Somatic mutations combined with clinical features can predict the postoperative prognosis of stage IIIA lung adenocarcinoma

Jiuzhen Li[1,2#^], Xuefeng Lin[3#], Xin Li[2], Weiran Zhang[2], Daqiang Sun[2]

[1]Graduate School, Tianjin Medical University, Tianjin, China; [2]Department of Thoracic Surgery, Tianjin Chest Hospital, Tianjin, China; [3]Tianjin Medical College, Tianjin, China

Contributions: (I) Conception and design: D Sun, J Li, X Lin; (II) Administrative support: D Sun; (III) Provision of study materials or patients: D Sun, X Lin, J Li; (IV) Collection and assembly of data: J Li, X Li; (V) Data analysis and interpretation: J Li; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Daqiang Sun, MD. Department of Thoracic Surgery, Tianjin Chest Hospital, No. 261 Taierzhuang South Road, Jinnan District, Tianjin, China. Email: sdqmd@163.com.

Background: Prognostic factors for stage IIIA lung adenocarcinoma (LUAD) are unclear. The current main treatment for stage IIIA LUAD is still controversial. Some Clinicians advocate synchronous chemoradiotherapy as the main treatment for stage IIIA LUAD. In contrast, some clinicians argue that there are still certain patients with stage IIIA LUAD who have a better postoperative prognosis. This study aimed to analyze preoperative factors as well as the association between somatic mutations and prognosis in stage IIIA LUAD [including overall survival (OS) time and the risk of postoperative recurrence].

Methods: This study retrospectively reviewed the data of patients with stage IIIA LUAD who underwent radical resection of lung cancer in the thoracic surgery department of Tianjin Chest Hospital from January 01, 2011 to September 30, 2016. All patients involved in the study provided written informed consent. The associations between OS and DFS and the clinical characteristics as well as somatic mutations of patients were analyzed separately. The Kaplan-Meier method was used for univariate analysis, and survival curves were drawn. Multivariate analysis was performed by the Cox regression model.

Results: For univariate analysis, the prognostic factors of OS were the level of preoperative CYFRA21-1, the number of metastatic lymph node stations (NMLS), maximum tumor diameter, EGFR (epidermal growth factor receptor) classical base mutations, and the number of copies of POLE (polymerase epsilon) mutation (NCPM). Preoperative total protein level, preoperative CYFRA21-1 level, the number of metastatic lymph nodes (NMLN), maximum tumor diameter, the number of mutated genes (NMG) in tumor samples, TP53 mutations, and the number of copies of POLE mutation (NCPM) were associated with disease-free survival (DFS). The multivariate analysis showed that the preoperative CYFRA21-1 level, the number of metastatic lymph node stations (NMLS), and EGFR typical base mutations were independent prognostic factors of OS. The number of mutated genes (NMG), EGFR classical base mutations, preoperative NSE level, maximum tumor diameter, and the number of metastatic lymph node stations (NMLS) were independent prognostic factors for DFS.

Conclusions: The preoperative level of tumor markers, the number of metastatic lymph node stations, and EGFR typical base mutations are important factors for the prognosis of patients with resectable stage IIIA LUAD.

Keywords: Resectable stage IIIA lung adenocarcinoma; prognostic factors; gene detection; EGFR mutation

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^ ORCID: 0000-0002-3142-4223.

Introduction

In recent years, significant progress has been made in the treatment of lung cancer, and the biological characteristics and progression mechanisms of lung cancer have become more deeply understood. Nevertheless, the overall prognosis of lung cancer is not optimistic. According to data released by China National Cancer Center in 2015, the incidence rate and mortality rate of lung cancer still rank first among all cancers (1). Non-small cell lung cancer (NSCLC) accounts for about 80% of total lung cancer cases, and lung adenocarcinoma is the most common pathological type. Statistical data show that only 25% of all confirmed cases are diagnosed early every year (2), while a significant number of patients still present to the clinic with progression to the middle or late stages. Surgical resection is the first choice treatment for stage I–II lung adenocarcinoma (3). Nonsurgical treatment is preferred for some stage IIIB and stage IV patients. For stage IIIA NSCLC, only 14–20% of patients are suitable for surgical resection, and importantly, the 5-year overall survival (OS) rate is only 13–36% (4). Because of the late stage, there may be difficulty in surgery and a relative increase in perioperative mortality and complications. Therefore, at present, the main treatment of stage IIIA NSCLC is still controversial. A large-scale investigation abroad pointed out that clinicians' acceptance of surgical treatment for stage IIIA NSCLC patients is poor (5). Most clinicians advocate concurrent chemoradiotherapy as the main treatment (6,7). On the other hand, some clinicians believe that certain patients with stage IIIA NSCLC still have the opportunity for surgery after comprehensive evaluation and screening. It has been reported that radical tumor resection can effectively prolong the postoperative survival of patients with stage IIIA NSCLC (8,9). Unfortunately, however, the overall prognosis of stage IIIA NSCLC is poor, regardless of whether it is operated on or not, and the 5-year survival rate is only 15–23% (10). Therefore, more and more researchers are questioning whether patients with stage IIIA NSCLC need surgical treatment. The incidence rate of lung adenocarcinoma ranks first, and the prognosis of lung squamous cell carcinoma is lower than that of lung adenocarcinoma (11). Most lung adenocarcinomas are peripheral type. Compared with patients with central squamous cell carcinoma, the operation risk is lower and is easier to complete. Based on the above reasons, we focused on the study of stage IIIA resectable lung adenocarcinoma. In actual clinical work, we observed that a considerable number of patients with stage IIIA lung adenocarcinoma had a good prognosis after surgical resection. However, there is still a lack of systematic analyses on the prognostic characteristics of these patients. The research on predicting prognosis of NSCLC by somatic mutation is increasing year by year. However, few studies have focused solely on the relationship between the prognosis of stage IIIA LUAD and somatic mutations. This study combined somatic mutations with clinical factors to predict postoperative prognosis in stage IIIA lung adenocarcinoma. We present the following article in accordance with the REMARK reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-130/rc).

Methods

Patients and sample collection

This study collected the clinical data of patients with stage IIIA lung adenocarcinoma who underwent radical resection in Tianjin Thoracic Hospital from January 2011 to September 2016. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of Tianjin Chest Hospital and informed consent was taken from all the patients.

Gene panel sequencing

Formalin fixed and paraffin embedded tumor specimens were collected for detection. Paired samples (tumor tissue + paracancerous tissue) were obtained from each specimen, and 15 sections of each kind of tissue were cut at a thickness of 7 μm. A 66 gene panel was used for sample detection. The quality control results included capture interval, average sequencing depth, base capture efficiency, total reads (m), map rate, repeatability, 1 ratio, 20 ratio, 50 ratio, and 100 ratio. Missense mutations, nonsense mutations, and CDs-Indel were detected, along with frameshift mutations, substitution mutations, stop-loss mutations, and splice site mutations. The number of mutations in each tumor slice was calculated, and the mutation sites with the highest mutation frequency were obtained. The high-frequency mutation genes were obtained by sequencing the number of gene variation samples from high to low in the gene unit. The high-frequency mutation sites were obtained by sequencing the number of gene variation samples from high to low in the gene unit.

Building the library sequencing pipeline

DNA extraction and quantification

The QIAamp DNA FFPE tissue kit was used to extract DNA from samples. The quality of extracted genomic DNA was detected by combining the following two methods: agarose gel electrophoresis was used to analyze the degree of DNA degradation and whether there were impurity bands, RNA, and protein contamination; and DNA concentration was accurately quantified using Qubit.

