Original Article

Druggable driver gene alterations in redefined large cell carcinoma in Chinese patients: an observational study

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Background: Few reports have investigated the genetic status of large cell carcinoma (LCC) in Chinese patients under the 2015 World Health Organization (WHO) classification. We aimed to analyze the distribution of druggable driver gene alterations, including mutations in epidermal growth factor receptor (*EGFR)*, Kirsten rat sarcoma 2 viral oncogene homolog (*KRAS*), proto-oncogene B-Raf (*BRAF*), and phosphatidylinositol-4,5 biphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) and translocations in echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (*EML4-ALK*) and ROS proto-oncogene 1 (*ROS1*), in a large population of patients with LCC under the 2015 WHO classification, and to assess the clinical outcomes of patients with LCC harboring these genetic alterations.

Methods: A cohort of 322 patients with LCC resected between June 2015 and December 2018 was included in this study. The clinical characteristics of the patients and data on the distribution of *EGFR*, *KRAS*, *BRAF*, *PIK3CA*, *EML4-ALK*, and *ROS1* alterations were retrospectively collected. The disease-free survival (DFS) of patients with LCC was analyzed using the log-rank test.

Results: Among the patients with redefined LCC, the proportion of males was much higher than that of females. Detection of LCC was more frequent in patients >60 years of age (71.4%). Mutations of *EGFR* were found in 3.6% of the LCC participants, predominantly in non-smokers. Mutations in *KRAS* were observed in 7.8% of the LCC patients, mainly in males and smokers. Mutations in *PIK3CA* and *EML4-ALK* translocations comprised 2.1% and 0.52% of the identified alterations, respectively. No alterations were identified in *ROS1* and *BRAF*. After molecular stratification, no significant difference in DFS was identified between wild-type (WT) and mutation groups (29.91±3.83 *vs.* 25.33±6.04 months, P=0.48).

Conclusions: Under the 2015 WHO criteria, LCC was more frequently detected in elderly male patients with inferior prognoses. The frequency of *EGFR* and *KRAS* mutations was found to be the highest. Mutations in *EGFR* occurred more frequently in non-smokers, whereas *KRAS* mutations occurred predominantly in males and smokers. The *PIK3CA* mutations and *EML4-ALK* translocations were rare in patients with LCC. Our data revealed that the identification of clinically actionable molecular alterations in LCC may help guide personalized cancer treatment decisions in the future.

Keywords: Gene alterations; large cell carcinoma (LCC); EGFR mutation; KRAS mutation

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Introduction

Large cell carcinoma (LCC) is the third most common subtype of non-small-cell lung cancer (NSCLC) after lung adenocarcinoma (LUAD) and squamous cell carcinoma (SCC). According to the 2015 World Health Organization (WHO) classification of lung tumors, the diagnosis of LCC has been restricted only to "resected tumors that lack any clear morphologic or immunohistochemical (IHC) differentiation towards LUAD, SCC, or small cell carcinoma" (1).

The updated classification highlights the significance of IHC staining in tumor classification. After IHC analysis, the resected and undifferentiated NSCLCs with immunopositivity for LUAD markers [thyroid transcription factor-1 (TTF-1) or napsin A], or squamous markers (p40, p63, or CK5/6), are now reclassified as solid LUADs or non-keratinizing SCC. Uncommon specific cancer types, such as large cell neuroendocrine carcinoma, basaloid carcinoma, and lymphoepithelioma-like carcinoma, are no longer included in the LCC category. Only those with marker-null phenotype or unclear immunophenotypes are currently classified as LCC (1,2).

Although the updated classification of lung cancer has led to an enormous change in the histological type of LCC, the treatment strategy for LCC remains unchanged. Compared with molecular changes in patients with LUAD, who benefit largely from treatments targeting epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase (*ALK*) translocations, the genomic alterations in redefined LCC have yet to be completely characterized (3,4). Due to the lack of an effective targeted therapy for LCC, chemotherapy remains the first-line treatment for patients with LCC (5,6).

