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Correlation analysis on epidermal growth factor receptor (EGFR) mutations and clinicopathological characteristics in lung adenocarcinomas

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Purpose: To analysis the correlation between EGFR mutations and clinicopathological features in lung adenocarcinomas.

Methods: 139 lung adenocarcinoma cases from the Second Hospital of Shandong University were conducted molecular detection of EGFR mutations. Multiple clinicopathological characteristics were collected and analyzed to identify the relationship with EGFR mutations. The amplification refractory mutation system (ARMS) was performed to detect the EGFR mutations.

Results: During the 139 cases, 96 lung adenocarcinoma cases had EGFR mutations. EGFR mutations were associated with smoking history ($P=0.0311$), tumor size ($P=0.0247$), tumor subtype ($P=0.0003$), rhabdomyoid differentiation ($P=0.0237$) and extracellular mucus ($P=0.0013$).

Conclusions: Smoking history, tumor size, tumor subtype, rhabdomyoid differentiation and extracellular mucus were related to EGFR mutations in lung adenocarcinoma. These histological characteristics might be meaningful to predict EGFR mutations.

KEYWORDS

EGFR mutation, lung adenocarcinoma, histology, pathology, molecular pathology

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide (1). Adenocarcinoma is the most common histological subtype of lung cancer, accounting for approximately 40% (2). Lung adenocarcinoma is a type of non-small cell lung cancer (NSCLC) that arises from glandular cells in the lung, typically in the outer or peripheral regions of the lung (3). The histological features of lung adenocarcinoma are diverse,

including glandular or acinar structures, papillary structures, solid or micropapillary growth pattern and so on. In 2011, the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) proposed the standardized classification system of lung adenocarcinoma and other lung cancer subtypes based on the histological features (4). According to the IASLC/ATS/ERS classification, the invasive non-mucinous lung adenocarcinoma can be divided into five subtypes based on the predominant architectural pattern: lepidic adenocarcinoma (LA), acinar adenocarcinoma (AA), papillary adenocarcinoma (PA), solid adenocarcinoma (SA) and micropapillary adenocarcinoma (MA). In addition, based on a study undertaken by the International Association for the Study of Lung Cancer (IASLC) Pathology Committee, a new grading system of invasive non-mucinous lung adenocarcinoma has been recommended as below: grade 1, lepidic-predominant with no or < 20% high-grade pattern (solid, micropapillary, cribriform, or complex glandular pattern); grade 2, acinar or papillary-predominant with no or < 20% high-grade pattern; grade 3: any tumor with \geq 20% high-grade pattern. These three grades respectively correspond to well-differentiation, moderately differentiation, and poorly differentiation (5).

Lung adenocarcinoma is a highly heterogeneous disease with various genetic and molecular alterations. These genetic alterations play vital roles in the occurrence and development of lung adenocarcinoma. One of the most frequently observed genetic mutations in lung adenocarcinoma is in the EGFR gene, which codes for a transmembrane receptor tyrosine kinase (6). EGFR mutations at the tyrosine kinase domain keep EGFR in an activation state, leading to cell proliferation and growth. EGFR is overexpressed and/or mutated in a variety of human cancers, including NSCLC (7). EGFR mutations occur in approximately 15-70% of all lung adenocarcinoma cases, with a higher prevalence in non-smokers, females and individuals of Asian origin (8–15). These mutations are mostly found in exons 18-21 of the EGFR gene and result in EGFR constitutive activation, promoting the downstream signaling pathways, such as the PI3K-AKT and MAPK pathways. During these mutations, the most common mutations are exon 19 deletions and exon 21 L858R point mutation, which account for approximately 85% of all EGFR mutations in NSCLC (16, 17). Exon 19 deletions result in the loss of amino acids 747-750, while the L858R mutation leads to a substitution of arginine for leucine at the position 858 (18). These

mutations occur in the tyrosine kinase domain of EGFR, which is responsible for the activation of downstream signaling pathways (19). This activation promotes tumor cell growth, survival, and metastasis, and confers resistance to chemotherapy and radiotherapy (19).

EGFR-mutated NSCLC is typically sensitive to EGFR tyrosine kinase inhibitors (TKIs), such as gefitinib, erlotinib, osimertinib, Lazertinib and almonertinib, which are small-molecule inhibitors that target the ATP-binding site of the EGFR tyrosine kinase domain (20–23). Treatment with EGFR TKIs has been shown to improve the progression-free survival (PFS) and overall response rates (ORR) compared to standard chemotherapy in patients with advanced EGFR-mutated NSCLC (24, 25).

In this research, we analyzed the relationship between EGFR mutations and the clinicopathological features of lung adenocarcinoma to better understand the function of EGFR mutations in lung adenocarcinoma. Besides the histological subtypes of lung adenocarcinoma, we also included a variety of morphological features, such as lymphocytic infiltration, extracellular mucin, fibrosis, mucinous tumor cells, tumor necrosis, abscess, hobnail cells, rhabdoid cells, spread through air spaces (STAS), abundant mitosis, prominent nucleoli, high-grade nuclei and nuclear inclusion bodies.