Library preparation

Genomic DNA was randomly broken up by the Covaris Fragmentor set at a length of 180–280 bp. Agilent customized reagent was used for library construction and capture. After end repair, phosphorylation, and addition of a tail, connectors were connected at both ends of the fragment to prepare the DNA library. The library with the specific index was hybridized with a biotin labeled probe in liquid phase, and then the target region was captured by magnetic beads. After linear amplification by PCR, the library was inspected and qualified for sequencing.

Library inspection

After the construction of the library, Qubit was used for preliminary quantification, and then Agilent 2100 was used to detect the insert size of the library. After the insert size met the expectations, qPCR was used to accurately quantify the effective concentration of the library, so as to ensure the quality of the library.

Computer sequencing

After passing the library inspection, Illumina HiSeq PE150 sequencing was performed according to the effective concentration of the library and data output requirements.

Mutation analysis of specimens

Obtaining the original gene sequences after sequencing, the information analysis process was performed, which was divided into two stages:

(I) Sequencing data quality evaluation: using mainly the statistics of sequencing error rate, data volume, and comparison rate, among others, we evaluated whether the database construction and sequencing met the standards, and subsequent analysis was conducted if they met the standards;

(II) Mutation information mining and analysis: high-quality sequences were aligned to the human reference genome, mutation information was detected in samples, somatic mutations of cancer paired samples were detected, and the detected mutations were analyzed and interpreted.

Outcome measures

OS was the time from the operation date to the last follow-up or death. Disease-free survival (DFS) was defined as the time from the date of surgery to disease recurrence or death from any cause.

Statistical analysis

SPSS 21.0 software was used for statistical analysis. Life table and the Kaplan-Meier method (log-rank test) were used for univariate analysis to calculate the survival rate, median survival time, and draw survival curves. A Cox proportional hazards model was used for multivariate analysis. Differences with $P<0.05$ were statistically significant.

Results

Clinical characteristics

According to the inclusion criteria, a total of 85 patients were included in this study. No patients underwent targeted therapy postoperatively. Among them, there were 43 males and 42 females, accounting for 50.6% and 49.4%, respectively. The age span of the patients ranged from 37 to 82 years old. The median OS was 43.20 months, the median DFS was 35.80 months, the mean follow-up time was 43.17 months, and the mean DFS was 34.25 months. The shortest OS was 5.2 months and the longest was 94.4 months. The shortest DFS was 1.2 months and the longest was 94.4 months. The 1- and 3-year OS were 94% and 65%, respectively. The 1- and 3-year DFS were 86% and 41%, respectively. The OS and DFS curves are shown in *Figure 1* and *Figure 2*.

Collation of non-dichotomous variables

For the above-mentioned continuous variables, the cut-off values were derived by calculating the area under the receiver operating characteristic (ROC) curve (AUC) according to OS and DFS. For the OS group cut-off values:

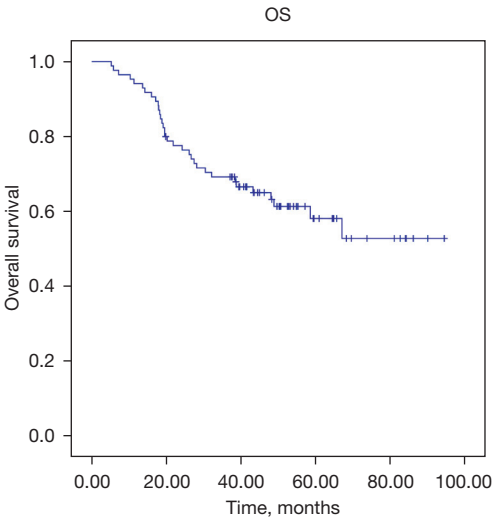

Figure 1 Overall survival (OS) curve of 85 patients with stage IIIA lung adenocarcinoma.

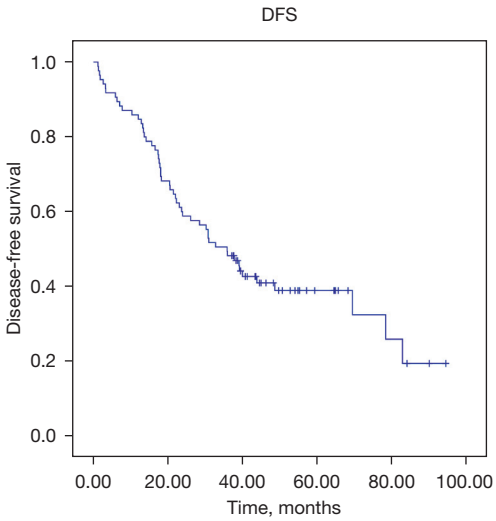

Figure 2 Disease-free survival (DFS) curve of 85 patients with stage IIIA lung adenocarcinoma.

age was 61.5 years, smoking index was 775, preoperative BMI was 24.95, preoperative hemoglobin level was 149.5 g, preoperative total protein level was 64.35 g, tumor marker quantitative NSE was 16.37, CYFRA21-1 was 3.81, CEA was 6.66, the number of metastatic lymph nodes (NMLN) was 1.5, the number of metastatic lymph node stations (NMLS) was 2, and the tumor diameter was 3.25 cm. For the DFS group cut-off values: age was 52.5 years, smoking index was 610, preoperative BMI was 22.75, preoperative hemoglobin level was 149.5 g, preoperative total protein level was 64.35 g, tumor marker quantitative NSE was 15.325, CYFRA21-1 was 2.05, CEA was 7.44, number of lymph node metastasis was 2.5, number of metastatic lymph node stations was 1.5 station, and tumor diameter was 3.25 cm.

Results of gene detection

There were 10,208 mutations in the 85 samples, with a maximum of 479 and a minimum of 13 in a single sample. The average sequencing depth of the samples ranged from 420.74 to 2910.74. The variation results are shown in *Figure 3*. Based on the variations, the number of samples with gene variations was arranged from high to low, and the high-frequency gene variations were obtained. The c.24_26del of IFNGR2 had the highest mutation frequency, followed by EGFR c.2235_2249del and c.2573t > G. We plotted the variation in at least 6 samples, as shown in *Figure 4*. According to the gene unit, the number of samples with gene variation was ranked from high to low to obtain high-frequency mutation genes, in which ATM was the most frequently mutated gene. In addition, the number of mutated genes in each sample was calculated. We mapped the genes that were mutated in at least 50 samples, as shown in *Figure 5*. The cut-off values for the number of copies of POLE mutation (NCPM), somatic mutations, gene mutations, nonsense mutations, and synonymous mutations were calculated by the AUCs of the ROC curves and are reported in *Tables 1*,*2*.

