Clinical characteristics and prognostic value of the KRAS G12C mutation in Chinese non-small cell lung cancer patients

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Abstract

Background: The KRAS mutation is the second most common genetic variant in Chinese non-small cell lung cancer (NSCLC) patients. At the 2019th World Conference of Lung Cancer, the KRAS G12C-specific inhibitor AMG510 showed promising results in the phase I clinical trial. However, the frequency, clinical characteristics, and prognostic significance of the KRAS G12C mutation in Chinese NSCLC patients are rarely reported.

Methods: Next-generation sequencing was used to confirm the KRAS mutation status in 40,804 NSCLC patients from multiple centers (mCohort). Survival data were collected retrospectively from 1456 patients at one of the centers, the Guangdong Lung Cancer Institute (iCohort).

Results: In the mCohort, 3998 patients (9.8%) were confirmed to harbor a KRAS mutation, of whom 1179 (29.5%) had the G12C subtype. In the iCohort, 130 NSCLC patients (8.9%) had a KRAS mutation and 42 (32.3%) had the G12C subtype. The G12C subgroup included more male patients (85.2% vs 67.4%, \( P < 0.0001 \)) and more smokers (76.2% vs 53.4%, \( P = 0.02 \)) than did the non-G12C subgroup. Both the KRAS mutation group and KRAS G12C mutation subgroup were associated with a shorter median overall survival (OS) than wildtype tumors (15.1 vs 26.7 months, hazard ratio [HR] \( _{KRAS} = 1.50, P = 0.002 \); 18.3 vs 26.7 months, HR \( _{G12C} = 1.66, P = 0.007 \)). In Cox regression analysis, smoking (HR = 1.39, \( P = 0.05 \)) and stage IV disease (HR = 2.72, \( P < 0.001 \)) remained as independent predictors of shorter OS. Both the KRAS mutation (HR = 1.30, \( P = 0.07 \)) and KRAS G12C mutation (HR = 1.47, \( P = 0.07 \)) reached borderline significance.

Conclusions: In the largest sample used thus far, our study found that approximately 10% of Chinese NSCLC patients had KRAS mutations. Of these, nearly 30% harbored the KRAS G12C mutation subtype, which was most common in male smokers. The KRAS G12C mutation is a biomarker of poor prognosis in Chinese NSCLC patients, which could potentially be improved by G12C-specific inhibitors in the future.

Keywords: KRAS mutation, KRAS G12C mutation, Prognosis, Non-small cell lung cancer, Chinese patients

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Background

Rapid developments have been achieved in the area of epidermal growth factor-receptor tyrosine kinase inhibitors (EGFR-TKIs) and immunotherapy with checkpoint inhibitors for lung cancer patients [1–5]. Although treatment resistance is inevitable, advances of third-generation EGFR-TKIs prolong the survival of patients with EGFR mutations. The KRAS mutation is the second most common genetic variant in Chinese non-small cell lung cancer (NSCLC) patients [6]. Many retrospective and prospective studies have attempted to treat KRAS mutation patients with EGFR-TKIs [7] and MAP-ERK kinase (MEK) inhibitors [8, 9], but none were successful. No targeted therapy for lung cancer patients [10–12]. In addition to immunotherapy with checkpoint inhibitors, KRAS G12C-specific inhibitors show promising preclinical and clinical results [13]. The World Conference of Lung Cancer in 2019 presented promising and up-to-date clinical data on the drug AMG510, which was given to 13 patients with non-small cell lung cancer (NSCLC) at a dose of 960 mg once per day. Seven patients achieved partial response and six achieved stable disease. The objective response rate was 54% and the disease control rate was 100%. Additionally, a series of clinical trials targeting KRAS G12C mutations with G12C-specific inhibitors, including RMC-4630 and MRTX849 are ongoing [14, 15].