In addition, we also collected and analyzed the data of lymph node metastasis, pleural invasion, vascular invasion and Ki67 proliferation index.

Materials and methods

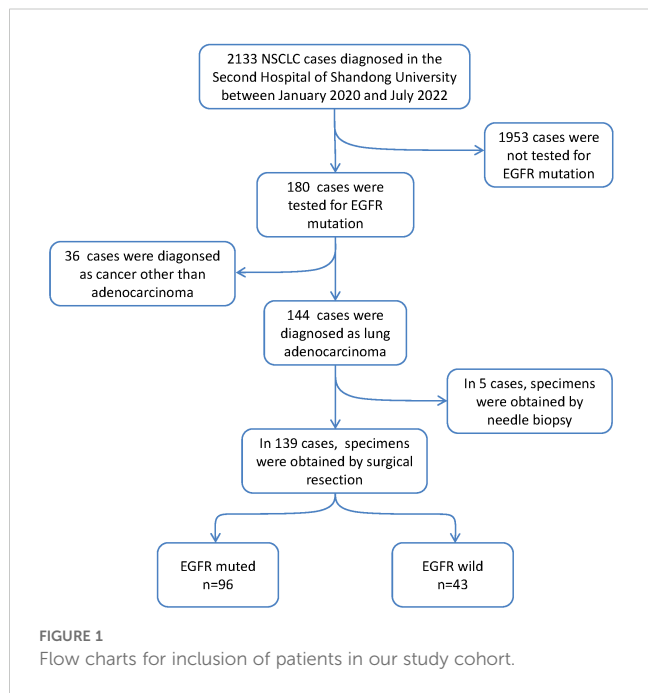
Patients

The prospective study was performed among 139 formalin-fixed paraffin-embedded (FFPE) tumors, which were diagnosed as non-mucinous lung adenocarcinoma and tested for EGFR mutation (Figure 1). All specimens were obtained from resected surgery. All patients were diagnosed and treated in the Second Hospital of Shandong University between January 2020 and July 2022. None of the patients received preoperative chemoradiotherapy. The clinical information of the 139 patients is shown in Table 1.

Histological analysis

All the pathological slides were examined and diagnosed according to the World Health Organization (WHO) classification system. The World Health Organization (WHO) classification system recognizes five subtypes of lung adenocarcinoma (Figure 2), which are characterized by distinct morphological features and genetic alterations (5). The most common subtype of lung adenocarcinoma is the acinar subtype, which is characterized by the presence of glandular structures that resemble acini, or grape-like clusters of cells. Other subtypes include the papillary subtype (which has finger-like projections of cells), the

Abbreviations: EGFR, epidermal growth factor receptor; ARMS, the amplification refractory mutation system; NSCLC, non-small cell lung cancer; IASLC, the International Association for the Study of Lung Cancer; ATS, American Thoracic Society; ERS, European Respiratory Society; LA, lepidic adenocarcinoma; AA, acinar adenocarcinoma; PA, papillary adenocarcinoma; SA, solid adenocarcinoma; MA, micropapillary adenocarcinoma; TKIs, tyrosine kinase inhibitors; PFS, progression-free survival; ORR, overall response rates; STAS, spread through air spaces; FFPE, formalin-fixed paraffin-embedded; IHC, immunohistochemistry; IMA, invasive mucinous adenocarcinoma.



solid subtype (which lacks glandular structures and is composed of sheets of cells), and the lepidic subtype (which consists of predominantly bland pneumocytic cells growing along the surface of alveolar walls and subordinately an invasive component measuring > 5 mm in greatest dimension), and the micropapillary subtype (which is composed of tumor cells growing in papillary tufts forming florets that lack fibrovascular cores) (5).

The lung adenocarcinoma has many microscopical variables, such as lymphocytes infiltration, extracellular mucus, fibrosis, mucinous epithelium, necrosis, abscess, pleural invasion, vessel invasion, STAS, lymphatic metastasis, hobnail cell, rhabdomyoid differentiation, mitosis, nucleolus, high grade nuclear and nuclear inclusion (Figure 3). We grouped our cohort according to the presence or absence of these morphological features, and analyzed the correlation between these morphological features and the EGFR mutations. The morphological features were described as follows. Lymphocytes infiltration: diffuse or small clusters of lymphocytes infiltration. Mucinous epithelium: lung adenocarcinoma with less than 10% of mucinous components. Extracellular mucus: significant extracellular mucous. STAS: tumor cells within air spaces in the lung parenchyma beyond the edge of the main tumor (5). Rhabdomyoid differentiation: refers to tumor cells rich in eosinophilic cytoplasm with eccentric nuclei resembling striated muscle cells, which can be found in a variety of tumors, such as parathyroid carcinoma (26), breast cancer (27), ovarian cancer (28), malignant melanoma (29), renal cell carcinoma (30), and glioblastoma (31). Pleural invasion, tumor cells invading the pleural. Vessel invasion, tumor cells invading the vessels. High grade nuclear: the nucleus of the tumor cells was 5 times larger than the lymphocytes nucleus. Hobnail cell: a centrally located nucleus with a bulging appearance and a narrow base, resembling a hobnail. All the histological evaluations were performed by two senior pathologists.