Few reports have investigated the genetic status of LCC in Chinese patients under the 2015 WHO classification. Therefore, in this study we aimed to analyze the distribution of druggable driver gene alterations, including *EGFR*, Kirsten rat sarcoma 2 viral oncogene homolog (*KRAS*), proto-oncogene B-Raf (*BRAF*), and phosphatidylinositol-4,5 biphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) mutations, and echinoderm microtubule-associated protein-like 4 (*EML4*)-*ALK*, and ROS proto-oncogene 1 (*ROS1*) translocations, and their clinical features in a large population of patients with LCC who underwent therapeutic resection. Additionally, we assessed the clinical outcomes of LCC patients with or without gene alterations. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-1675).

Methods

Study design

We conducted a retrospective cohort study by manually reviewing and extracting data from the electronic medical records of patients diagnosed with LCC at the Shanghai Pulmonary Hospital, Affiliated to the Tongji University in China, between June 2015 and December 2018. Patients' clinical characteristics, driver gene mutation status, and disease-free survival (DFS) were determined.

Patient cohort

A consecutive cohort of 322 patients was included in this study. All patients underwent surgical resection at the Shanghai Pulmonary Hospital, Affiliated to the Tongji University in China, between June 2015 and December 2018. All tumors were diagnosed according to the 2015 WHO criteria and staged according to the seventh edition of the tumor-node-metastasis (TNM) system. The study was conducted in accordance with the tenets of the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board at the Shanghai Pulmonary Hospital (FK19-177), and informed consent was provided by all participants.

Driver gene mutation analysis

The amplification-refractory mutation system (ARMS) was used as the molecular diagnostic method in our study. Genomic DNA and total RNA were extracted from five serial slices of a 5-μm paraffin section using the DNA FFPE Tissue Kit and RNeasy Kit (Qiagen, Hilden, Germany). Mutations in *EGFR*, *KRAS*, *BRAF*, and *PIK3CA* genes, as well as *EML4-ALK* and *ROS1* translocations were detected using ACCB Diagnostics Kit (ACCB Biotech Ltd., Beijing, China), according to the manufacturer's protocol (7). The test could detect mutations at a sensitivity of 1% in no less than 5 ng/μL of DNA and RNA samples.

Groupings

Patients with redefined LCC were divided into two groups. The mutation group included all cases with driver

gene mutations identified in the current study, including *EGFR*, *KRAS*, and *PIK3CA* mutations, and *EML4-ALK* translocations. Patients with mutations other than the ones mentioned above were assigned to the wild-type (WT) group.

Clinical data collection

Data regarding participant characteristics at the time of lung cancer diagnosis, including age, sex, smoking history, tumor size and site, pathological TNM stage, and histological type were collected retrospectively. Calculation of DFS was from the date of surgical resection until the date of confirmed recurrence from any cause.

Follow-up

At the time of surgical hospitalization, all patients were asked to provide their personal telephone number and that of a contact person to be used during active follow-up. Patients with redefined LCC were contacted if they had not visited the clinic for 3 months after the date of the last visit. Patients were considered lost to follow-up if they had not visited the clinic for 6 months, and telephone contact was not achieved at least twice on 2 separate days.

Statistical analysis

Statistically significant differences in categorical variables between the groups were analyzed using the chi-squared (χ^2) or Fisher's exact test, as appropriate. The Kaplan-Meier method was used to estimate DFS, and the log-rank test for univariate analysis. The Cox proportional hazards model was used for multivariate analysis. The covariates considered for multivariate analysis were gender, age, TNM stage, tumor size, and smoking status. No missing data were observed in the current study. All tests were two-sided, and a P value <0.05 was defined as statistically significant. Statistical analyses were carried out using SPSS version 20.0 (SPSS Statistics, IBM, Chicago, IL, USA).

Results

Redefinition of LCC by hematoxylin and eosin (HE) staining and IHC analysis

According to the 2015 WHO criteria, negative IHC staining for TTF-1, napsin A, chromogranin A (Chr A), synaptophysin (Syn), p40, p63, and CK5/6 in a resected specimen was defined as LCC. Representative samples with immunopositivity for each marker and typical HE staining of LCCs are shown in *Figure 1*. We included IHC staining of LUAD and lung squamous cell carcinoma (LUSC) tissue sections to serve as positive controls (*Figure 1*). Moreover, HE and IHC staining for 1 case of *KRAS*-mutated LCC was performed (Figure S1) to demonstrate that driver gene alteration positive samples were not LUAD or LUSC specimens.

