value of the preoperative CEA level, a classical marker for lung adenocarcinoma [17,18]. In this study, we showed for the first time that CEA level > 2.0 ng/ml was associated with NDRG2 low group (Table 2, Figure 2), and showed a poorer overall survival than those with CEA level < 2.0 ng/ml (Figure 3).

Previous studies showed that advanced NSCLC patients with EGFR mutations detected in circulating tumor DNA (ctDNA) could be used as biomarker for prognosis prediction[19]. Their analyses showed that EGFR mutations detected in blood were associated with better OS and PFS[20]. We reported the EGFR mutation status in patients with adenocarcinoma and its correlation with NDRG2 expression. Mutant EGFR expression was positively related to better overall survival in the presence of NDRG2 high expression (Table 2, Figure 3).

MYC and EGFR have been identified as potential biomarkers that predict the efficacy of the targeted therapy in cancer[21,22]. We analyzed the value of the combined detection of NDRG2 and EGFR in the prognosis of lung adenocarcinoma. The subjects with NDRG2-high/ EGFR(+) had the best outcome, while the NDRG2-low/EGFR(-) had the worst. Cox analysis revealed that NDRG2-low/EGFR(+), NDRG2-high/EGFR(+) and vascular invasion were independent prognostic factors of overall survival (Table 3).

However, this study has several limitations. First, it was a retrospective setting and performed in a single center. Second, the number of patients was small with an insufficient cases of each lung cancer subtype. Hence, further study is needed to explore the putative association between NDRG2/EGFR level and prognosis of patients with NSCLS.

Conclusions

In summary, this study reported the differential expression of NDRG2 in LUAD with both immunohistochemistry and protein level. In addition, the relationship between NDRG2/EGFR expression and clinical characteristics of LUAD, especially prognosis status, was investigated for the first time. NDRG2/EGFR can be used as a novel prognostic biomarker in LUAD patients.

Abbreviations

NDRG2: N-Myc downstream-regulated gene2

LUAD: Lung adenocarcinoma

EGFR: Epidermal growth factor receptor

CEA: Carcinoembryonic antigen

NSCLC: Non-small cell lung cancer

TKIs: Tyrosine kinase inhibitors

PBS: Phosphate buffer saline

DAB: Diaminobenzidine

SDS-PAGE: Sodium dodecyl sulfate polyacrylamide gel electrophoresis

PVDF: Polyvinylidene fluoride

HRP: Horseradish peroxidase

SD: Standard deviation

ctDNA: circulating tumor DNA

TNM: Tumor lymph node metastasis

OS: Overall survival

PFS: Progression-free survival

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Declarations

Author Contributions

Conceptualization, B.Y. and W-D.Z.; methodology, B.Y., X-P.L. and H-G.Z.; software, B.Y. and T.X.; formal analysis, T.X. and X-H.L.; investigation, T.J. and W-C.W.; resources, B.Y., X-P.L., L.Z. and W-L.Y.; writing-original draft preparation, B.Y. and H-G.Z.; writing-review and editing, X-P.L., T.J., T.X., X-H.L., Y-L.W. and W-C.W.; supervision, T.J. and W-D.Z.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and had been authorized by the Ethics Committee of Tianjin First Central Hospital of Nankai University (Tianjin, China; approval no. 2018N054KY) before beginning the study. Each patient in this study provided signed informed consent.

Consent for publication

Not applicable

Conflicts of Interest

The authors declare no conflict of interest.

Availability of data and materials

The data of the LUAD is available from the corresponding author on request.

Tables

Table 1. Patient characteristics.