Analysis of prognostic factors

Univariate analysis

The variables involved included: age, gender, preoperative BMI, preoperative total protein level, preoperative hemoglobin level, smoking history, smoking index, preoperative tumor markers (NSE, CEA, CYFRA21-1), number of lymph node metastasis, number of metastatic lymph node metastasis, positive or negative lymph nodes of the inferior tracheal protuberance, primary tumor location, maximum tumor diameter, N stage, N2 metastasis, IFNGR2 c.24_26del, EGFR classic base mutation, ALK mutation, TP53 mutation, KRAS mutation, PIK3CA mutation, POLE mutation, IFNGR2 mutation, number of copies of POLE mutations(NCPM), number of somatic mutations, number of mutated genes in tumor samples,

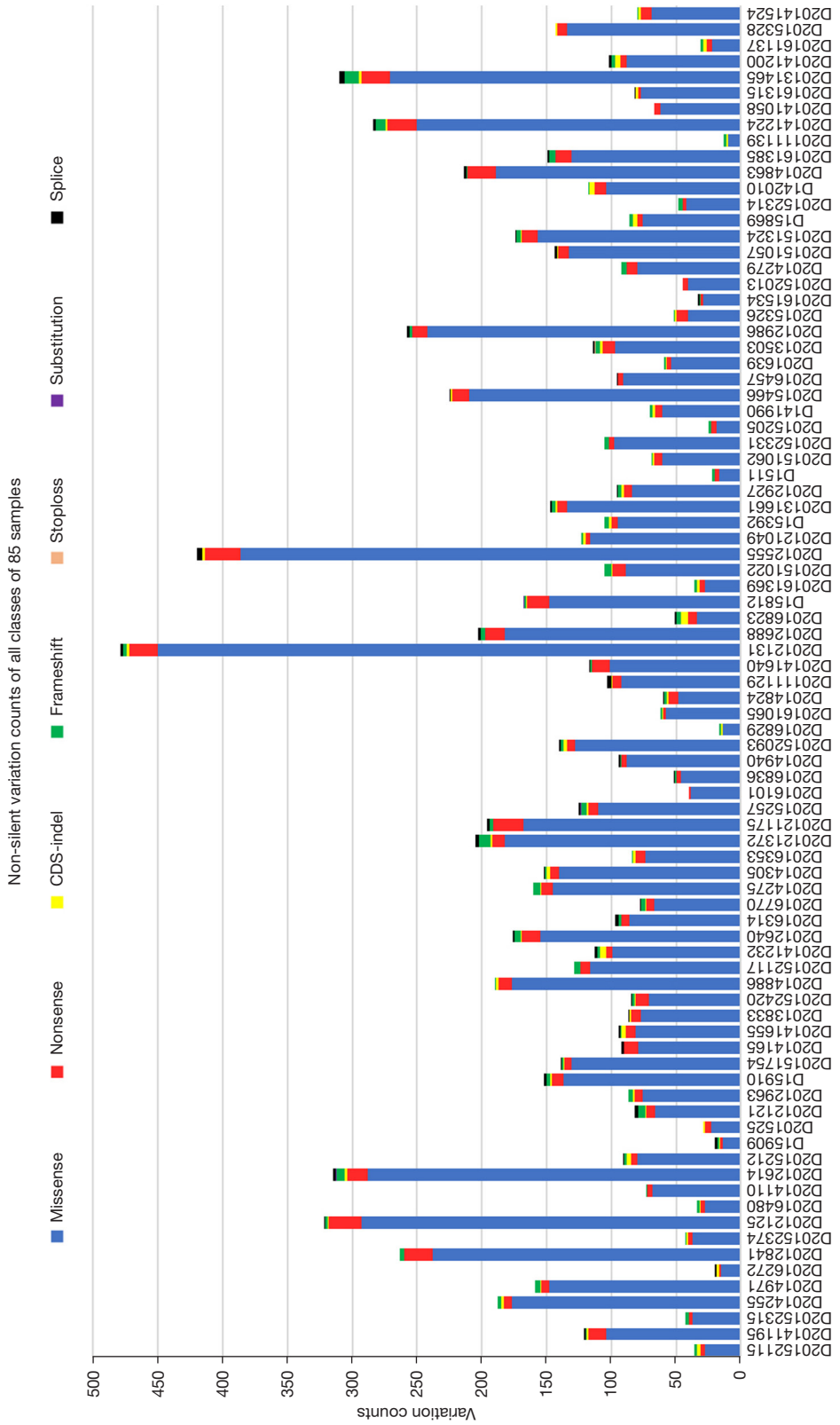

Figure 3 Summary of gene variation types in 85 cases of stage IIIA lung adenocarcinoma.

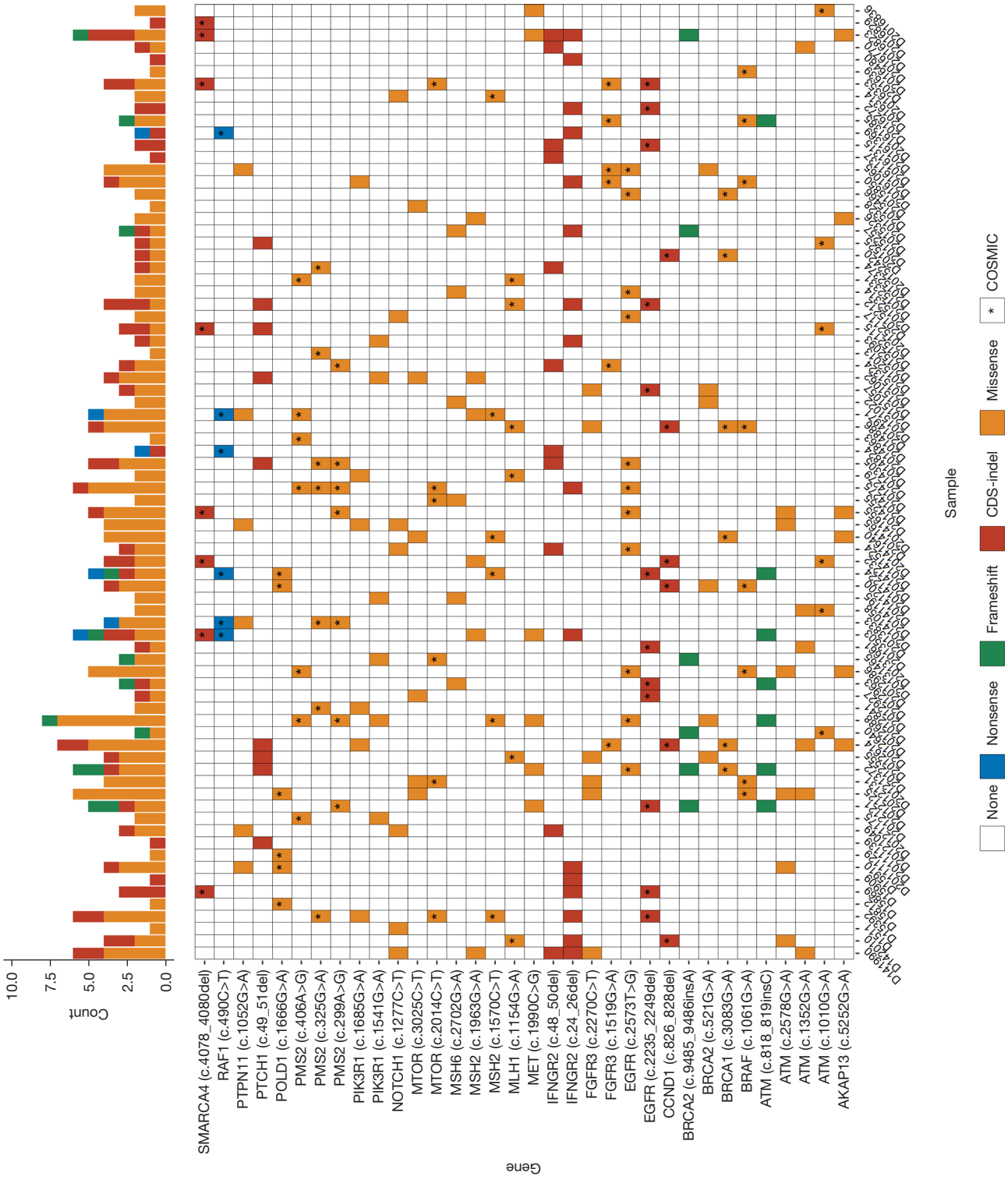

Figure 4 High frequency variations in 85 cases of stage IIIA lung adenocarcinoma.

