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Gene mutation, clinical characteristics and pathology in resectable lung adenocarcinoma

Ji'an Zou[1,2], Wei Han[1,2], Yan Hu[1,2], Chao Zeng[1,2], Jina Li[1,2], Weixuan Lei[1,2], Jieming Cao[1,2], Quanming Fei[1,2], Mengqi Shao[1,2], Junqi Yi[1,2], Zeyu Cheng[1,2], Li Wang[1,2], Fang Wu[3,4,5,6] and Wenliang Liu[1,2*]

Abstract

Objective With the wide use of CT scan in clinical practice, more lung cancer was diagnosed in resectable stage. Pathological examination and genetic testing have become a routine procedure for lung adenocarcinoma following radical resection. This study analyzed special pathological components and gene mutations to explore their relationship with clinical characteristics and overall survival.

Methods Clinical, pathological, and gene mutation data from 1,118 patients were collected. All patients underwent surgery at the Department of Thoracic Surgery, the Second Xiangya Hospital of Central South University. Patients were grouped based on pathological components and gene mutations. Differences in clinical features and overall survival were analyzed as well.

Results Patients with mucinous, neuroendocrine, and poor-differentiated components were presented with more prognostic risk factors, including pleural invasion, carcinothrombosis, STAS, and advanced stages, along with varying frequencies of gene mutations. These factors significantly shortened overall survival. ALK and KRAS mutations were also associated with risk factors such as solid nodules, pleural invasion, STAS, and later stages. However, a significant reduction in overall survival was observed only in patients with the KRAS mutation. Relationship between gene mutations and pathological components still requires further investigation.

Conclusion Special pathological components (mucinous, neuroendocrine, and poor-differentiated) and gene mutations had an influence on biological behavior of tumors, resulting in different clinical characteristics and prognosis.

Keywords Lung adenocarcinoma, Gene mutation, Pathology, Computed topography, Surgery

*Correspondence:
Wenliang Liu
liuwenliang@csu.edu.cn
[1] Department of Thoracic Surgery, The Second Xiangya Hospital, Central South University, Changsha, Hunan 410011, China
[2] Hunan Key Laboratory of Early Diagnosis and Precision Treatment of Lung Cancer, The Second Xiangya Hospital of Central South University, Changsha, China
[3] Department of Oncology, The Second Xiangya Hospital, Central South University, Changsha, Hunan 410011, China
[4] Hunan Cancer Mega-Data Intelligent Application and Engineering Research Centre, Changsha, Hunan 410011, China
[5] Hunan Key Laboratory of Tumor Models and Individualized Medicine, The Second Xiangya Hospital, Central South University, Changsha, Hunan 410011, China
[6] Hunan Key Laboratory of Early Diagnosis and Precision Therapy in Lung Cancer, The Second Xiangya Hospital, Central South University, Changsha, Hunan 410011, China

Introduction

Lung cancer ranks first globally in both incidence and mortality rates [1]. With the increased use of CT scans due to COVID-19 [2], a significant number of early-stage lung cancers have been detected, leading to a higher proportion of patients eligible for surgical resection [3]. Targeted therapy has rapidly advanced in lung cancer treatment, playing a crucial role not only in maintenance therapy but also in neoadjuvant and adjuvant settings [4]. The effective use of targeted therapy relied on next-generation sequencing (NGS). Epidermal growth factor receptor (EGFR) was the first target identified in lung cancer treatment, showing significant survival advantages over chemotherapy [5]. Since then, mutations such as anaplastic lymphoma kinase (ALK) fusion, ROS1 fusion, Kirsten rat sarcoma (KRAS), RET, and mesenchymal to epithelial transition factor (MET) have also been discovered [6]. These driver gene mutations lead to different clinical characteristics and survival outcomes among patients with different mutations.

Pathological examination remained the gold standard for tumor diagnosis, providing comprehensive insight for lung cancer. Lung adenocarcinoma was classified into several pathological subtypes, such as lepidic, acinar, papillary, micropapillary and solid. Previous studies have shown that micropapillary and solid components were correlated with poor prognosis [7–9]. Other rare types like mucinous and neuroendocrine components can be observed [10]. Although prior researches have investigated the characteristics of these populations, comprehensive comparisons across multiple cohorts were lacking [11]. Lung cancer was often initially detected via CT scans, with common manifestations including solid or ground-glass opacity (GGO) [12]. Identifying the relationship between imaging features, gene mutations, and pathological components can aid in clinical decision-making for patients.

For resectable lung cancer, clinical characteristics, pathology and gene mutations are almost unavoidable topics. This study aimed to investigate the differences in clinical characteristics and prognosis among various lung adenocarcinoma populations by focusing on pathological components and gene mutations.