Clinical characteristics	Total n	%
Age, years		
≤65	42	47.2
>65	47	52.8
Sex		
Male	52	58.4
Female	37	41.6
Smoking status		
Non-smoker	41	46.1
Smoker	48	53.9
Blood type		
A	29	32.6
B	27	30.3
O	24	27.0
AB	9	10.1
Lobe location		
Right	52	58.4
Upper lobe of right lung	30	57.7
Middle lobe of right lung	5	9.6
Inferior lobe of right lung	12	23.1
Center-type of right lung	5	9.6
Left	37	41.6
Upper lobe of left lung	21	56.8
Inferior lobe of left lung	13	35.1
Center-type of left lung	3	8.1
T		
1a	9	10.1
1b	11	12.4
1c	18	20.2
2a	21	23.6
2b	13	14.6
3	7	7.9
4	10	11.2
N		
0	29	32.6
1	20	22.5
2	27	30.3
3	13	14.6
M		
0	49	55.1
1a	20	22.5
1b	6	6.7
1c	14	15.7
Stage		
I	24	27.0
II	15	16.9
III	10	11.2
IV	40	44.9
Vascular invasion		
No	38	42.7
Yes	51	57.3
EGFR		
positive	31	34.8
negative	58	65.2

T, tumor; N, node; M, metastasis; EGFR, epidermal growth factor receptor

Table 2. Patient characteristics according to NDRG2 level.

Parameters	Total patients (n=89)			Operated patients (n=34)		
	NDRG2 low group	NDRG2 high group	P-value	NDRG2 low group	NDRG2 high group	P-value
Gender			0.988			0.710
Male	31	21		6	15	
Female	22	15		5	8	
Age (years)			0.996			0.705
<65	25	17		3	9	
≥65	28	19		8	14	
Smoking status			0.771			0.717
Non-smoker	19	14		5	13	
Smoker	34	22		6	10	
Blood type			0.265			0.905
A	15	14		5	9	
B	20	7		1	4	
AB	4	5		2	5	
O	14	10		3	5	
Stage			<0.001			0.072
I	6	18		5	16	
II	6	9		3	7	
III	8	2		2	0	
IV	33	7		1	0	
			<0.001			0.028
I+II	12	27		8	23	
III+IV	41	9		3	0	
CEA			<0.001			<0.001
<2.0	4	24		0	14	
≥2.0	49	12		11	9	
Vascular invasion			<0.001			0.008
No	19	32		6	22	
Yes	34	4		5	1	
EGFR			0.001			0.030
Negative(-)	42	16		9	9	
Positive(+)	11	20		2	14	

NDRG2, N-Myc downstream-regulated gene2; CEA, carcinoembryonic antigen (ng/ml); EGFR, epidermal growth factor receptor.

Table 3. Prognostic value of NDRG2/EGFR conjoined expression in multivariate analysis by Cox regression.