An overview of clinical features in LCC patients

As presented in *Figure 2*, of 322 patients, 192 were redefined as LCC and included in the analysis. The clinicopathological data are summarized in *Table 1*. The proportion of males was much higher than that of females (94.3% *vs.* 5.7%). Detection of LCC was more frequent in patients >60 years of age (71.4%). Of the 192 cases, 119 (62%) were stage I, 35 (18.2%) were stage II, and 38 (19.8%) were stage III. There was no significant difference in smoking status or tumor size and site.

Driver gene mutation profile in patients with LCC

Mutations were identified in 27 of the 192 cases. As shown in *Table 2*, the common driver gene mutation observed in the cohort included 7 cases (3.6%) of *EGFR* mutations, 1 (0.52%) of *EML4-ALK* translocation, 15 (7.8%) of *KRAS* mutations, and 4 (2.1%) of *PIK3CA* mutations. No alterations were identified in *ROS1* and *BRAF*.

Clinical features of mutated LCC

The distribution and clinical features of the 27 cases harboring driver gene mutations are listed in *Table 3*. Of the 7 cases harboring *EGFR* mutations, including 6 cases of *EGFR* L858R, and 1 of *EGFR* 19-del, 5 were male, and 2 of them had a history of smoking. All the cases in the *EML4-ALK* translocation, *KRAS*, and *PIK3CA* mutations group were male. Of the 15 cases in the *KRAS* mutation group, 9 were smokers. The mutation type observed in the cohort of 15 patients with *KRAS* mutations included *KRAS* G12C (7/15), *KRAS* G12D (5/15), and *KRAS* G12V (3/15). Of the 4 cases in the *PIK3CA* mutation group, only 1 was a smoker. Only 1 case, a current smoker, was identified in the *EML4-ALK* translocation group.