Methods

Informed consent and ethics

The institutional review board ethics committee of the the Second Xiangya Hospital of Central South University approved the study protocol and publication of data (ethical approval number: LYF2021096). The individuals provided written informed consent for the publication of the study data. Data security and privacy were protected throughout the study.

Patients

All patients were diagnosed with resectable lung cancer and have undergone radical surgery in the department of thoracic surgery, the Second Xiangya Hospital of Central South University. Patients must be diagnosed with lung adenocarcinoma according to pathological results. And all patients have received next-generation sequencing (NGS). Unsuccessful surgery, non-malignant lesions and other pathological types were excluded. The final pathological cancer stages were assessed according to the eighth edition of the Union for International Cancer Control and American Joint Committee on Cancer TNM classification.

Collection of data

All the clinical and pathological features were collected in the system in the Second Xiangya Hospital of Central South University. In total, 1118 patients were collected between 2017 and 2022 and last follow-up was done in May 2024.

Group by pathology

The whole population was divided into four groups by pathological diagnosis. 1) Mucinous group: lung adenocarcinoma with mucinous component. 2) Neuroendocrine group: lung adenocarcinoma with neuroendocrine component accounting for less than 50%. 3) Poor-differentiated group: lung adenocarcinoma with poor differentiation (solid and micropapillary). 4) Reference group: lung adenocarcinoma without any component mentioned in former three groups.

Histological evaluation and gene mutation analysis

Resected surgical specimens were cut at 3-mm intervals and fixed in 10% buffered formalin. Embedded in paraffin, all specimens were stained with H&E for histological examination. Two pathologists reviewed the specimens and categorized the histological subtype of each tumor according to the classification of lung adenocarcinoma. The expression of PD-L1 was evaluated using combined positive score (CPS) using specimens from surgical resection. Gene mutation was examined using the next generation sequencing methods performed by geneplus.

Statistical analysis

All statistical analyses were performed using R Studio (R 4.3.1 version), difference between clinical features and gene mutations were evaluated using t test and $\chi 2$ test. All figures are created using R Studio (R 4.3.1 version)

and Adobe Illustrator 2020. All tables are created using Microsoft Word and Excel.

Results

Clinical and pathological features in all patients and among four groups

Clinical and pathological features across the four groups are summarized in Table 1, while comparisons of PD-L1 levels are shown in Supplementary Fig. 1 and 2. The number of smokers was significantly higher in the poor-differentiated group. A higher proportion of solid nodules was observed in the poor-differentiated and mucinous groups. Tumors in the poor-differentiated, mucinous, and neuroendocrine groups were generally more invasive, as evidenced by higher rates of pleural invasion, carcinothrombosis, and STAS. However, only poor-differentiated and mucinous tumors were significantly associated with more advanced cancer stages. In the neuroendocrine group, early-stage tumors were more likely to metastasize distantly,

Table 1 Clinical and pathological features among for groups. *p* value was calculated compared with reference group using χ2 test ($p < 0.05$: *, $p < 0.01$: **, $p < 0.001$: ***). GGO: ground glass opacity. STAS: spread through air space

	mucinous	p	neuroendocrine	p	poor-differentiated	p	reference	total
age	55.8		55.4		59.7		56.5	57
sex								
male	31		21		139		484	675
female	33		19		81		313	446
smoke								
yes	18		10		79	***	146	253
never	46		30		141		651	868
nodule								
solid	29	***	5		124	***	107	265
GGO	35		35		96		690	856
pleura invasion								
yes	20	***	8	*	64	***	72	164
no	44		32		156		725	957
carcinothrombosis								
yes	3	**	2	*	22	***	2	29
no	61		38		198		795	1092
STAS								
yes	10	***	2	**	40	***	1	53
no	54		38		180		796	1068
N stage								
N0	57	***	37		164	***	782	1040
N1	4		1		19		4	28
N2	3		2		37		11	53
stage								
I	54	***	36	*	164	***	781	1035
II	6		2		22		6	36
III	4		2		34		10	50
lepidic								
yes	5	**	1	**	19	***	186	211
no	59		39		201		612	911
solid								
yes	10	-	1	-	68	-	0	79
no	54		39		152		798	1043
micropapillary								
yes	8	-	1	-	58	-	0	67
no	56		39		162		798	1055

often resulting in unresectable disease. Conversely, the lepidic component, known as a protective factor for lung cancer patients [7], was significantly less prevalent in the poor-differentiated, mucinous, and neuroendocrine groups. Higher PD-L1 levels were observed in male smokers with solid manifestation on CT scans, patients with advanced disease or invasive pathological components.