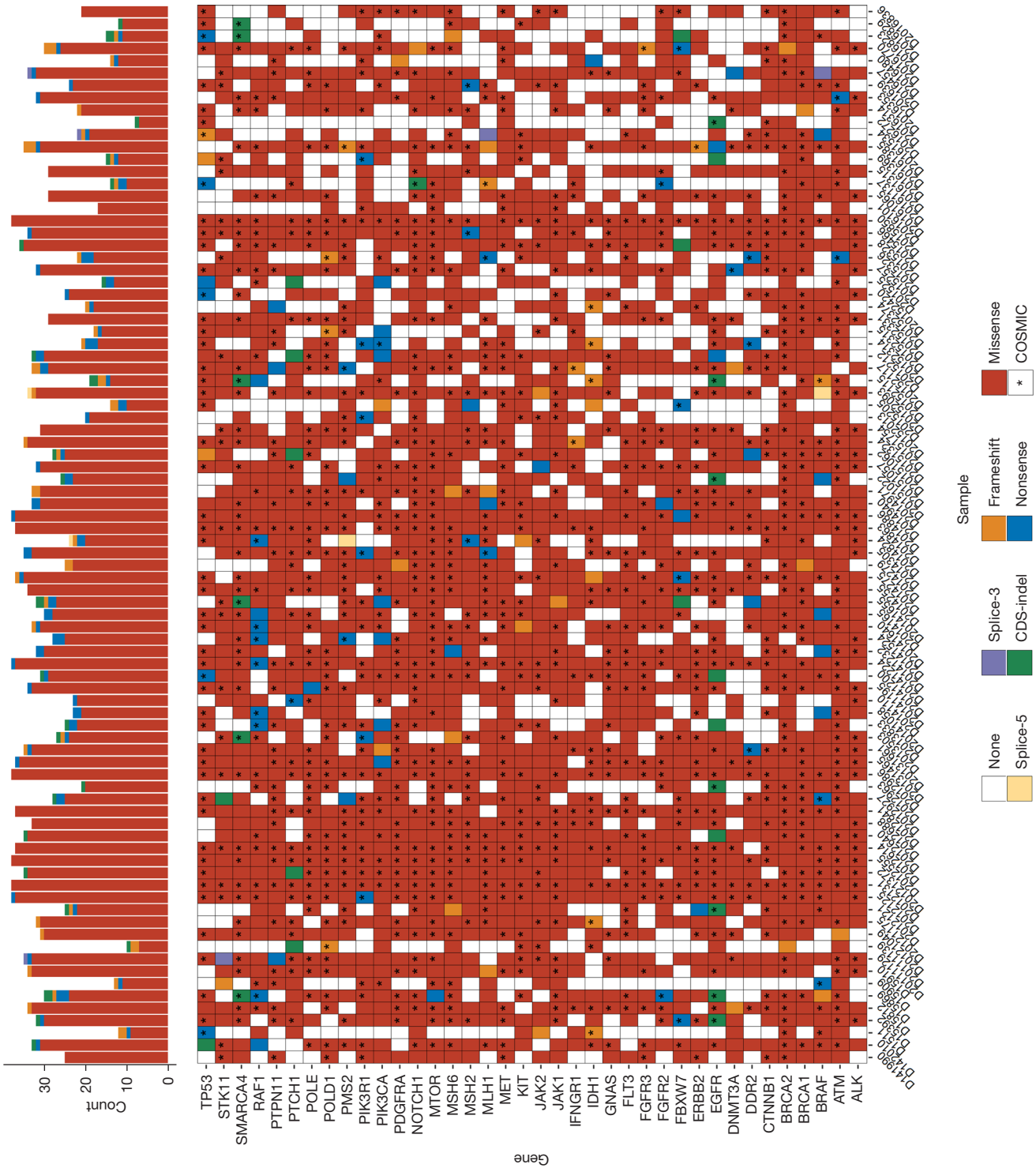

Figure 5 High-frequency mutation genes in 85 cases of stage IIIA lung adenocarcinoma.

Table 1 Univariate analysis of prognostic factors for stage IIIA lung adenocarcinoma (OS)

Characteristics	N (%)	P value
Gender		0.872
Male	43 (50.6)	
Female	42 (49.4)	
Age (y)		0.436
≤61	48 (56.5)	
>61	37 (43.5)	
BMI (kg/m²)		0.168
<24.95	46 (54.1)	
≥24.95	39 (45.9)	
Preoperative hemoglobin		0.673
<149.5	69 (81.2)	
≥149.5	16 (18.8)	
Preoperative total protein		0.06
<64.35	21 (24.7)	
≥64.35	64 (75.3)	
Smoking history		0.672
No	40 (47.1)	
Yes	45 (52.9)	
Smoking index		0.212
<775	63 (74.1)	
≥775	22 (25.9)	
NSE		0.105
<16.37	71 (83.5)	
≥16.37	14 (16.5)	
CEA		0.63
<6.66	51 (60.0)	
≥6.66	34 (40.0)	
CYFRA21-1		<0.001
<3.81	67 (78.8)	
≥3.81	18 (21.2)	
NMLN[a]		0.306
≤1	29 (34.1)	
>1	56 (65.9)	
LNTP[b]		0.241
No	54 (63.5)	
Yes	31 (36.5)	
NMLS[c]		0.045
<2	35 (41.2)	
≥2	50 (58.8)	
Tumor position		0.756
Left	31 (36.5)	
Right	54 (63.5)	
N2 metastasis		0.118
Yes	69 (81.2)	
No	16 (18.8)	
N stage		0.192
N0	10 (11.8)	
N1	6 (7.0)	
N2	69 (81.2)	
Tumor diameter (cm)		0.015
<3.25	45 (52.9)	
≥3.25	40 (47.1)	
IFNGR2 c.24_26del		0.876
No	70 (82.4)	
Yes	15 (17.6)	
EGFR classical base mutation[d]		0.045
No	62 (72.9)	
Yes	23 (27.1)	
ALK mutation		0.364
No	29 (34.1)	
Yes	56 (65.9)	
TP53 mutation		0.186
No	28 (32.9)	
Yes	57 (67.1)	
KRAS mutation		0.252
No	50 (58.8)	
Yes	35 (41.2)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	N (%)	P value
PIK3CA mutation		0.69
No	14 (16.5)	
Yes	71 (83.5)	
POLE mutation		0.185
No	29 (34.1)	
Yes	56 (65.9)	
NCPM[e]		0.038
≤6	64 (75.3)	
>6	21 (24.7)	
IFNGR2 mutation		0.821
No	38 (44.7)	
Yes	47 (55.3)	
Number of somatic variations		0.073
<95	41 (48.2)	
≥95	44 (51.8)	
Number of gene mutations		0.093
≤37	27 (31.8)	
>37	58 (68.2)	
Missense mutation		0.108
<82.5	40 (47.1)	
>82.5	45 (52.9)	
Nonsense mutation		0.162
<8.5	57 (67.1)	
>8.5	28 (32.9)	

[a], the number of metastatic lymph node (NMLN); [b], lymph nodes of the inferior tracheal protuberance (LNTP); [c], the number of metastatic lymph node stations (NMLS); [d], EGFR classical mutation (c.2235_2249del and c.2573t > G); [e], the number of copies of POLE mutation (NCPM). BMI, body mass index; NSE, neuron specific enolase; CEA, carcinoembryonic antigen; EGFR, epidermal growth factor receptor; POLE, polymerase epsilon.

missense mutations, and nonsense mutations.