TABLE 1 The correlation between EGFR mutations and the clinical features.

	N	Mutant EGFR	Wild type EGFR	P value
Gender				0.1690
Male	56	35	21	
Female	83	61	22	
Age				0.9683
>59	65	45	20	
≤59	74	51	23	
Location				0.0923
Left	52	32	20	
Right	86	64	22	
Left & Right	1	0	1	
Smoking				0.0311
Yes	27	14	13	
No	112	82	30	
Hypertension				0.3845
Yes	46	34	12	
No	93	62	31	
Diabetes Mellitus				0.9769
Yes	16	11	5	
No	123	85	38	
Family History				0.6417
Yes	12	9	3	
No	127	87	40	
Tumor count				0.7818
Multiple	43	29	14	
Single	96	67	29	
Size				0.0247
≤1.5cm	74	45	29	
>1.5cm	65	51	14	
Lymphatic metastasis				0.2384
Yes	16	9	7	
No	123	87	36	

The bold and italic values mean statistically significant.

EGFR mutation analysis

Formalin-fixed paraffin-embedded (FFPE) lung cancer tissues were obtained after surgery and biopsy puncture. The DNA were extracted from the FFPE samples using the AmoyDx FFPE DNA/RNA Extraction Kit (Amoy Diagnostics, Xiamen, China). The PCR amplification was performed with the SuperARMS EGFR Mutation

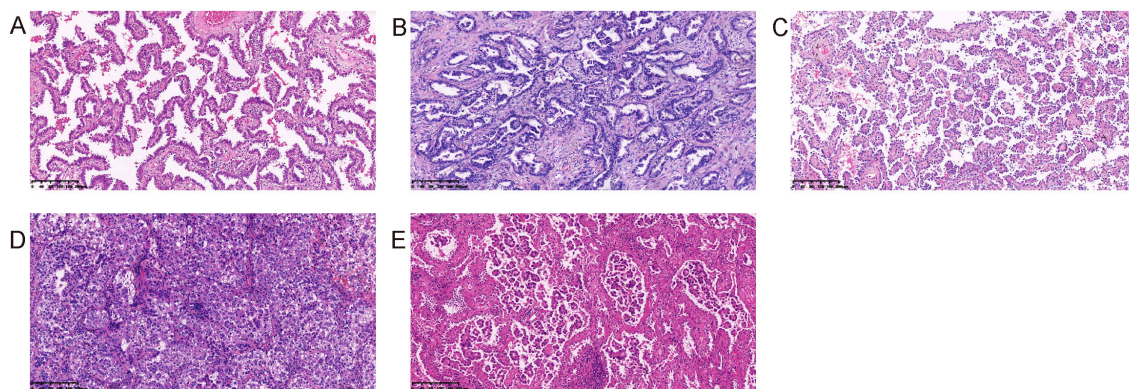


FIGURE 2
Five histological subtypes of lung adenocarcinoma. (A) Lepidic adenocarcinoma; (B) Acinar adenocarcinoma; (C) Papillary adenocarcinoma; (D) Solid adenocarcinoma; (E) Micropapillary adenocarcinoma.