Gene mutation status in all patients and among four groups

Gene mutation status across the four groups was summarized in Table 2 and Fig. 1. Gene mutation status of our cohort aligned with typical findings in Asian patients [13]. In the mucinous group, there was a significantly lower rate of EGFR mutation, accompanied by a higher incidence of KRAS mutation and ALK fusion. At ELCC 2024, mucinous lung adenocarcinoma was reported to have fewer TP53 and BRAF mutations, but we did not observe this in our study. Similarly,

Table 2 Gene mutation rate for EGFR, ALK, KRAS, ROS1, RET and MET in four groups

	mucinous	p	neuroendocrine	p	poor-differentiated	p	reference	total
EGFR	18.8% (12/64)	***	20.0% (8/40)	***	48.1% (106/220)		52.4% (418/798)	48.5% (544/1122)
ALK fusion	17.1% (11/64)	***	0% (0/40)	-	7.2% (16/220)		1.3% (10/798)	3.3% (37/1122)
KRAS	29.7% (19/64)	***	5.0% (2/40)		13.2% (29/220)	*	3.0% (24/798)	6.6% (74/1122)
ROS1 fusion	0% (0/64)	-	0% (0/40)	-	2.7% (6/220)		0.2% (2/798)	0.7% (8/1122)
RET	0% (0/64)	-	0% (0/40)	-	2.7% (6/220)		0.8% (6/798)	1.1% (12/1122)
MET	1.6% (1/64)		0% (0/40)		4.6% (10/220)		2.9% (23/798)	3.0% (34/1122)

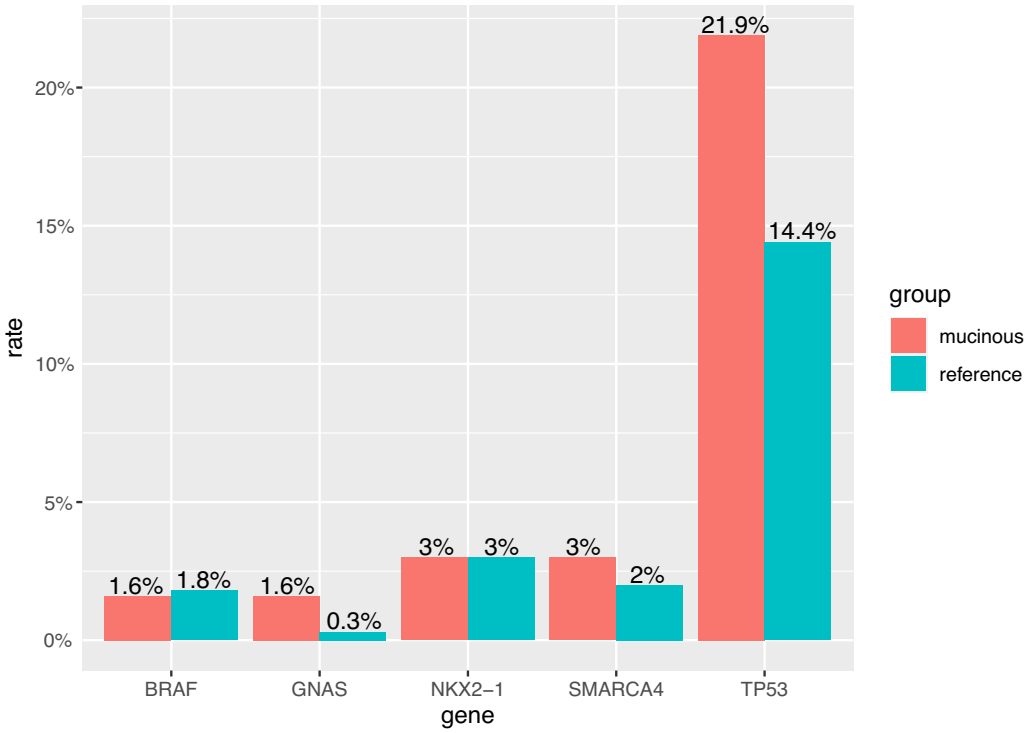

Fig. 1 Other gene mutations related to mucinous group

higher mutation frequencies of STK11, SMARCA4, NKX2-1, and GNAS reported in other studies could not be validated in our cohort either (Fig. 1). In the neuroendocrine group, EGFR mutation was also less frequent. Mutations such as ROS1 fusion, MET, and RET could rarely be seen in both the mucinous and neuroendocrine groups. In the poor-differentiated group, only a higher rate of KRAS mutations was noted. Based on the gene mutation profiles, the mucinous and neuroendocrine groups appeared more distinct, whereas tumor cells in the poor-differentiated group showed greater similarity to the reference group.