The results showed that the preoperative CYFRA21-1 level (P<0.001), the number of metastatic lymph node stations (P=0.045), the maximum tumor diameter (P=0.015), EGFR classical base mutation (P=0.045), and the number of POLE mutation copies (P=0.038) were associated with

Table 2 Univariate analysis of prognostic factors for stage IIIA lung adenocarcinoma (DFS)

Characteristics	N (%)	P value
Gender		0.883
Male	43 (50.6)	
Female	42 (49.4)	
Age (y)		0.497
≤52	14 (16.5)	
>52	71 (83.5)	
BMI (kg/m^2)		0.132
<22.75	19 (22.4)	
≥22.75	66 (77.6)	
Preoperative hemoglobin		0.938
<149.5	69 (81.2)	
≥149.5	16 (18.8)	
Preoperative total protein		0.028
<64.35	21 (24.7)	
≥64.35	64 (75.3)	
Smoking history		0.796
No	40 (47.1)	
Yes	45 (52.9)	
Smoking index		0.319
<610	61 (71.8)	
≥610	24 (28.2)	
NSE		0.068
<15.325	63 (74.1)	
≥15.325	22 (25.9)	
CEA		0.062
<7.44	55 (64.7)	
≥7.44	30 (35.3)	
CYFRA21-1		0.012
<2.05	26 (30.6)	
≥2.05	59 (69.4)	
NMLN[a]		0.085
<2.5	42 (49.4)	
>2.5	43 (50.6)	

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	N (%)	P value
LNTP[b]		0.067
No	54 (63.5)	
Yes	31 (36.5)	
NMLS[c]		0.003
<2	35 (41.2)	
≥2	50 (58.8)	
Tumor position		0.594
Left	31 (36.5)	
Right	54 (63.5)	
N2 metastasis		0.158
Yes	69 (81.2)	
No	16 (18.8)	
N stage		0.296
N0	10 (11.8)	
N1	6 (7.0)	
N2	69 (81.2)	
Tumor diameter (cm)		0.002
<3.25	45 (52.9)	
≥3.25	40 (47.1)	
IFNGR2 c.24_26del mutation		0.79
No	70 (82.4)	
Yes	15 (17.6)	
EGFR classical base mutation[d]		0.08
No	62 (72.9)	
Yes	23 (27.1)	
ALK mutation		0.167
No	29 (34.1)	
Yes	56 (65.9)	
TP53 mutation		0.016
No	28 (32.9)	
Yes	57 (67.1)	
KRAS mutation		0.091
No	50 (58.8)	
Yes	35 (41.2)	
PIK3CA mutation		0.718
No	14 (16.5)	
Yes	71 (83.5)	
POLE mutation		0.096
No	29 (34.1)	
Yes	56 (65.9)	
NCPM[e]		0.018
<3.5	48 (56.5)	
>3.5	37 (43.5)	
IFNGR2 mutation		0.393
No	38 (44.7)	
Yes	47 (55.3)	
Number of somatic variations		0.102
<84.5	32 (37.6)	
≥84.5	53 (62.4)	
Number of gene mutations		0.048
<30.5	19 (22.4)	
≥30.5	66 (77.6)	
Missense mutation		0.072
<82.5	40 (47.1)	
≥82.5	45 (52.9)	
Nonsense mutation		0.105
<7.5	47 (55.3)	
≥7.5	38 (44.7)	

[a], the number of metastatic lymph nodes (NMLN); [b], lymph nodes of the inferior tracheal protuberance (LNTP); [c], the number of metastatic lymph node stations (NMLS); [d], EGFR classical mutation (c.2235_2249del and c.2573t > G); [e], the number of copies of POLE mutation (NCPM). BMI, body mass index; NSE, neuron specific enolase; CEA, carcinoembryonic antigen; EGFR, epidermal growth factor receptor; POLE, polymerase epsilon.

OS. The 3-year cumulative survival rates of patients with preoperative CEA level <6.66 and ≥6.66 were 70% and 57%, respectively. There was a difference between the two groups, but the difference did not reach significance (P=0.063). Preoperative total protein level (P=0.028), preoperative CYFRA21-1 level (P=0.012), number of

metastatic lymph node stations (P=0.003), maximum tumor diameter (P=0.002), number of mutated genes in tumor samples (P=0.048), TP53 mutations (P=0.016), and number of mutated copies of POLE (P=0.018) were associated with DFS. It should be noted that the median DFS was 45.9 and 21.7 months in the negative group and positive group for inferior tracheal protuberance lymph nodes, respectively. Although the difference was large, there was no significant difference between the two groups (P=0.067). The median DFS was 40.8 months and 21.6 months in groups with preoperative NSE level <15.325 and ≥15.325, respectively, and there was no significant difference between the two groups (P<0.05). The median DFS of patients with preoperative CEA level <7.44 and ≥7.44 were 44.8 and 22.8 months, respectively. The ratio was close to 2:1, but there was no significant difference between the two groups. The specific results are shown in *Tables 1*,*2* and *Figures 6*,7.

Multivariate analysis

A Cox regression model was used to analyze the related factors. The results showed that preoperative CYFRA21-1 level (P<0.001), number of lymph node metastasis (P=0.006), and EGFR classical base mutation (P=0.009) were independent prognostic factors of OS. The number of mutated genes in tumor samples (P=0.011), EGFR classical base mutation (P=0.002), preoperative NSE level (P<0.001), maximum tumor diameter (P<0.001), and the number of lymph node metastasis (P=0.001) were independent prognostic factors for DFS. The specific results are shown in *Tables 3*,*4*.

Discussion

Lung cancer is the most common and the most deadly tumor in China. The incidence rate and mortality rate of lung cancer are still the highest according to data from China National Cancer Center in 2015 (1). NSCLC accounts for about 85% of total lung cancer cases (2), and lung adenocarcinoma has the highest incidence rate. In recent years, there have been more and more studies on the prognostic factors of resectable stage IIIA lung adenocarcinoma. However, the conclusions lack consistency, and so far there is no systematic evaluation standard.

Some studies have pointed out that age is not a prognostic factor for locally advanced lung adenocarcinoma (12). In our study, 85 patients with stage IIIA lung adenocarcinoma were divided into two groups according to their age. Univariate analysis showed that the OS and DFS were both P>0.05, with no statistical significance. Similarly, age was not an independent prognostic factor. We speculated that this may be related to the low operation rate and small sample size of elderly patients.

It is still controversial whether gender can be used as a prognostic factor for lung adenocarcinoma. It has been reported that male is a negative correlation factor for the prognosis of patients with lung adenocarcinoma at home and abroad (13,14). However, a large sample study conducted by Jubelirer *et al.* (15) showed that there was no significant difference in prognosis between male and female patients. In this study, univariate analysis showed that gender was not a prognostic factor for OS and DFS (P=0.872 for OS, P=0.883 for DFS). Multivariate analysis also showed that gender was not an independent prognostic factor. Much larger samples with more detailed stratification would be needed to determine whether sex has a prognostic role.