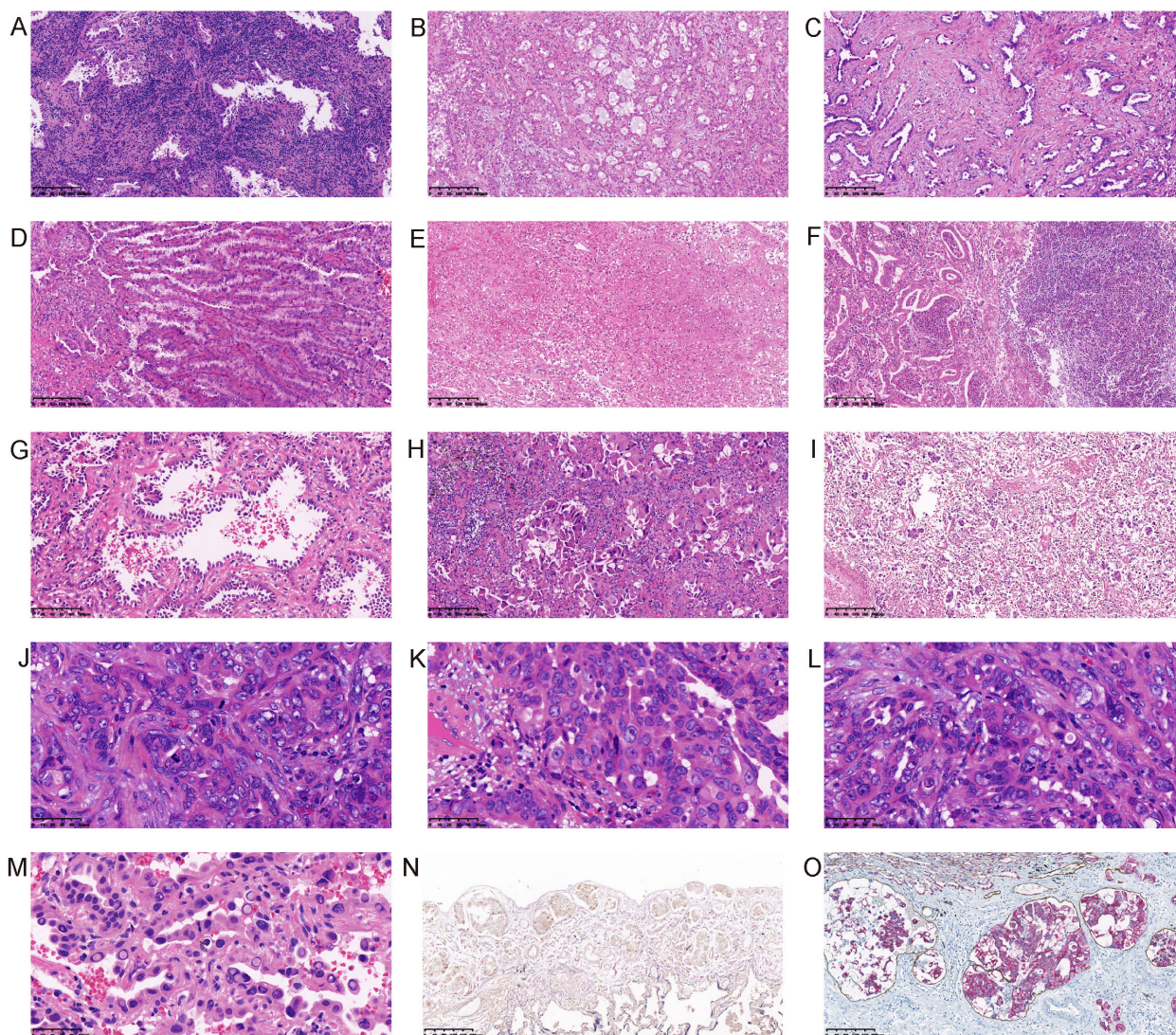


FIGURE 3
Morphological features of lung adenocarcinoma. (A) Lymphocytes infiltration; (B) Extracellular mucin; (C) Fibrosis; (D) Mucinous epithelium; (E) Necrosis; (F) Abscess; (G) Hobnail cell; (H) Rhabdomyoid differentiation; (I) STAS; (J) Mitosis; (K) Nucleolus; (L) High grade nuclear; (M) Intranuclear inclusion; (N) Pleural invasion (Elastin fiber staining showed that the elastic fibers in the visceral pleura were interrupted by tumor invasion); (O) Lymphatic vessel invasion (The immunohistochemical double staining of CK and D2-40 showed the intravascular cancer embolus).

Detection Kit (Amoy Diagnostics, Xiamen, China) on cobas z480 analyzer (Roche). The EGFR mutations at exons 18–21 were analyzed. All kits and devices were used following the manufacturer's protocol.

Immunohistochemistry

The immunohistochemistry (IHC) is a routine technique that can provide additional information of marker proteins in lung adenocarcinoma, such as TTF-1 (thyroid transcription factor 1), Napsin A and CK7 (cytokeratin 7). Other indicators were also tested, such as P63, Ki67, and so on. These markers can help distinguish lung adenocarcinoma from other lung cancer subtypes and the metastatic tumors. The IHC was performed as previously described (32). The immunohistochemical double staining is a method of simultaneous detection the expression of two different antigens in the same tissue slice. This technique involves two primary antibodies, followed by two different secondary antibodies conjugated to different chromogens. In this study, the method was used to simultaneously stain CK and D2-40 in the same tissue section, so as to distinctly determine whether the tumor cells invaded the lymphatic vessels.

Statistical analysis

The correlations between clinicopathological characteristics and EGFR mutations were analyzed using the chi-square test. All

statistical analyses were performed using the Graphpad software. $P < 0.05$ was considered as statistically significant.