Additional characteristics of gene mutation in all patients were summarized in Supplementary Fig. 3 and 4. Among patients with KRAS mutation, EX2 was predominant (88%), while EX3 was less common (12%). The most frequent KRAS mutation subtypes were G12C (38.7%), G12D (20%), and G12V (17.3%). For patients with EGFR mutation, EX19 and EX21 accounted for the majority of subtypes (32.6% and 48.7%, respectively), with EX18 and EX20 representing 5.7% and 9.7%, respectively. Furthermore, correlations between different mutations were analyzed, but no evidence of positive relationships between any two mutations was found. Interestingly, EGFR mutations tended to exclude the coexistence of other gene mutations.

Clinical and pathological features between different gene mutation status

Clinical and pathological features according to mutation status were shown in Table 3 and Supplementary Table 1. Patients with EGFR mutation was more often female and non-smokers, while KRAS mutation was more frequently observed in male patients with smoking history. In patients with EGFR mutation, more nodules were presented with GGO. In contrast, patients with ALK fusion or KRAS mutation exhibited more solid nodules.

Increased pleural invasion was observed in ALK fusion + patients and more STAS was shown in both ALK fusion + /KRAS + patients with later stage. EGFR + patients had a higher likelihood of harboring lepidic and micropapillary components, while ALK fusion + patients showed more solid and micropapillary components. In patients with KRAS mutation, fewer lepidic components and more solid components were presented. PD-L1 levels were higher in patients with ALK and KRAS mutations (Supplementary Fig. 2).

Survival analysis

Survival results related to clinicopathological features are summarized in Fig. 2, while the survival outcomes related to genetic mutations could be seen in Fig. 3. Overall survival analysis indicated poorer outcomes for the poor-differentiated, mucinous, and neuroendocrine groups. Among the common driver mutations, only KRAS mutation was associated with a shortened overall survival for

Table 3 Pathological features between gene mutation status. *p* value was calculated compared with reference group using χ2 test ($p < 0.05$: *, $p < 0.01$: **, $p < 0.001$: ***). STAS: spread through air space

	EGFR +	EGFR-	p	ALK fusion +	ALK fusion-	p	KRAS +	KRAS-	p
pleura invasion									
yes	75	104		13	164	**	12	165	
no	468	474		25	919		62	882	
carcinothrombosis									
yes	13	19		3	28		4	26	
no	530	559		35	1055		70	1021	
STAS									
yes	19	33		8	46	***	11	42	***
no	524	545		30	1037		63	1005	
lepidic									
yes	169	42	***	3	208		6	205	*
no	375	536		35	876		68	843	
solid									
yes	39	40		9	70	***	11	68	*
no	505	538		29	1014		63	980	
micropapillary									
yes	37	30	*	9	58	***	4	63	
no	507	548		29	1026		70	985	