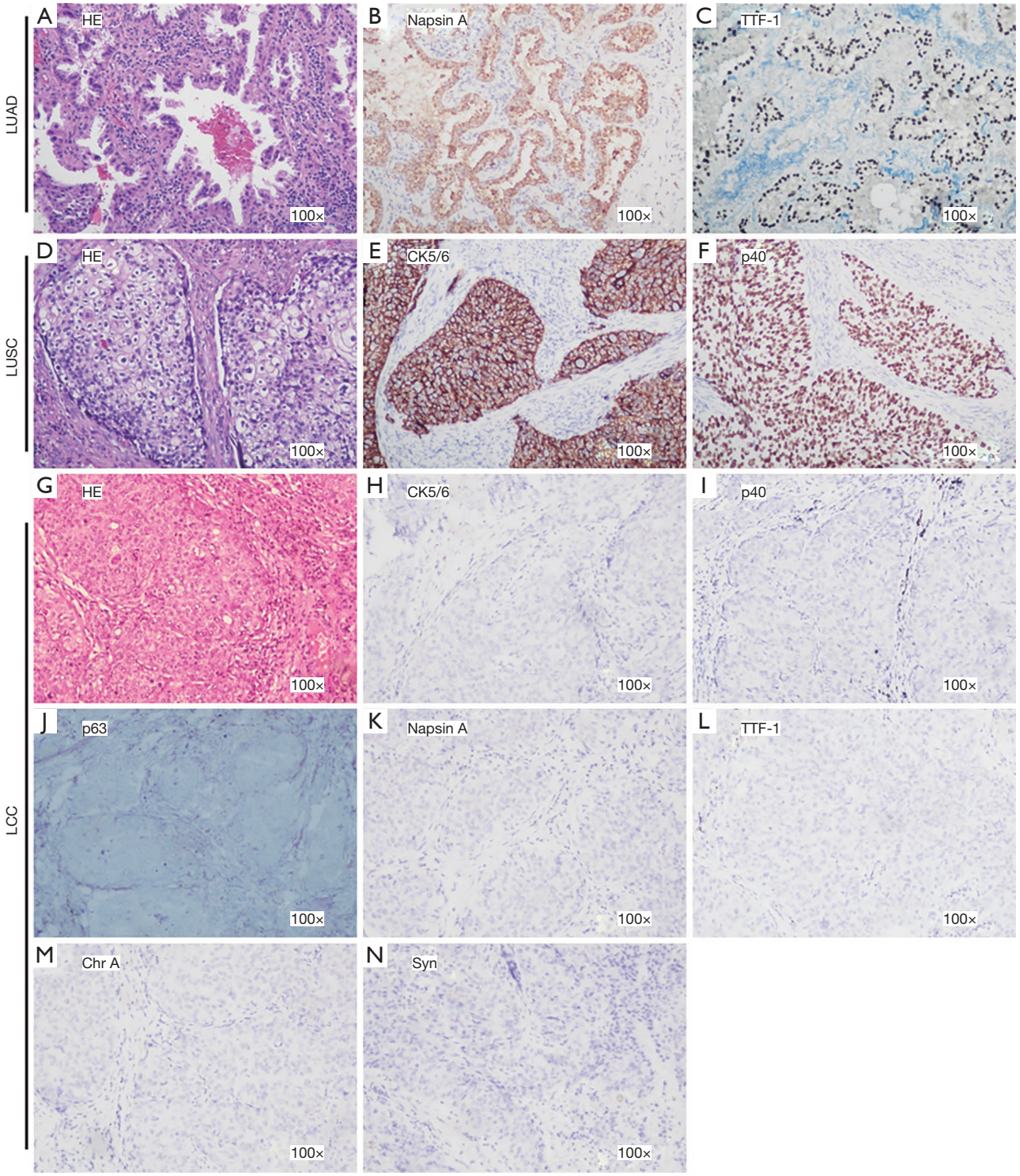

Figure 1 Histological features of large cell carcinoma (LCC). (A,B,C) hematoxylin and eosin (HE) staining and immunohistochemical (IHC) staining features of lung adenocarcinoma (LUAD); (D,E,F) HE and IHC staining features of lung squamous cell carcinoma (LUSC); (G) morphological features of LCC in HE-stained tissue sections; (H,I,J,K,L,M,N) IHC staining for TTF-1, napsin A, chromogranin A (Chr A), synaptophysin (Syn), p40, p63, and CK5/6 (magnification 100×). Under the 2015 WHO criteria, IHC staining-negative phenotypes are classified as LCC.

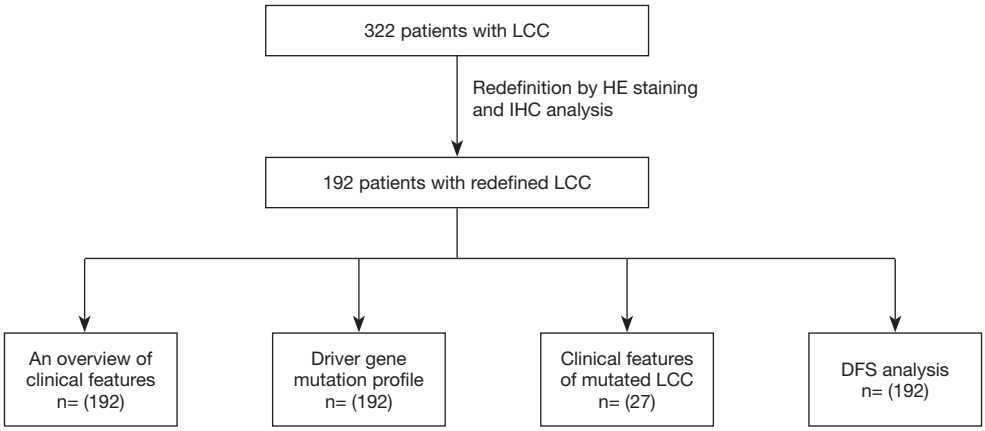

Figure 2 Flowchart illustrating the inclusion of redefined LCC patients and study design. LCC, large cell carcinoma.

Analysis of DFS

We divided all the participants with redefined LCC into two groups. The mutation group included cases with all driver gene mutations identified in the current study, including *EGFR*, *KRAS*, and *PIK3CA* mutations, and *EML4-ALK* translocation. Patients with mutations other than those mentioned above were assigned to the WT group. As shown in *Figure 3*, no significant difference in DFS was identified between these two groups (29.911±3.826 *vs.* 25.333±6.035 months, P=0.476). Since *KRAS* mutation was the most common mutation in LCC, we then examined whether the presence of *KRAS* mutation alone could lead to reduced DFS. Our analysis demonstrated that there was no significant difference in DFS between the *KRAS*-positive patients and non *KRAS*-positive patients (P=0.232).