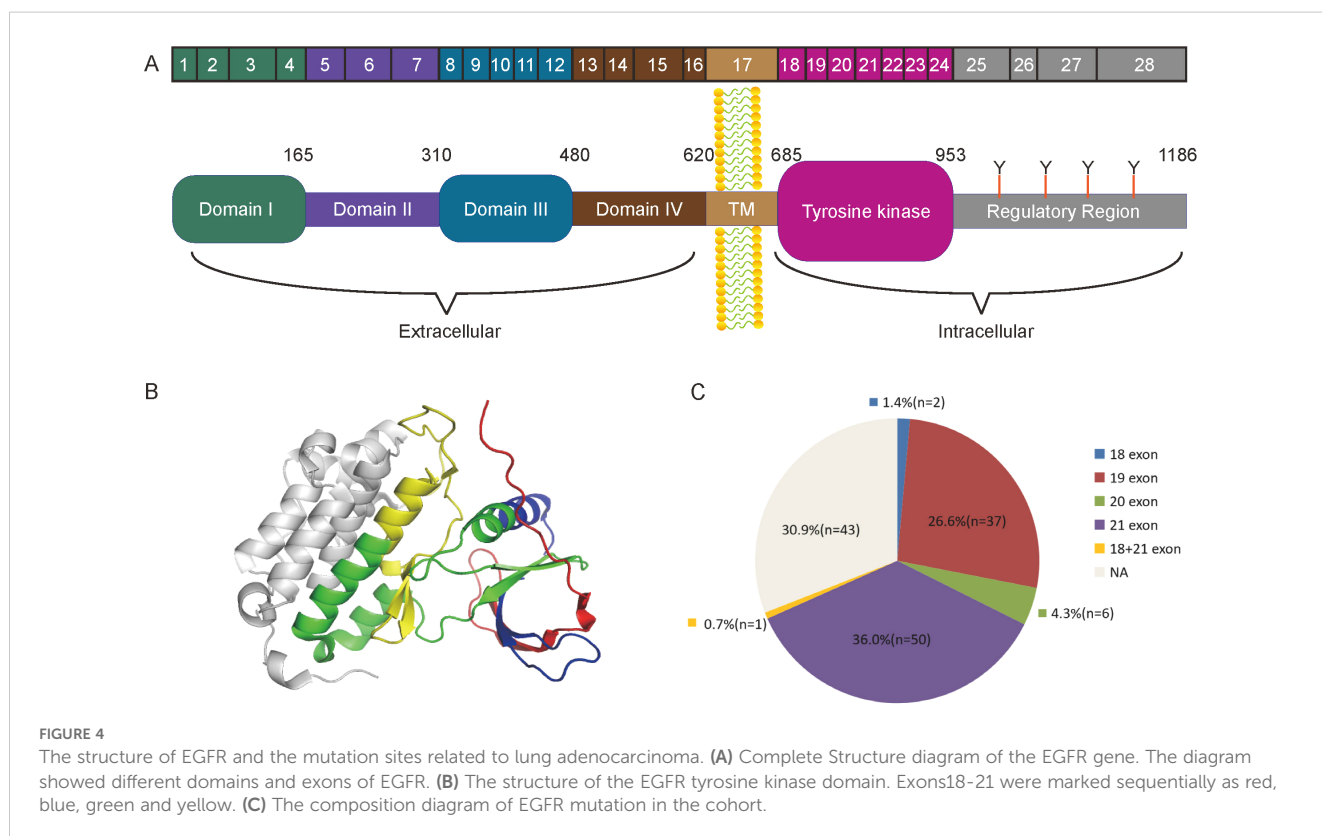
Results

Clinical characteristics of the cohort

Clinical information of 139 patients was shown in Table 1. There were 56 males (40.3%) and 83 females (59.7%). The median age at diagnosis was 59 years (range 33–83 years). 27 (19.4%) patients were current or former smokers, and 112 (80.6%) were non-smokers. 46 (33.1%) patients had a hypertension history and 16 (11.5%) patients had a history of diabetes. 12 (8.6%) patients had a family history of lung cancer in their immediate family, and 127 (91.4%) patients denied a family history of lung cancer. 52 (37.4%) cases were located in the left lung, 86 (61.9%) cases in the right lung, and 1 (0.7%) case in both lungs. 43 (30.9%) patients had multiple tumors. The median size of the tumors was 1.5 cm (range 0.5–8cm). 16 cases (11.5%) were with lymphatic metastasis.

Correlation between EGFR mutations and clinical features

The common detected mutations of EGFR in lung cancer range from exon 18 to exon 21 (Figures 4A, B). We detected these EGFR mutations in the cohort, and found that EGFR mutations occurred in 96 (69.1%) cases. In these mutated cases, the most common



EGFR mutation was a missense mutation (L858R) in exon 21 (47/96, 49.0%) and the second most common was an in-frame deletion in exon 19 (37/96, 38.5%) (Figure 4C). The detailed information of EGFR mutations in the cohort was shown in Tables 1, 2. EGFR mutations were more frequently occurred in never smokers (73.2% vs. former or current smokers 51.9%; $P=0.0311$) and patients with tumor diameter larger than 1.5cm (78.5% vs. tumor diameter less than 1.5cm 60.8%; $P = 0.0247$). In this study, the EGFR mutations had no significant correlation with gender, age, tumor location, hypertension, diabetes mellitus, family history and tumor counts.