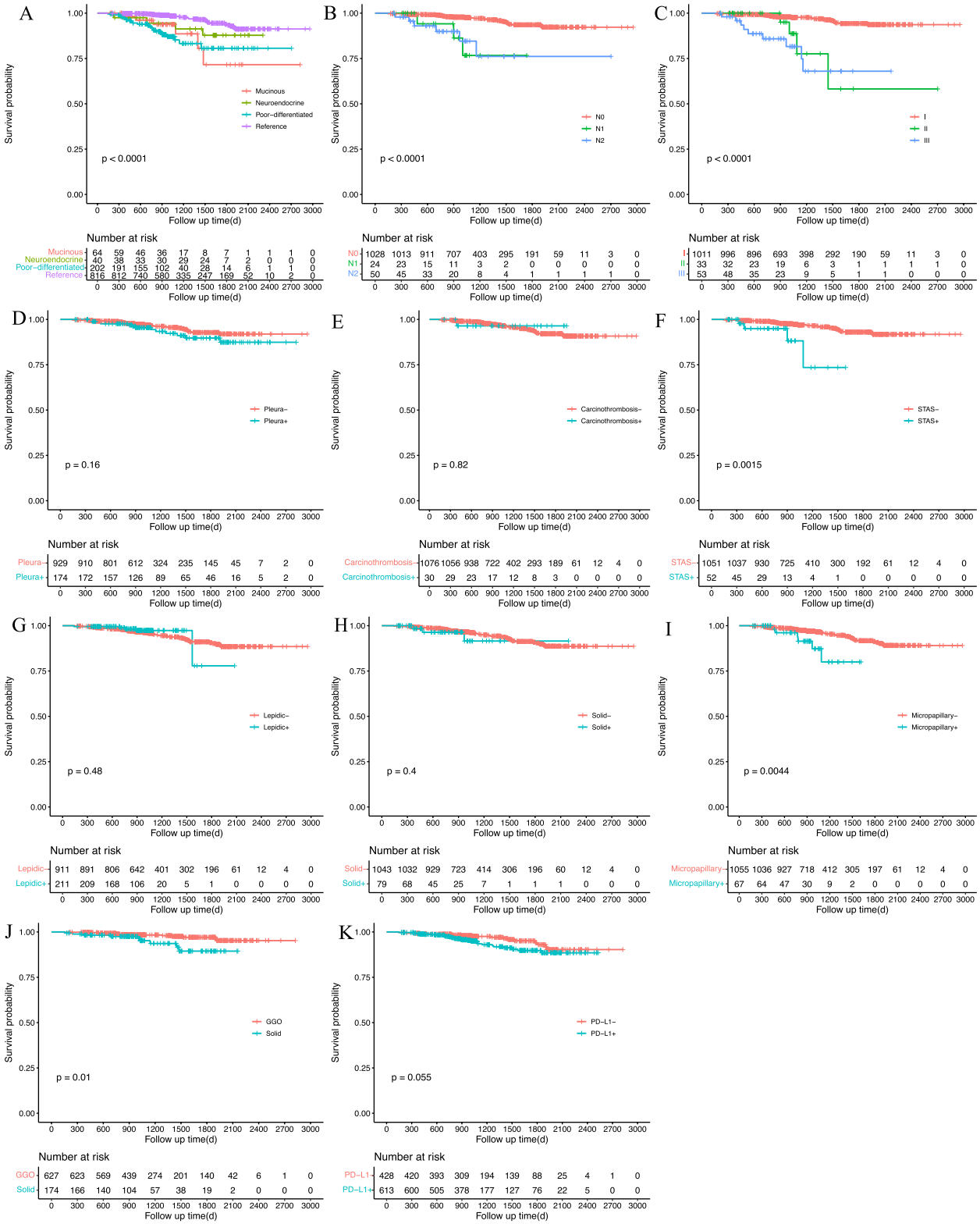

Fig. 2 Comparison of overall survival times between clinical and pathological features. **A**: among four groups, **B**: N stage, **C**: stage, **D**: pleural invasion, **E**: carcinothrombosis, **F**: STAS, **G**: lepidic component, **H**: solid component, **I**: micropapillary component, **J**: CT manifestation, **K**: PD-L1 level