Recently, more and more attention has been paid to the relationship between preoperative nutritional status and tumor prognosis in the medical field. An Asian study suggested that preoperative BMI is an independent prognostic factor for resectable NSCLC, and patients with low BMI have a poor prognosis (16). In this study, a total of 85 patients were divided into two groups according to preoperative BMI, and the median survival times of the <24.95 and >24.95 groups were 84 and 58.6 months, respectively. There was no significant difference between the two groups (P=0.168). Multivariate analysis showed that preoperative BMI could not be used as an independent prognostic factor. Although there was no statistical significance, the prognosis of patients with high BMI in this study was poor, contrary to the results of the literature, which was related to the small sample size. This still needs to be verified using a retrospective analysis with a larger sample size. It has been pointed out that hemoglobin level is an independent prognostic factor for locally advanced NSCLC (17,18). We collected the preoperative serum hemoglobin levels of 85 patients and divided them into two groups: <149.5 and ≥149.5 g. The results showed that there was no significant difference in OS or DFS between the two groups (P=0.673, P=0.938). Multivariate analysis also showed that there was no significant difference in OS and DFS between the two groups (P>0.05). In addition, we collected the preoperative serum total protein levels of patients and divided them into two groups: <64.35 and ≥64.35 g. Univariate analysis showed that there was no significant difference in OS between the two groups

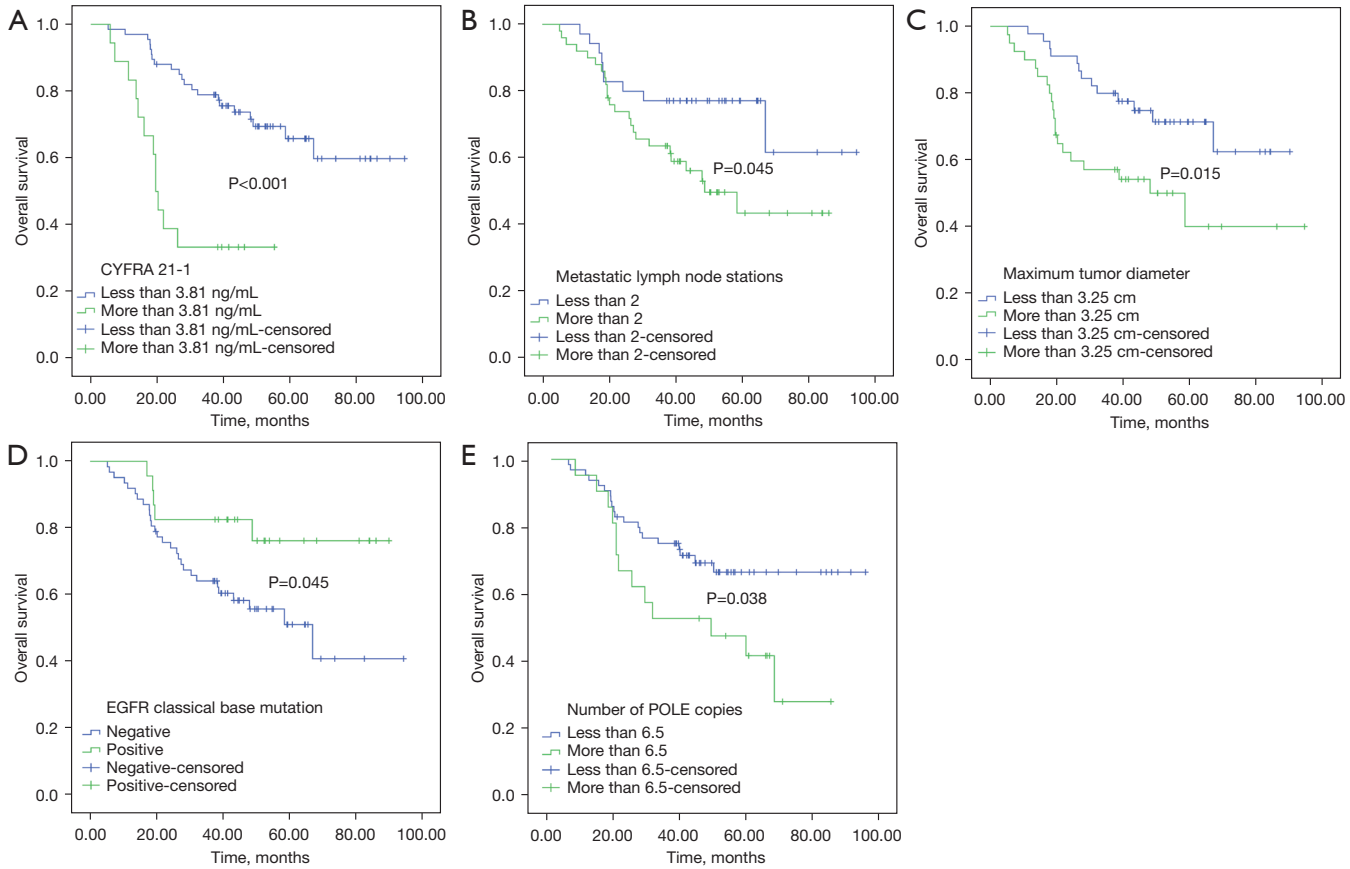

Figure 6 Survival curves for overall survival (OS). (A) Kaplan-Meier estimates of preoperative CYFRA21-1 level; (B) Kaplan-Meier estimates of the number of metastatic lymph node stations; (C) Kaplan-Meier estimates of the maximum tumor diameter; (D) Kaplan-Meier estimates of epidermal growth factor receptor (EGFR) classical base mutation; (E) Kaplan-Meier estimates of the number of polymerase epsilon (POLE) mutation copies.

(P=0.060), but there was a significant difference in DFS between the two groups (P=0.028). Multivariate analysis showed that there was no significant difference in survival time between the two groups, and it was not an independent prognostic factor (P>0.05). We have noticed that in clinical practice, patients with good preoperative or postoperative nutritional status are better than those with poor nutritional status in terms of postoperative recovery, postoperative complications, chemoradiotherapy tolerance, and long-term prognosis. However, there is still a lack of in-depth research using large sample sizes in the real world. We believe that preoperative nutritional status can be systematically included in the prognostic evaluation of patients with resectable stage IIIA lung adenocarcinoma in the future.

As for whether preoperative tumor markers can be used as prognostic factors for stage IIIA lung adenocarcinoma, there are a large number of studies at home and abroad which show that serum CEA and CYFRA21-1 levels are related to the prognosis of lung adenocarcinoma. There is also data showing that serum CEA and CYFRA21-1 levels are negatively correlated with the prognosis of lung adenocarcinoma (19-22). Preoperative levels of CEA, NSE, and CYFRA21-1 were included in our study, and survival analysis was performed. For the OS group: CEA was divided into <6.66 and ≥6.66 groups, NSE was divided into <16.37 and ≥16.37 groups, and CYFRA21-1 was divided into <3.81 and ≥3.81 groups. Univariate analysis showed that there was no significant difference in survival between the former two groups (P=0.630, P=0.105), and there was a significant difference in survival between the two groups in terms of preoperative CYFRA21-1 level (P<0.001). Multivariate analysis showed that preoperative CYFRA21-1 level was an independent prognostic factor for patients with stage IIIA lung adenocarcinoma (P<0.001).