Discussion

In the present study, the druggable driver gene mutation profiles and clinical outcomes were evaluated in a large cohort of postoperative patients with LCC. Detection of LCC was more frequent in elderly male patients, and the prognosis for all LCC patients was poor. The overall mutation rates of driver genes in LCC, including mutations in *EGFR*, *KRAS*, *EML4-ALK*, and *PIK3CA*, were lower in LCC than in LUAD.

Evaluation of the clinical characteristics of the LCC participants in this study revealed no differences in smoking status or tumor size and site. However, LCC was more frequently detected in males and in patients aged ≥60 years, consistent with the results of a study from another center in China (8). Mutation in *EGFR* occurred more frequently in both male and female non-smokers, whereas *KRAS* mutation occurred solely in males, and more frequently in smokers. *EML4-ALK* translocation and *PIK3CA* mutation were also observed in males, and patients with *PIK3CA* mutation tended to be smokers.

In our study, the incidence of *EGFR* mutation in patients with LCC was 3.6%, which was much lower than that reported in patients with LUAD (9-11). An L858R mutation in exon 21 of the *EGFR* gene is reportedly the most common type of mutation in patients with LUAD (9,10). Consistently, *EGFR* L858R mutations accounted for 85.7% of common *EGFR* mutations in the current report, and remained the dominant *EGFR* mutation in LCC. However, the uncommon *EGFR* mutations reported in LUAD, including 20-ins and T790M, were not observed in LCC (12,13).

Mutations that activate *EGFR*, including exon 19 deletions or exon 21 L858R, exhibit favorable outcomes after treatment with *EGFR*-TKI (3,14,15). In our study, 1 of 7 patients with EGFR-tyrosine kinase inhibitor (TKI)-sensitive *EGFR* mutations received EGFR-TKI (gefitinib) as the first-line treatment (data not shown here). However, the patient showed no response to gefitinib therapy, suggesting that the therapeutic effect of EGFR-TKI might be related to the histological subtype of tumor tissues.

KRAS mutations are the second most frequent oncogenic aberrations in LUAD, with typical mutation rates of around 10% in Asians and up to 30% in Caucasians (11,16). In this study, the rate of *KRAS* mutations was 7.8%, remaining the most frequent in patients with LCC, which is consistent with previous findings (8,17). Despite its prevalence,

Table 1 The clinicopathological characteristics of 192 patients with LCC

Characteristics	N (%)
Sex	
Female	11 (5.7)
Male	181 (94.3)
Age, years	
Mean [range]	64.74 [39–80]
Median	65.5
≤60 (median =56)	55 (28.6)
>60 (median =69)	137 (71.4)
Smoking	
Non-smoker	98 (51.0)
Smoker	94 (49.0)
TNM stage (male/female)	
I (113/6)	119 (62.0)
II (33/2)	35 (18.2)
III A (35/3)	38 (19.8)
TNM stage (non-smoker/smoker)	
I (57/62)	119 (62.0)
II (20/15)	35 (18.2)
III A (21/17)	38 (19.8)
Tumor size	
≤3 cm	92 (47.9)
>3 cm	100 (52.1)
Site	
Left	98 (51.0)
Right	94 (49.0)

The clinical features of 192 patients with LCC are summarized. LCC, large cell carcinoma; TNM, tumor-node-metastasis.

Table 2 Driver gene mutation profile in patients with LCC (n=192)

Genes	N (%)
EGFR	
Wide type	185 (96.4)
Mutation	7 (3.6)
EML4-ALK	
Wide type	191 (99.5)
Mutation	1 (0.5)
KRAS	
Wide type	177 (92.2)
Mutation	15 (7.8)
ROS1	
Wide type	192 (100.0)
Mutation	0
BRAF	
Wide type	192 (100.0)
Mutation	0
PIK3CA	
Wide type	188 (97.9)
Mutation	4 (2.1)

LCC, large cell carcinoma; EGFR, epidermal growth factor receptor; EML4-ALK, translocations in echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase; KRAS, Kirsten rat sarcoma 2 viral oncogene homolog; ROS1, ROS proto-oncogene 1; BRAF, proto-oncogene B-Raf; PIK3CA, phosphatidylinositol-4,5 biphosphate 3-kinase catalytic subunit alpha.