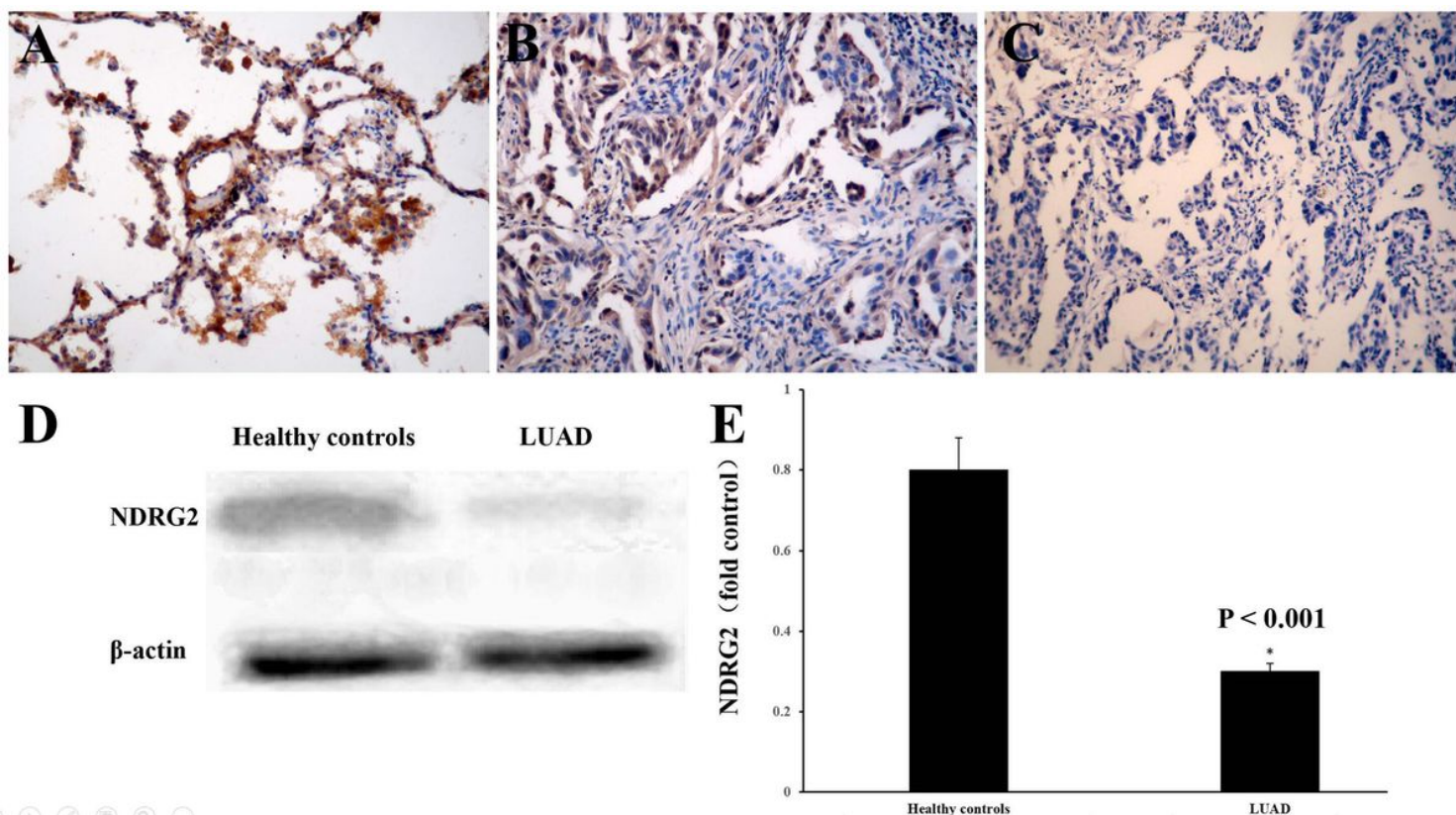|	B	SE	Wald	Df	P-value	HR	95.0 % CI for Exp(B)	
							Lower	Upper
Age	0.080	0.261	0.094	1	0.760	0.923	0.554	1.539
Sex	-0.171	0.317	0.290	1	0.590	1.186	0.637	2.209
Smoking status	0.066	0.309	0.046	1	0.831	0.936	0.511	1.716
Lobe location	0.186	0.262	0.502	1	0.479	0.831	0.497	1.388
Vascular invasion	1.500	0.342	19.202	1	<0.001	4.480	2.291	8.760
NDRG2-low/EGFR(-)			19.842	3	<0.001			
NDRG2-low/EGFR(+)	1.873	0.464	16.261	1	<0.001	6.508	2.619	16.174
NDRG2-high/EGFR(-)	0.576	0.556	1.073	1	0.300	1.779	0.598	5.292
NDRG2-high/EGFR(+)	1.258	0.476	6.984	1	0.008	3.519	1.384	8.949