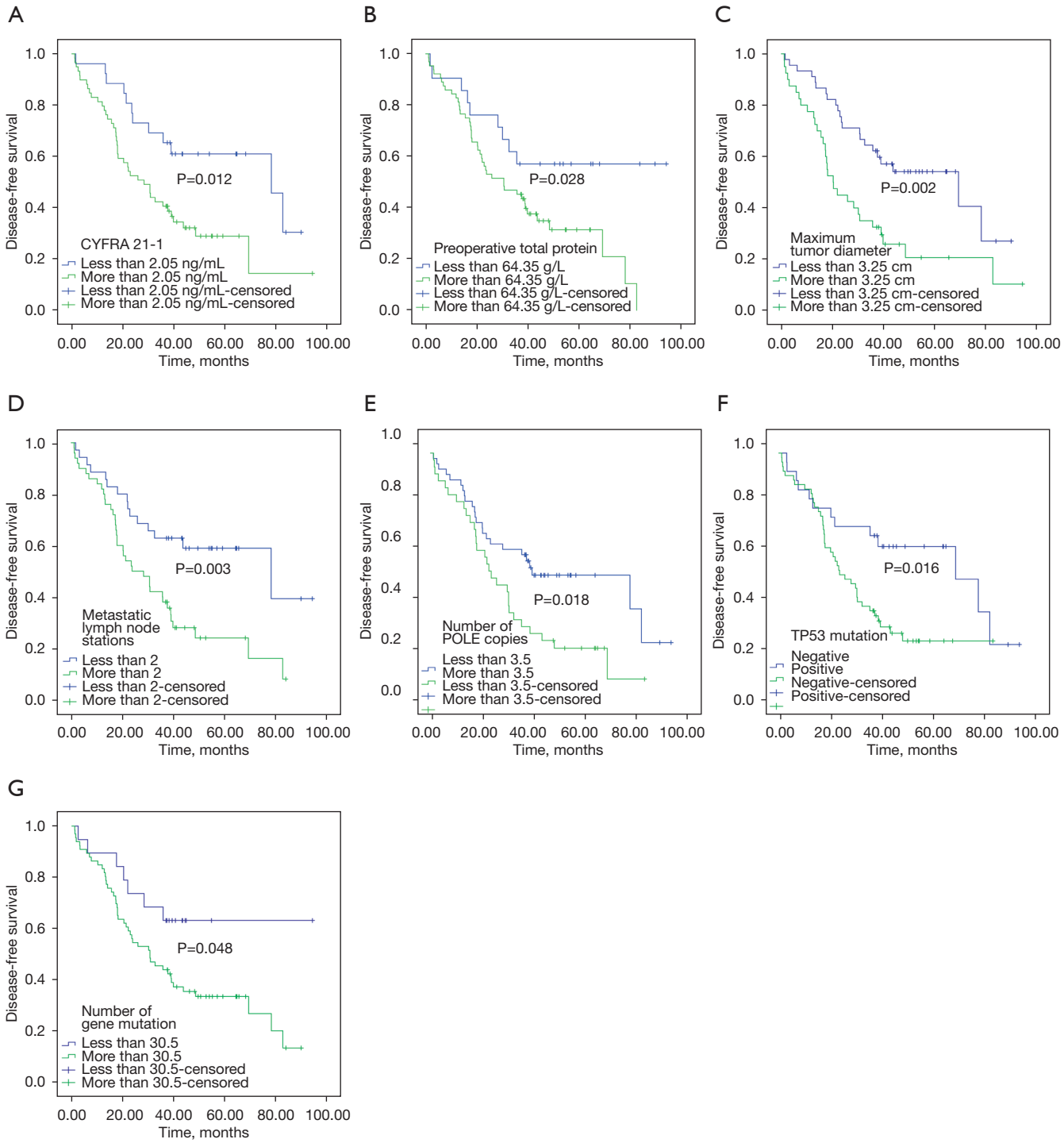

Figure 7 Survival curves for disease-free survival (DFS). (A) Kaplan-Meier estimates of preoperative CYFRA21-1 level; (B) Kaplan-Meier estimates of preoperative total protein level; (C) Kaplan-Meier estimates of maximum tumor diameter; (D) Kaplan-Meier estimates of metastatic lymph node stations; (E) Kaplan-Meier estimates of the number of polymerase epsilon (POLE) mutation copies; (F) Kaplan-Meier estimates of TP53 mutation; (G) Kaplan-Meier estimates of the number of gene mutations.

Table 3 OS: multivariate analysis of the prognosis of 85 patients with stage IIIA lung adenocarcinoma

Variable	P value	HR	95% CI
EGFR classical base mutation	0.009	0.271	0.101–0.726
CYFRA21-1	<0.001	4.673	2.169–10.067
NLSM[c]	0.006	3.059	1.374–6.811

[c], the number of metastatic lymph node stations (NLSM). OS, overall survival; HR, hazard ratio; CI, confidence interval; EGFR, epidermal growth factor receptor.

Table 4 DFS: multivariate analysis of the prognosis of 85 patients with stage IIIA lung adenocarcinoma

Variable	P value	HR	95% CI
EGFR classical base mutation	0.002	0.316	0.155–0.644
NSE	<0.001	3.200	1.683–6.082
NLSM[c]	0.001	3.140	1.648–5.982
Number of gene mutations	0.011	2.918	1.282–6.642
Tumor diameter	<0.001	2.792	1.569–4.969

[c], the number of metastatic lymph node stations (NLSM). DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; NS, neuron specific enolase; EGFR, epidermal growth factor receptor.

For the DFS group: CEA was divided into <7.44 and ≥7.44 groups, NSE was divided into <15.325 and ≥15.325 groups, and CYFRA21-1 was divided into <2.05 and ≥2.05 groups. Univariate analysis showed that only preoperative CYFRA21-1 level had a significant difference in survival (P=0.012). Multivariate analysis showed that preoperative NSE level was an independent prognostic factor for patients with stage IIIA lung adenocarcinoma (P<0.001). Overall, we boldly speculate that preoperative serum tumor markers have great potential for the prognosis of resectable stage IIIA lung adenocarcinoma, but whether they can be used as part of the criteria for screening patients with resectable stage IIIA or locally advanced lung adenocarcinoma still needs to be supported by large sample data.

Smoking is a recognized lung cancer risk factor, but not all patients have a smoking history. In recent years, study has shown that the incidence rate of lung adenocarcinoma is higher in patients without a smoking history (23). Current smoking status is still controversial as a prognostic factor for stage IIIA lung adenocarcinoma. It has been reported that the larger the amount and the longer the time of smoking, the worse the prognosis of patients (24,25). In contrast, it has been demonstrated that smoking has no statistical significance for the postoperative prognosis of stage IIIA NSCLC (26,27). In this study, patients were divided into two groups according to smoking history. Univariate and multivariate analysis showed that there was no significant difference in survival time between the two groups (P>0.05). At the same time, we calculated the smoking index of the patients, calculated the critical value by an ROC curve, and converted the variables. The OS group was divided into the <775 and ≥775 group. Univariate analysis showed that there was no significant difference in the survival time between the two groups (P=0.212), which was also confirmed by multivariate analysis (P>0.05). The DFS group was divided into the <610 and >610 group. Univariate and multivariate analysis showed that there was no significant difference in survival time between the two groups (P>0.05). The results of this study may be related to the small sample size. There might be differences between patients with long-term and heavy smoking history and patients without a smoking history. Prognostic differences between the 2 need to be measured in a more comprehensive manner, including the differences in lung function caused by smoking, the changes in lung tissue cells at the molecular level, and intracellular specific protein variations and epigenetic changes.