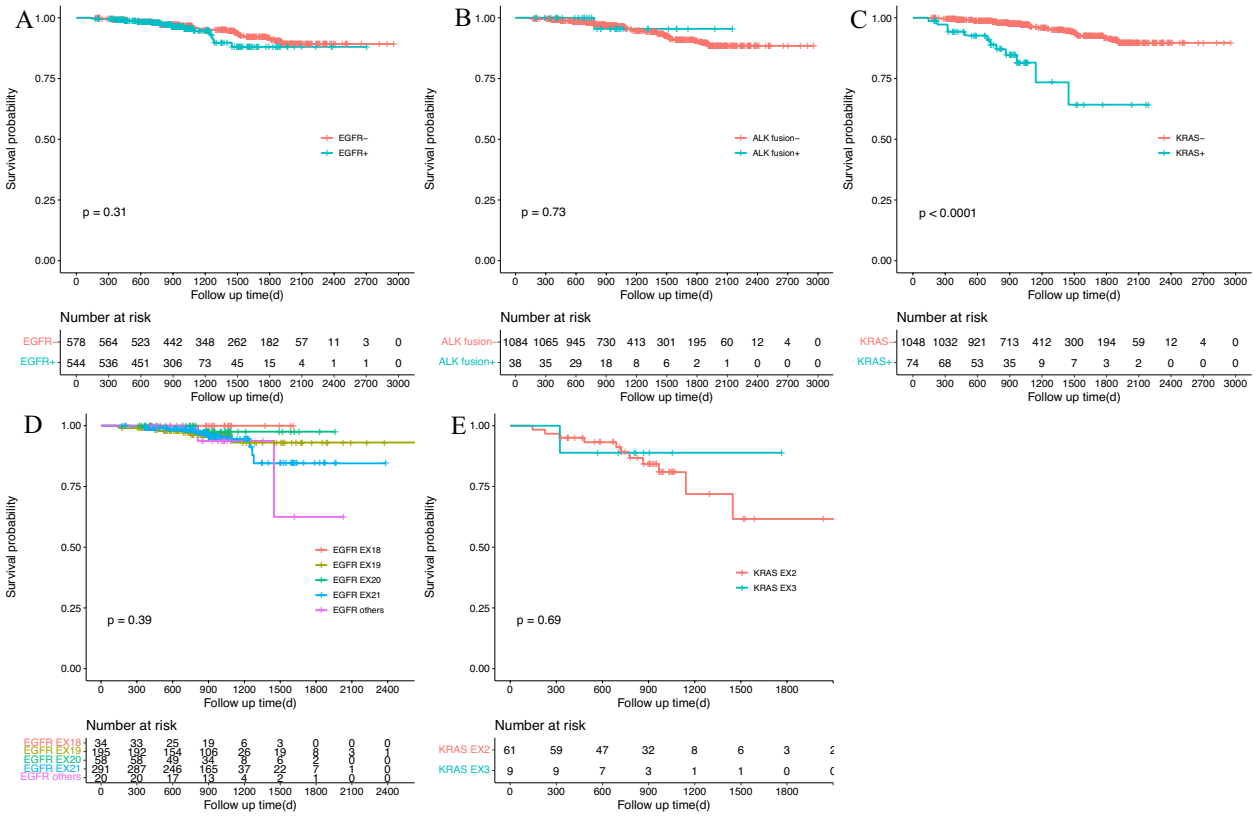

Fig. 3 Comparison of overall survival times between genetic mutations. **A**: EGFR mutation, **B**: ALK fusion, **C**: KRAS mutation, **D**: EGFR mutation subtypes, **E**: KRAS mutation subtypes

patients. This may due to the use of targeted therapy after surgery, which mitigates the aggressive nature associated with the gene mutation. The poor prognosis of mucinous group may also be linked to the high frequency of KRAS mutation. Furthermore, patients presenting with GGO had longer overall survival, confirming that solid components were a risk factor for prognosis. Both STAS and micropapillary components were identified as adverse prognostic factors [7, 14], but no significant differences were observed concerning pleural invasion and carcinothrombosis. Although the survival period was shorter in the poor-differentiated population, the presence of well-differentiated components (lepidic) did not significantly impact prognosis. Lastly, patients exhibiting higher PD-L1 expression were found to have shorter overall survival.

Discussion

Clinical and pathological characteristics in four groups

Lung mucinous adenocarcinoma has been reported with lower lobe predominance, bilateral involvement, distinguishing gene mutation patterns (higher KRAS mutation) and poorer prognosis [15, 16], with consistent results in our study. However, the nodules of lung mucinous adenocarcinoma typically lack imaging features on CT [15], making biopsy crucial for accurate diagnosis [17]. Studies from 2016 to 2023 compared lung mucinous adenocarcinoma with large cohorts of non-mucinous adenocarcinoma [16, 17], but no significant differences in clinical characteristics or survival have been found. Additionally, neither mixed adenocarcinoma components nor postoperative chemotherapy significantly affect overall survival [17]. In terms of gene mutation, there was a high rate of ALK fusion but with poorer prognosis compared with reference group, which may be the result of the invasive nature of mucinous component. Moreover, relationship between KRAS mutation and immunotherapy remained complicated [18–20], which will be discussed later.

Among lung adenocarcinomas, neuroendocrine carcinomas (e.g., small cell lung cancer) was known for aggressiveness, early metastasis, and relatively poor prognosis [21]. Around 2000, a number of physicians studied the effectiveness of surgical treatment for such patients, but only a subset of studies concluded that > 5% of neuroendocrine differentiation components can affect survival [22]. In addition, incidence of driver mutation on this group was investigated but without international

peer review [11]. However, in our cohort, the relative high proportion of EGFR mutation, possibly representing an intermediate state in the transformation of EGFR-positive lung adenocarcinoma into small cell lung cancer [23]. Moreover, mechanisms and examples of conversion to SCLC from NSCLC with targeted therapies (mainly EGFR) have been studied previously [14, 24, 25]. And we believed that our study will help to gain a more in-depth understanding of this process, which can facilitate personalized medicine, such as modification of chemotherapy regimens, closer detection of distal metastases (especially brain metastases), prophylactic radiotherapy.