Figures

Figure 1

NDRG2 expression in LUAD patients and healthy controls(Figure 1A-E). Immunohistochemical (IHC) staining showed the expression of NDRG2 in normal lung tissues (Figure 1A), LUAD (Fig. 1B) and negative control (Figure 1C) (x 200). NDRG2 protein expression was determined by Western blot assay (Fig. 1D). Quantification of protein expression was normalized to β-actin using a densitometer (Figure 1E). It was significantly downregulated in patients with adenocarcinoma compared with that in healthy controls at protein levels (*$P < 0.001$).
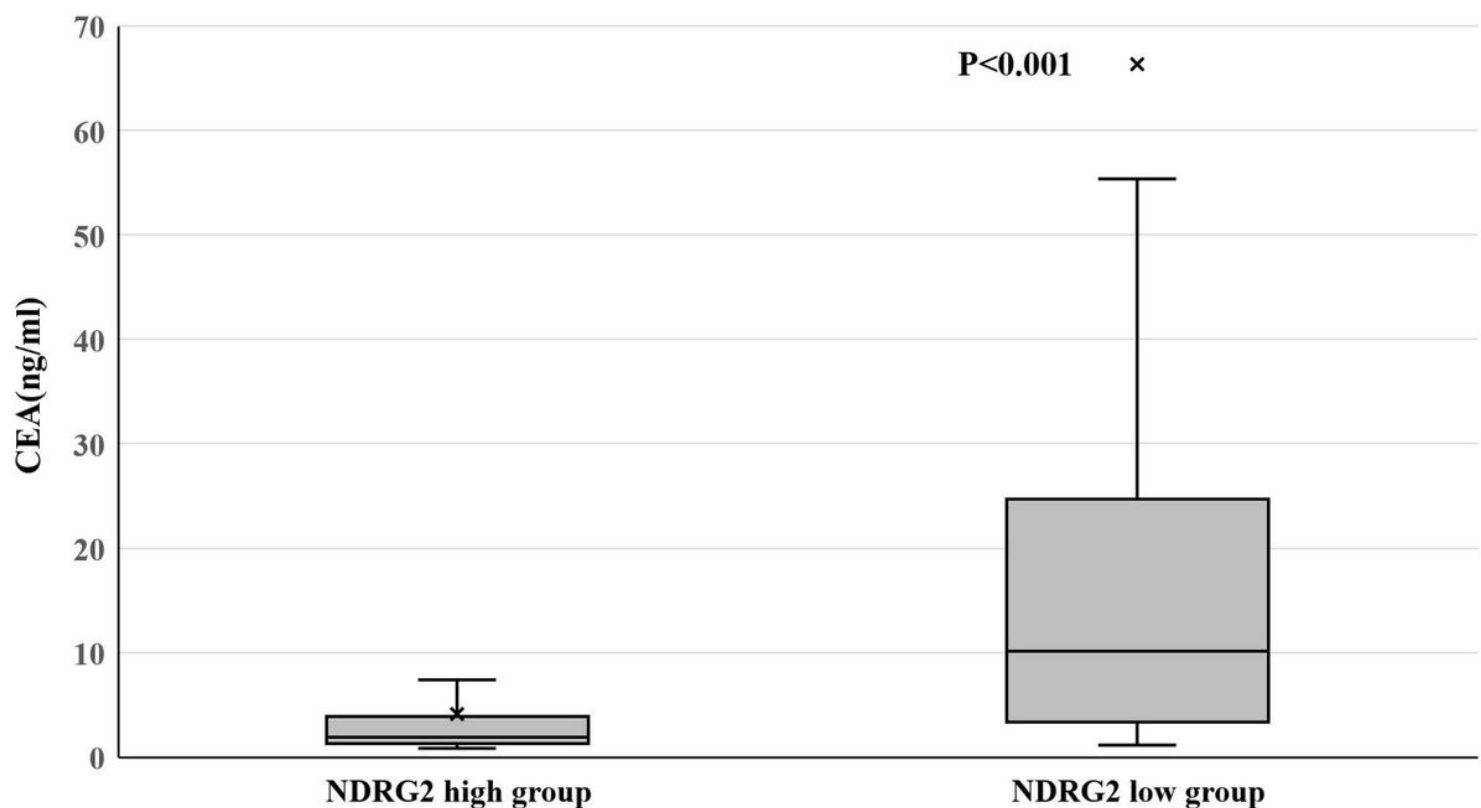