Correlation between EGFR mutations and pathological features

Five histological subtypes of lung adenocarcinoma included lepidic subtype, acinar subtype, papillary subtype, solid subtype and micropapillary subtype. In this research, the EGFR mutation rate was significantly related to the histological subtypes of lung adenocarcinoma ($P=0.0003$) (Table 3). Furthermore, the acinar subtype adenocarcinoma had a higher EGFR mutation rate than solid subtype adenocarcinoma ($P=0.0007$) and lepidic subtype adenocarcinoma ($P<0.0001$) (Table 3, Figure 5A). Also, the papillary subtype adenocarcinoma had a higher EGFR mutation rate than solid ($P=0.0358$) and lepidic ($P=0.0269$) subtype adenocarcinoma (Table 3, Figure 5A). Although in this study, the EGFR mutation rate was almost unrelated to the differentiation grade ($P=0.0546$), the incidence rate of EGFR mutation in patients with moderately differentiated lung adenocarcinoma was higher than patients with well differentiated adenocarcinoma ($P = 0.0162$) (Table 3, Figure 5B).

Significantly, EGFR mutation occurred more frequently in tumors with rhabdomyoid differentiation (88.0% vs. tumors without rhabdomyoid differentiation, 64.9%; $P = 0.0237$) and tumors without extracellular mucus (73.8% vs. tumors with extracellular mucus, 35.3%; $P = 0.0013$) (Table 3). Furthermore, the exon 21 mutation occurred more frequently in tumors with rhabdomyoid differentiation (86.4% vs. tumors without rhabdomyoid differentiation, 41.9%; $P = 0.0077$) (Table 4,

Figure 6). However, the EGFR mutation rate had no relationship with the proliferation index (Ki67 expression ratio). The detailed correlation information of EGFR mutations and histological features were shown in Tables 3, 4.

Discussion

EGFR mutation is known to be the most common mutation type of lung adenocarcinoma, which is associated with specific clinical features. In this study, all the patients were of East Asian ethnicity. The EGFR mutation rate was 69.1% (96/139), much higher than that of Caucasian patients (33–36). Previously research indicated that EGFR mutations occurred more frequently in women, never smokers and East Asian ethnicity (8–15, 37, 38). Consistent with this, EGFR mutations occurred more frequently in never smokers ($P=0.0311$) in this research. But inconsistent with previous researches, there was no significant difference in EGFR mutation incidence between women and men ($P=0.1690$). Previous studies showed that EGFR mutation preferentially occurred in patients with maximal tumor size less than 3 cm (14). In our research, the median tumor diameter was 1.5cm, which was selected as the cut-off value. The EGFR mutation occurred more frequently in tumors with a diameter larger than 1.5cm ($P=0.0247$). There was no more statistical correlation between EGFR mutation rate and other clinical features (Table 1).

According to the IASLC/ATS/ERS classification criteria, the non-mucinous lung adenocarcinoma could be divided into five histological subtypes and three differentiation grades. The classification criteria were mainly based on tumor morphology, lacking the study of molecular changes. Nowadays, the correlation between molecular changes and morphology characteristics of lung adenocarcinoma has attracted the research interests greatly, especially the EGFR mutations. Recent research showed that the lung adenocarcinoma with solid subtype had a lower EGFR mutation rate (39–42). The other research indicated that EGFR mutations occurred most frequently in acinar lung adenocarcinoma and least frequently in solid lung adenocarcinoma (43). Consistently, in our study, lung adenocarcinoma with acinar and papillary subtype had a higher EGFR mutation rate than solid and lepidic subtype. In addition, we found that the EGFR mutation occurred more frequently in moderately differentiated lung adenocarcinoma than well differentiated adenocarcinoma.

The lung adenocarcinoma has heterogenous histological characteristics, such as cell atypia, nuclear characteristics, cytoplasmic morphology, interstitial abnormality, mitosis rate, and so on. In this research, we also explored the correlation between EGFR mutation and these morphological features.

Interestingly, we found that EGFR mutation occurred more frequently in adenocarcinoma with rhabdomyoid differentiation. Besides, EGFR mutation of the adenocarcinoma with rhabdomyoid differentiation mainly occurred at exon 21. Our research indicated that EGFR mutations at exon 21 may result in rhabdomyoid differentiation, which connected the genetic changes with the

TABLE 2 The detailed information of EGFR mutations in the cohort.