In our study, poor-differentiation was defined as the presence of micropapillary or solid component, which has been explored by many researchers [7–9] and were generally associated with aggressive biological behavior [7]. The amount of micropapillary component (>=5%) was a widely accepted predictor of poorer prognosis [8]. Lepidic component was regarded as protective factors of NSCLC, so that sublobular resection was proposed for patients with lepidic differentiation as early as 2017 [9]. Subsequent studies indicated that lepidic component was a positive prognostic factor in GGO [26], tumors < 3 cm [27] and all lung adenocarcinoma patients [28]. However, other research has reported that the presence of lepidic component did not improve survival outcomes [7]. In our cohort, patients with micropapillary component were presented with shorter overall survival, whereas there was no significant difference related to solid or lepidic differentiation. Considering the low percentage of these subgroups, statistical error stemming from insufficient sample size could occur so that prospective studies of larger scale will be needed. Notably, 80% of our patients were T1 (881/1104) and micropapillary component had an impact on survival, whereas solid component did not, partially validating the results of previous studies [14]. These results suggested that relying solely on the maximum diameter of the primary tumor (T-stage) couldn't fully predict the impact of the poor-differentiated component or guide adjuvant therapy for patients with stage IA NSCLC either [29]. Fortunately, the predictive role of ctDNA-based minimal residue disease (MRD) monitoring has been demonstrated recently in resectable NSCLC patients with a maximum diameter of the primary tumor greater than 2 cm [30]. Longitudinal ctDNA-based MRD detection could predict most of recurrence (87.2%, 41/47) and the survival benefits were not limited to staging, with the limitation of undetectable brain recurrence [31–33]. As the risk factors for postoperative adjuvant therapy in stage I lung cancer patients remain inconclusive [29, 34], ctDNA-based MRD monitoring may be an option for patients with poorly differentiated components. However, given that postoperative recurrence in driver gene-positive lung adenocarcinoma (especially EGFR mutations) predominantly involves brain metastases (27.4%, 29/106) [35–37], such detection methods need further improvement before being applicable in clinical practice. We believe that with advancements in biomedical science and the continuous investigation of clinical trials, cancer patients will undoubtedly receive more precise diagnoses and treatments in the future.

The impact of gene mutation on clinical/pathological features and prognosis

It was widely accepted that EGFR mutation was more frequent in Asian female patients without smoking history [38], and similar results were shown in our patients. However, whether EGFR was related to GGO remained controversial [7, 39]. Our result showed a higher prevalence of EGFR mutation in GGO and confirmed results by Li et al. [40]. But this result wasn't consistent with review published by Cheng et al. [38], in which no significant difference was observed. Howevever, no survival impacts of EGFR + mutation was shown. Additionally, ALK fusion was possibly associated with lymph node metastasis and pleura invasion [41–43], with more solid and micropapillary components potentially leading to poorer prognosis [44, 45]. However, we failed to find significant difference between ALK fusion + / ALK fusion—patients in survival analysis, which may due to low percentage of the subgroup. KRAS mutation could always be seen in male smokers and its influence on prognosis remained unclear [46]. In our cohort, KRAS mutation was related to poor prognosis, which may be the result of more invasive nature without standard targeted therapy. While existing medical treatments have provided limited benefits to this group of patients, the emergence of new therapies offers a silver lining. With the meticulous study of the KRAS mutation and developments of biochemistry [47], nowadays it is possible to directly target KRAS with small molecular inhibitors [48]. Allele-specific KRAS G12C inhibitors such as Sotorasib [49, 50] and Adagrasib [51] have entered phase III clinical trials with ORR of 28.1%-45.9%. Also, articles on Divarasib (KRAS G12C inhibitors) in NSCLC patients have been published with the ORR of 53.4% [52], while new KRAS inhibitors including G12C inhibitors, G12D inhibitors, multi-RAS inhibitors and immune therapies were being investigated in phase-I studies [48, 53, 54]. However, resistance were usually observed in patients using KRAS inhibitors, including primary resistance [55–57], adaptive resistance [58–60] and histological transformation [61–63]. As a consequence, it's crucial to investigate co-occurring genetic mutations and baseline transcriptional features of KRAS pathway, developing new mutation-selective inhibitors and panRAS/KRAS

inhibitors. What's more, combination therapies will also play an important role in improving prognosis. When treating lung cancer, KRAS inhibitors could be combined with RTK inhibition [59], SOS1 and SHP2 inhibitors [48], downstream MAPK blockade [64, 65] and immunotherapy [57, 66, 67]. With the gradual completion of KRAS inhibitors for lung cancer, it is expected to play an important role in (neo)adjuvant settings and contributing to better prognosis for patients.

Overall, tumors with driver mutations tend to be more aggressive thus more likely to metastasize (especially to the brain [68–71]), and targeted therapies were able to suppress tumor growth thus improve prognosis. However, the availability of targeted drugs varied greatly depending on hospital resources and the financial capabilities. In China, genetic testing for cancer has not been included in the national health insurance system and is primarily conducted by third-party companies, imposing a significant financial burden on patients. Additionally, negative test results, or positive results that fail to result in promising efficacy of targeted therapy, deter some patients from undergoing genetic testing. As such, more robust evidence linking gene mutation and prognosis needed to be obtained in phase III randomized controlled trials (RCT)s, narrowing the scope of genetic testing to improve detection rates while reducing the burden on patients.