Figure 2

Associations between NDRG2 and clinicopathological features. CEA levels, were significantly lower in the patients with NDRG2 high group than those in the patients with NDRG2 low group(P < 0.001). CEA, carcinoembryonic antigen; NDRG2, N-Myc downstream-regulated gene2.
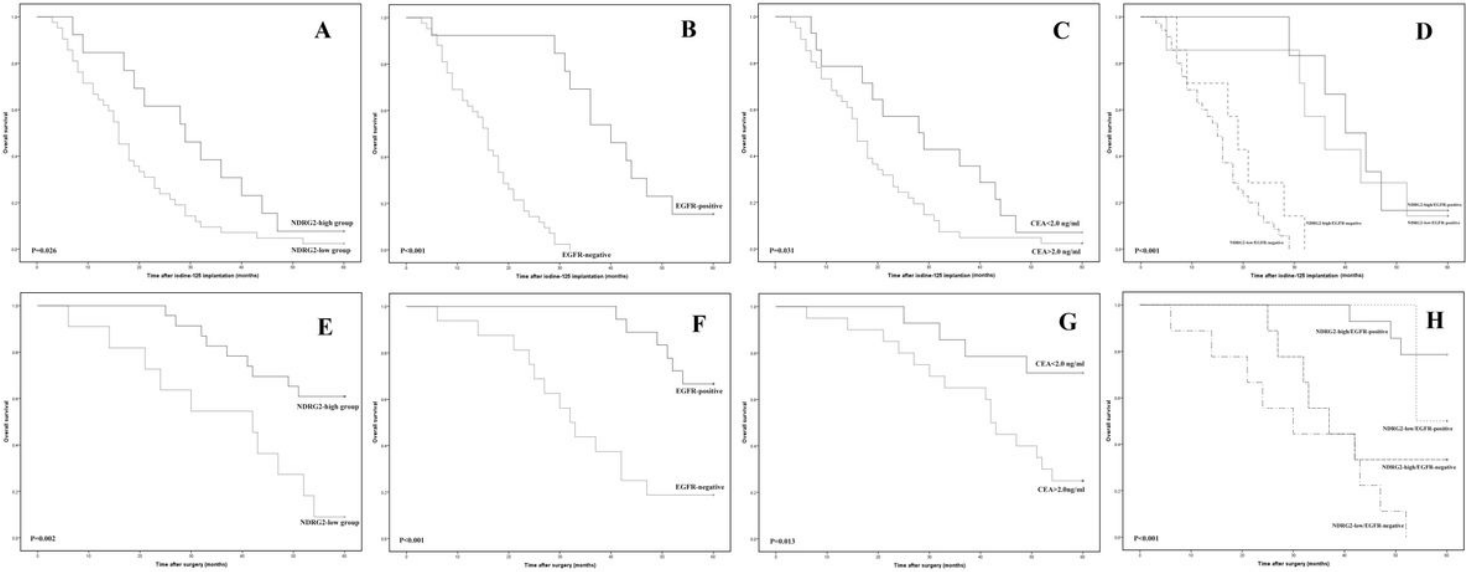

Figure 3

Patient characteristics according to NDRG2 level. Figure 3 Overall survival of LUAD patients(Figure 3A-H). Overall survival of the iodine-125 radioactive seeds brachytherapy for advanced LUAD patients(Figure 3A-D). The patients with low NDRG2 expression (P = 0.026, Figure 3A), those with EGFR negative expression (P < 0.001, Figure 3B), and those CEA > 2.0 ng/ml (P=0.031, Figure 3C), exhibited significantly poorer overall prognoses. 4 groups of NDRG2 and EGFR expression in LUAD. Patients with NDRG2-low/EGFR-negative co-expression profile had the worst outcome for overall survival among the 4 groups (P < 0.001, Figure 3D). Overall survival of operated patients(Figure 3E-H). The patients with low NDRG2 expression (P = 0.002, Figure 3E), those with EGFR negative expression (P < 0.001, Figure 3F), and those CEA > 2.0 ng/ml (P = 0.013, Figure 3G), exhibited significantly poorer overall prognoses. 4 groups of NDRG2 and EGFR expression in LUAD. Patients with NDRG2-low/EGFR-negative co-expression profile had the worst outcome for overall survival among the 4 groups (P < 0.001, Figure 3H).