Gene	Exon	Amino acid change	N (%)
EGFR	18	G719X	2 (2.08%)
	19	Amino acid deletion	37 (38.54%)
	20	V769_D770insASV	4 (4.17%)
		S768I	2 (2.08%)
	21	L858R	47 (48.96%)
		L861Q	3 (3.13%)
	18 + 21	G719X、L858R	1 (1.04%)

TABLE 3 The association between EGFR mutations and the histological characteristics.

	N	Mutant EGFR	Wild type EGFR	P value
Histological Subtypes				0.0003
LA	28	12	16	
AA	69	57	12	
PA	20	15	5	
SA	13	5	8	
MA	9	7	2	
Differentiation				0.0546
Well-differentiated (G1)	24	12	12	
moderately differentiated (G2)	82	62	20	
Poorly differentiated (G3)	33	22	11	
Lymphocytes infiltration				0.718
Yes	94	64	30	
No	45	32	13	
Extracellular mucus				0.0013
Yes	17	6	11	
No	122	90	32	
Fibrosis				0.9618
Yes	78	54	24	
No	61	42	19	
Mucous epithelium				0.5482
Yes	22	14	8	
No	117	82	35	
Necrosis				0.6848
Yes	11	7	4	
No	128	89	39	
Abscess				0.1759
Yes	3	1	2	
No	136	95	41	
Hobnail cell				0.2842
Yes	43	27	16	
No	96	69	27	
rhabdomyoid differentiation				0.0237
Yes	25	22	3	
No	114	74	40	
STAS				0.4448
Yes	27	17	10	
No	112	79	33	
Mitosis				0.3454

(Continued)

TABLE 3 Continued

	N	Mutant EGFR	Wild type EGFR	P value
<1/10HPF	89	59	30	
≥1/10HPF	50	37	13	
Nucleolus				0.6022
Yes	33	24	9	
No	106	72	34	
High grade nuclear				0.2107
Yes	39	30	9	
No	100	66	34	
Nuclear inclusion				0.1184
Yes	15	13	2	
No	124	83	41	
Pleural invasion				0.4698
Yes	38	28	10	
No	101	68	33	
Vessel invasion				0.1758
Yes	10	5	5	
No	129	91	38	
Ki67				0.8095
<10%	42	29	13	
≥10%	48	32	16	

The bold and italic values mean statistically significant.

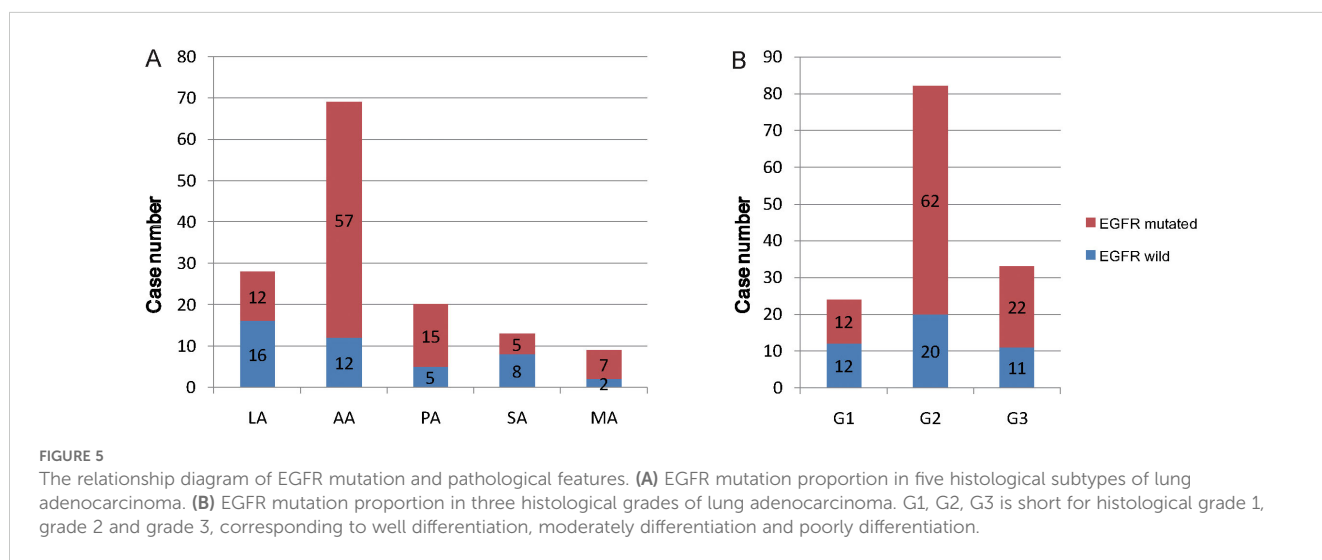
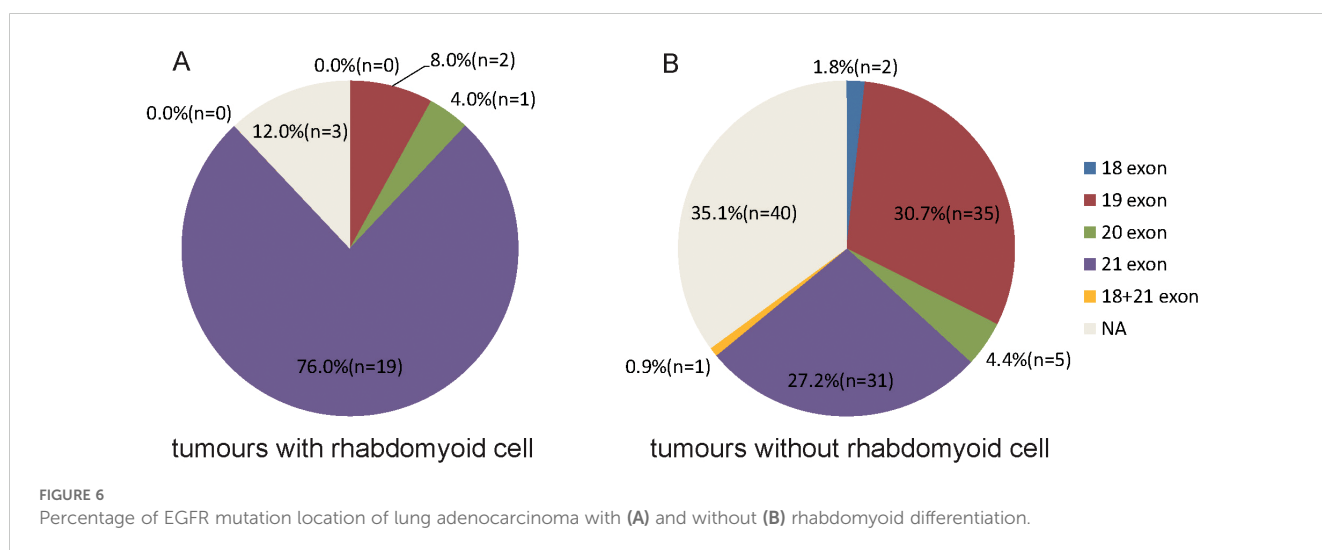