The level of PD-L1 between different patients

PD-L1 testing has already become a routine immunohistochemical assay and was also used as a biomarker predicting the efficacy of immunotherapy [72]. According to previous analyses, only patients with BRAF and MET mutations tended to benefit from immunotherapy, while high PD-L1 expression in ALK/ROS1/RET fusions and KRAS mutations did not translate into survival benefits of immunotherapy [73, 74]. In addition, patients with EGFR mutations benefited very little from immunotherapy especially in exon19/21 subtype or with T790M [73, 75], with some even developing hyperprogression [76, 77]. As a consequence, most patients with gene mutation (especially EGFR mutation, ALK and ROS1 fusions) were largely excluded from studies of immunotherapy until the emergence of combination therapy in 2021 [73]. Nowadays, treatments on EGFR-TKIs resistant patients were being progressively investigated (ORIENT-31, KEYNOTE-789, TATTON, IMpower150, ATLANTIC and CheckMate 722), but the benefit was still limited. Efficacy will be improved with the addition of antiangiogenic therapy [78–80], but may lead to intolerable adverse effects or even lead to drug discontinuation. It is now widely believed that the poor efficacy of immunotherapy in driver mutation-positive patients is related to the tumor microenvironment (TME). It is confirmed that CD8 + T cell infiltration was reduce in EGFR + patients with the increasing of tumor mutation burden (TMB), making the tumor "cold" [73]. In addition, tumor-associated macrophages [81], CD4 + T cells [82] and other stromal cells [83] were involved to prevent cytotoxic immune cells from infiltrating and result in poor efficacy. On the other hand, resistance could be overcome if TME was modified by some treatments [84–86]. In our cohort, high PD-L1 levels were related to gene mutation and poorer prognosis, consistent with previous studies [87–91]. Overall, our study provided a piece of evidence for the relationship between gene mutation and PD-L1 levels in resecatble lung adenocarcinoma. Moving forward, research should focus on benefiting patients with gene mutation and high PD-L1 expression by immunotherapy.

Limitations

This was a single-center retrospective cohort study, which was prone to geographical and institutional biases that might affect generalizability. Geographically, our patients mainly came from Hunan Province so the results could only represent the clinicopathological or genetic feature of a single region. Institutionally, single-center studies may be influenced by clinical practices and data quality of our department. Other limitation included lost of follow-up, small sample size and low proportion of certain subgroups (e.g., ALK fusion +). In this article, we compared the results of previous studies and treatment guidelines to mitigate the impact of these limitations. However, stronger conclusions required more rigorous study designs and larger sample sizes.

Conclusion

In our patients, tumors with mucinous, neuroendocrine, and poor-differentiated components were presented to be more invasive, with differing gene mutation status and association with poorer prognosis. For these patients, adjuvant and neoadjuvant therapies should be considered based on gene mutation and immunohistochemistry results, and techniques such as MRD can also be used for postoperative monitoring thereby potentially increasing the cure rate. However, patients with driver gene mutation may not benefit from immunotherapy regardless of high PD-L1 expression. As a result, research into the tumor microenvironment, mutation subtypes and new immunotherapeutic markers may make a difference. Overall, this study provided new analytical perspectives for postoperative pathological components and gene mutation, which need to be confirmed by studies of larger scale and may contribute to the development of precision medicine in the future.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12957-025-03680-x.

Supplementary Material 1. Supplementary Figure 1: Difference of PD-L1 between clinical characteristics. A: smoke, B: sex, C: manifestation on CT, D: N stage, E: stage, F: Group.

Supplementary Material 2. Supplementary Figure 2: Difference of PD-L1 between gene mutations. A: EGFR mutation, B: ALK fusion, C: KRAS mutation.

Supplementary Material 3. Supplementary Figure 3: Mutation subtypes of EGFR and KRAS in all patients. A: subtypes of EGFR mutation, B/C: subtypes of KRAS mutation.

Supplementary Material 4. Supplementary Figure 4: Correlations between mutations. There will be × in the grid if $p<0.05$.

Supplementary Material 5.

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None.

Authors' contributions
Ji'an Zou wrote the main manuscript and participated in all figures and tables. Wei Han, Yan Hu, Chao Zeng, Jina Li has taken part in data analysis and revision of the article. Weixuan Lei, Jieming Cao, Quanming Fei, Mengqi Shao, Junqi Yi, Zeyu Cheng were involved in data curation. Li Wang aquired the funding. Fang Wu revised the whole article. Wenliang Liu has supervised the whole process of the research.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The institutional review board ethics committee of the the Second Xiangya Hospital of Central South University approved the study protocol and publication of data (ethical approval number: LYF2021096). The individuals provided written informed consent for the publication of the study data. Data security and privacy were protected throughout the study.

Competing interests
The authors declare no competing interests.

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