At present, research on the correlation between lymph node metastasis and the prognosis of stage IIIA lung adenocarcinoma focuses on N2 patients. Some studies suggest that patients with skip N2 metastasis have a better prognosis than patients with non-skip metastasis (28-30). According to lymph node metastasis, N2 metastasis can be divided into single station N2 metastasis and multi-station N2 metastasis. At present, the prognosis of patients with single station N2 lymph node metastasis is better than that of patients with multi-station N2 metastasis. In addition, the number of lymph node metastasis is negatively correlated with prognosis (31). This study aimed to investigate the prognostic impact of the number of metastatic lymph node stations. The number of lymph node stations: less than 2 stations and more than 2 stations. Univariate analysis showed that the median OS of the two groups were 84.0 and 54.2 months, and the difference was statistically significant (P=0.045). The median DFS of the two groups were 77.7 and 24.0 months, respectively, and the difference was statistically significant (P=0.003). Multivariate analysis showed that the number of lymph node metastasis stations

was an independent prognostic factor for OS and DFS (P<0.05). The relative risk of death in patients with lymph node metastasis ≥2 stations was 3.059 times higher than that in patients with lymph node metastasis <2 stations, and the relative risk of recurrence in patients with lymph node metastasis ≥2 stations was 3.140 times higher than that in patients with lymph node metastasis <2 stations.

By searching the literature, we found that some studies demonstrated that the larger the tumor diameter, the worse the prognosis of stage IIIA lung adenocarcinoma (27,32,33). We recorded the postoperative tumor diameter of 85 patients with stage IIIA lung adenocarcinoma and divided them into two groups: <3.25 and ≥3.25 cm. Univariate analysis showed that the cumulative 3-year survival rates of the two groups were 75% and 54%, respectively, and the difference was statistically significant (P=0.015). The median DFS of the two groups was 65.7 and 22.2 months, respectively, and the difference was statistically significant (P=0.002). Multivariate analysis showed that the maximum diameter of the tumor was only an independent prognostic factor for DFS (P<0.001). The relative recurrence risk ratio of patients with size ≥3.25 cm was 2.792 times that of patients with size <3.25 cm.

With the further development of the field of genetics, gene mutations have been recognized as prognostic factors of lung cancer, and there is a significant correlation between driver gene mutations and the clinical treatment outcomes of NSCLC patients (34). Some retrospective studies have reported that gene mutations are independent prognostic factors for NSCLC (35-38). The trial conducted by Zhang *et al.* in China showed that the common gene mutation targets in lung adenocarcinoma were EGFR, KRAS, and TP53, compared to TCGA, EGFR was found to have higher frequency of somatic mutations in LUAD patients (38.3% *vs.* 14.0%) (39). Our research also confirmed this phenomenon, and we found that the positive rate of EGFR mutation was 27.1%. Extensive studies have shown that EGFR, KRAS, ALK, and TP53 mutation-positive stage IIIA lung adenocarcinoma patients have a poor prognosis (40-47). In this study, tumor samples from 85 patients with stage IIIA lung adenocarcinoma were sectioned, genetic testing was performed, and the mutated genes were analyzed for their associations with survival. The results of univariate analysis showed that the OS of those who were positive for the classical base mutations in EGFR (c.2235_2249del and c.2573t > G) was significantly longer than those who were negative, and the difference in survival between the two groups was statistically significant (P=0.045). Multivariate analysis showed that there were significant differences in OS and DFS between patients positive and negative for EGFR canonical base mutations (P=0.009, P=0.002). The relative risk of death in positive patients was only 0.271 times that in negative patients, and the relative risk of recurrence was only 0.316 times that in negative patients. This is in contrast to the above literature results, possibly due to the fact that other studies included all EGFR mutation types, and there may be some mutation types that are not meaningful to the prognosis or treatment of patients with lung adenocarcinoma. There was only a significant difference in the DFS between the two groups of patients with positive and negative TP53 mutation (P=0.016).

In addition, we collated the number of high-frequency mutated gene copies within the test results to perform survival analysis, and the results of univariate analysis suggested a statistically significant difference in OS between patients with POLE mutated gene copy numbers <6.5 and >6.5 (P=0.038). The number of copies of POLE mutations were divided into <3.5 and >3.5 groups, and the results showed that there was a significant difference in progression-free survival (PFS) time between the two groups (P=0.018). Multivariate analysis showed that it was not an independent prognostic factor for stage IIIA lung adenocarcinoma (P>0.05). We included the entire number of mutated gene copies within the tumor sample and showed statistically significant differences in PFS only by the number of mutated gene copies in the univariate analysis (P=0.048). Lung cancer is an abnormal proliferative disease of cells caused by somatic gene mutations. The whole disease course involves multiple genes, and there is variability among individuals, making the mutation landscape different for each patient. The application of a single gene mutation to predict patient prognosis is not rigorous (48). Therefore, more in-depth study is needed to reveal the available information in lung adenocarcinoma gene mutations so as to predict patient prognosis or to be included in the screening criteria of resectable patients with stage IIIA lung adenocarcinoma.

Postoperative adjuvant therapy is recognized as an independent prognostic factor for stage IIIA NSCLC. The results of 2 foreign phase III trials both showed that the 5-year survival rate and DFS rate of the postoperative chemotherapy group for stage IIIA NSCLC were better than those of the surgery alone group (49,50). In addition, the results of the LUX-lung 3, LUX-lung 6, and LUX-lung 7 trials showed that the prognosis of patients with lung adenocarcinoma who received targeted therapy was

better (51,52). The domestic research data of Yue *et al.* and Zhong *et al.* showed that patients with EGFR mutation positive stage IIIA NSCLC who received erlotinib had significantly prolonged DFS or PFS compared with those who received traditional chemotherapy (53,54). In this study, a detailed review of the inpatient medical records and telephone follow-up of 85 patients with stage IIIA lung adenocarcinoma revealed that all patients received regular chemotherapy postoperatively. Since the article was a retrospective study, when targeted agents became less popular or short-term deterioration after operation, only 1 patient received EGFR-TKI treatment after disease progression. There was no control group for postoperative adjuvant therapy, and the prognostic impact of postoperative adjuvant therapy was not observed. Three large trials, Lux-lung3, Lux-lung6 and Lux-lung7, showed that EGFR-TKI played a significant role in the prognosis of lung adenocarcinoma and significantly improved the prognosis (51,52). Although most of the 85 patients with lung adenocarcinoma did not undergo EGFR-TKI therapy, our findings suggest that EGFR positive patients have a better prognosis. It is not clear whether our conclusions can be applied to patients receiving EGFR-TKI therapy.

Conclusions

Fewer than 2 metastatic lymph node stations, positivity for EGFR classical base mutations (c.2235_2249del and c.2573t > G), lower blood tumor marker levels, lower number of mutated genes, and smaller tumor diameter were associated with better postoperative outcomes. Preoperative blood levels of tumor markers, the number of metastatic lymph node stations, and EGFR classical base mutations were significant prognostic factors in patients with resectable stage IIIA lung adenocarcinoma.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of Tianjin Chest Hospital and informed consent was taken from all the patients.

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