mutant *KRAS* has endured as an intractable therapeutic target, even after decades of extensive effort (18). Recently, pharmacokinetic and pharmacodynamic improvements of direct G12C inhibitors (ARS-1620, AMG 510, and MRTX849) have raised great excitement, and MRTX849 and AMG 510 are currently being tested in first-in-human clinical trials (NCT03785249 and NCT03600883, respectively) (19,20). However, the therapeutic potential of these inhibitors can be impaired by the intrinsic resistance mechanism, suggesting the need for drug combination strategies (21,22). Indeed, CK2 (a catalytic sub-unit encoded by CSNK2A1) was reported as a promising co-target for overcoming MEK/ERK inhibitor resistance in patients with LUAD with *KRAS* (G12C) mutation (23). The combination of ARS-1620 with *PIK3* inhibitors could maximize the response rate and reduce the development of adaptive resistance mechanisms *in vitro* and *in vivo* (21). Nonetheless, as the majority of the data were generated from patients with LUAD, the therapeutic efficacy of these inhibitors in patients with LCC warrants further studies.

Mutations in the *PIK3CA* gene occur less frequently, at about 2–5%, and are prevalent in squamous NSCLC (24,25). In the current study, 4 patients presented the

Table 3 Clinical features of mutated LCC

No.	Mutation type	Sex	Age	Smoking	TNM stage	Tumor size	Site
1	EGFR-L858R	Male	64	Non-smoker	I	<3 cm	Right
2	EGFR-L858R	Male	72	Non-smoker	III	>3 cm	Left
3	EGFR-L858R	Female	70	Non-smoker	I	>3 cm	Left
4	EGFR-L858R	Female	80	Non-smoker	II	>3 cm	Right
5	EGFR-L858R	Male	54	Current smoker	I	<3 cm	Right
6	EGFR-L858R	Male	74	Current smoker	I	<3 cm	Left
7	EGFR-19del	Male	45	Non-smoker	II	>3 cm	Left
8	KRAS-G12C	Male	70	Non-smoker	I	<3 cm	Right
9	KRAS-G12C	Male	63	Current smoker	I	<3 cm	Left
10	KRAS-G12C	Male	72	Non-smoker	I	<3 cm	Left
11	KRAS-G12D	Male	65	Non-smoker	I	<3 cm	Right
12	KRAS-G12C	Male	54	Non-smoker	II	<3 cm	Right
13	KRAS-G12V	Male	52	Current smoker	I	>3 cm	Right
14	KRAS-G12D	Male	57	Non-smoker	I	<3 cm	Right
15	KRAS-G12D	Male	50	Previous smoker	I	<3 cm	Right
16	KRAS-G12C	Male	67	Non-smoker	II	<3 cm	Right
17	KRAS-G12V	Male	75	Current smoker	I	>3 cm	Right
18	KRAS-G12D	Male	69	Current smoker	II	<3 cm	Left
19	KRAS-G12C	Male	72	Current smoker	I	<3 cm	Left
20	KRAS-G12V	Male	63	Current smoker	I	<3 cm	Right
21	KRAS-G12C	Male	71	Current smoker	I	>3 cm	Left
22	KRAS-G12D	Male	62	Current smoker	I	<3 cm	Right
23	ALK-EA2	Male	66	Current smoker	I	>3 cm	Left
24	PI3K-E545K	Male	69	Non-smoker	I	<3 cm	Right
25	PI3K-E454K	Male	56	Non-smoker	II	>3 cm	Left
26	PI3K-E545K	Male	46	Non-smoker	II	>3 cm	Left
27	PI3K-E542K	Male	74	Current smoker	I	<3 cm	Left

The distribution and clinical features of the 27 cases harboring driver gene mutations are listed in this table. LCC, large cell carcinoma; EGFR L858R, an amino acid substitution of the leucine at position 858 by an arginine at exon 21 in EGFR; EGFR-19del, EGFR exon 19 deletion; KRAS-G12C, a single point mutation with a glycine-to-cysteine substitution at exon 12 in KRAS; KRAS-G12V, a single point mutation with a glycine-to-valine substitution at exon 12 in KRAS; KRAS-G12D, a single point mutation with a glycine-to-aspartic acid substitution at exon 12 in KRAS; ALK-EA2, EML4-ALK translocations exhibiting fusions between exon 20 of EML4 and exon 20 of ALK; PI3K-E454K, a single amino-acid substitution at glutamine 454 to lysine in the activating segment of PI3K; PI3K-E545K, a single amino-acid substitution at glutamine 545 to lysine in the activating segment of PI3K; PI3K-E542K, a single amino-acid substitution at glutamine 542 to lysine in the activating segment of PI3K.