TABLE 4 The correlation between EGFR mutation and the Rhabdomyoid feature.

	N	With rhabdomyoid differentiation	Without rhabdomyoid differentiation	P value
Mutant EGFR				<i>0.0077</i>
EGFR18 exon	2	0	2	
EGFR19 exon	37	2	35	
EGFR20 exon	6	1	5	
EGFR21 exon	50	19	31	
EGFR18 + 21 exon	1	0	1	
Wild type EGFR	43	3	40	

The bold and italic values mean statistically significant.



morphological characteristics of lung adenocarcinoma. Lung adenocarcinomas with rhabdoid differentiation are morphologically similar to rhabdoid cells, but are essentially lung adenocarcinomas. They still express lung adenocarcinoma-specific immunohistochemical markers, such as TTF-1 and NapsinA, but do not express myogenic immunohistochemical markers, such as MyoD-1 or Desmin. Several studies have shown that meningiomas and renal cell carcinomas with rhabdoid differentiation have more aggressive biological behaviors and poor prognosis (44, 45). However, there is no report on lung adenocarcinoma with rhabdoid differentiation, neither on the relationship between EGFR mutation and lung adenocarcinoma with rhabdoid differentiation. The mechanism of rhabdoid differentiation is unknown and needs further study.

We also found that the non-mucous adenocarcinomas with extracellular mucus had a lower EGFR mutation rate. The pathogenesis of lung adenocarcinoma and invasive mucinous

adenocarcinoma (IMA) was totally different. The IMA had a much lower EGFR rate than typical lung adenocarcinoma (46, 47). The lung adenocarcinoma with extracellular mucus may be a complex of typical lung adenocarcinoma and IMA. Therefore, the genetic characteristics also may be affected.

Conclusions

In summary, our research revealed that the EGFR mutation state was associated with smoking history, histological subtypes, tumor size, and some rare histological features, such as rhabdomyoid differentiation and extracellular mucus. In-depth study of morphological characteristics is conducive to early prediction of genetic changes, which is meaningful to postoperative chemotherapy.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving humans were approved by Research Ethics committee of the second hospital of Shandong University (KYLL-2023LW057). The studies were conducted in accordance with the local legislation and institutional requirements. The human samples used in this study were acquired from primarily isolated as part of your previous study for which ethical approval was obtained. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

HW: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Resources, Software, Writing – original draft. CJ: Methodology, Formal Analysis, Writing – original draft. HL: Funding acquisition, Supervision, Validation, Visualization, Writing – review & editing. CZ: Formal Analysis, Project administration, Supervision, Validation, Visualization, Writing – review & editing.

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