PIK3CA mutation at a rate of 2.1%, similar to that in squamous NSCLC. The *PIK3CA* mutation has been reported to occur in parallel with other oncogenic driver mutations, and it has also been discovered in *EGFR*-mutant NSCLCs that have developed acquired resistance to EGFR-TKIs, possibly representing escape mechanisms

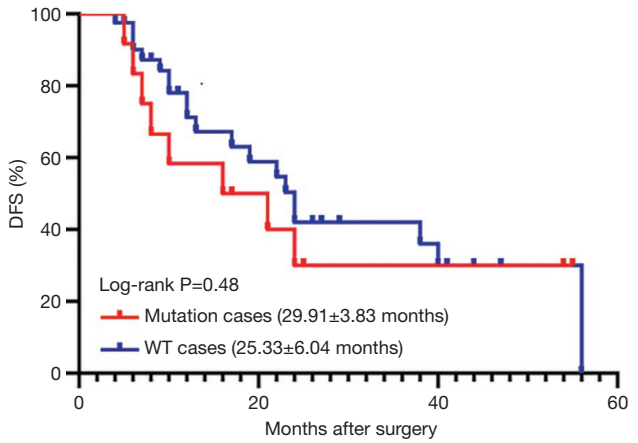

Figure 3 Kaplan-Meier curves of disease-free survival (DFS) according to mutation status in patients with LCC. The P value for the difference between the two curves was determined by log-rank test. LCC, large cell carcinoma.

from the TKI inhibition (26-28). Several small molecules targeting *PIK3CA* have been evaluated in multiple clinical trials, either in monotherapy or in combination strategy. Data from these clinical trials demonstrated that single-agent PI3K inhibitors offer limited, if any, activity, while combination with other targeted agents and/or cytotoxic chemotherapy may prove to be more efficacious (28).

In our study, *EML4-ALK* translocation was detected in 1 patient with LCC. Although targeting *EML4-ALK* translocation with ALK inhibitors has become the cornerstone of managing advanced non-squamous NSCLC harboring *EML4-ALK* translocation, the relevance of ALK inhibitors in LCC is poorly defined (4).

In terms of prognosis, the median DFS observed in our study was 29.911 and 25.333 months in WT and mutation groups, respectively. These DFS periods were much shorter than those observed in lung SCC at the same center, which were 45.9 and 49.5 months in *EGFR*-positive and *EGFR*-negative patients, respectively (29).

This study had several limitations. First, despite the inclusion of large-scale data compared with those of previous studies, our results were produced from patients admitted at a single institution, which can lead to a participant selection bias. Second, due to the relatively low frequency of *EGFR* mutations in LCC and limited number of patients who accepted the EGFR-TKI therapy, we could not draw definite conclusions concerning the efficacy of EGFR-TKIs in LCC patients harboring *EGFR* mutations.

Overall, LCC was more frequently detected in elderly male patients with inferior prognoses under the 2015 WHO criteria. The most frequent gene mutations observed in LCC were those of *EGFR* and *KRAS*. Activating *EGFR* mutation occurred more frequently in non-smokers of both genders, whereas *KRAS* mutation occurred solely in males and more frequently in smokers. The *PIK3CA* mutations and *EML4-ALK* translocations were rare in patients with LCC. Our data revealed that the identification of clinically actionable molecular alterations in LCC could help in the research and development of targeted drugs for treating LCC, and may guide personalized cancer treatment decisions in the future.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/tcr-20-1675

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-20-1675). The authors have no conflicts of interest to declare.

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. The study was conducted in accordance with the tenets of the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board at the Shanghai Pulmonary Hospital (FK19-177), and informed consent was provided by all participants.

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