It was reported that 30% of Caucasian NSCLC patients harbored KRAS mutations, of which 35 ~ 45% were of the G12C subtype [16, 17]. Therefore, the incidence of KRAS G12C mutations in NSCLC in those Caucasian patients was nearly 12%. In Asians, however, the frequency of KRAS G12C mutations has rarely been studied. In the mCohort, 3998 NSCLC patients had KRAS mutations; 25 patients had two KRAS mutation subtypes, and the frequency of KRAS mutations was 9.8%. Of the patients with KRAS mutations, 1179 (29.5%) were confirmed to harbor G12C mutations (Fig. 1a). The proportions of the other three major KRAS codon 12 subtypes were as follows: G12V, 18.3% (N = 731); G12D, 17.3% (N = 693); and G12A, 8.4% (N = 334) (Fig. 2).

In the iCohort, 130 of 1456 NSCLC patients (8.9%) were confirmed to have KRAS mutations, of whom 42 (32.3%) harbored G12C mutations; there were 304 wild-type patients (excluding EGFR mutation, ALK fusion, ROS1 fusion and BRAF mutation) (Fig. 1b). The distribution of KRAS mutation subtypes was comparable to that in the mCohort. For the other three major codon 12 subtypes, the proportions were as follows: G12D, 19.2% (N = 25); G12V, 13.1% (N = 17); and G12A, 6.9% (N = 9) (Fig. 2).

Methods

Patients

From January 2016 to September 2019, the NGS results from 40,804 NSCLC patients from multiple centers (mCohort) were analyzed; of these patients, 3998 had KRAS mutations. In total, 1776 patients with KRAS mutations had NGS results analyzed from tumor tissue, 1646 from tumor tissue and liquid biopsy, and 576 from liquid biopsy alone (e.g., peripheral blood, pleural effusion and cerebrospinal fluid). Clinical data of these patients were pooled retrospectively and the factors included in the analysis were age, sex, pathology, and clinical stage at the time of diagnosis. Smoking history and survival data of 1456 NSCLC patients from one of the centers, the Guangdong Lung Cancer Institute (iCohort), were collected retrospectively from the electronic medical records.

Analysis

The chi-square test was used to compare categorical data. Overall survival (OS) was measured from the date of pathological diagnosis of lung cancer to the date of death or last follow-up, with a cut-off date of September 2019. Kaplan-Meier survival curves were generated to estimate OS in different genomic groups. The univariate and multivariate Cox proportional hazards model was used to evaluate the prognostic value of KRAS and KRAS G12C mutations on OS. Statistical significance was defined as a p-value less than 0.05.

Results

Frequency of KRAS G12C mutations in Chinese NSCLC patients

In the mCohort, 3998 NSCLC patients had KRAS mutations; 25 patients had two KRAS mutation subtypes, and the frequency of KRAS mutations was 9.8%. Of the patients with KRAS mutations, 1179 (29.5%) were confirmed to harbor G12C mutations (Fig. 1a). The proportions of the other three major KRAS codon 12 subtypes were as follows: G12V, 18.3% (N = 731); G12D, 17.3% (N = 693); and G12A, 8.4% (N = 334) (Fig. 2).

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Clinical characteristics of patients with the KRAS G12C mutation

The clinical and pathological characteristics of NSCLC patients with KRAS G12C and non-G12C KRAS mutations were compared in the mCohort (Table 1). The mean ages of the G12C and non-G12C subtype patients were 63 and 62 years old, respectively (P = 0.02). The proportion of male patients was higher in the G12C subgroup than that in the non-G12C subgroup (85.2% vs 67.4%, P < 0.0001). Most of the G12C and non-G12C subtype patients were diagnosed with adenocarcinoma (rates were more than 90% in both groups). Nearly 40% of the patients were diagnosed with stage IV disease in the G12C and non-
G12C subgroups. In the iCohort, the clinical and pathological characteristics of the patients with G12C and non-G12C mutations were comparable to those in the mCohort. Of note, in the iCohort, 76.2% of the patients in the G12C subgroup were former or current smokers, compared with 53.4% of those in the non-G12C subgroup ($P = 0.02$).

The clinical characteristics of KRAS mutation and wildtype tumors were also compared in the iCohort. In the KRAS mutation and wildtype subgroups, 79.2 and 71.7% of the patients were male ($P = 0.10$), respectively, with median ages of 63 and 61 years ($P = 0.01$); 60.8 and 53.3% were former or current smokers ($P = 0.15$), respectively. Most patients in both the KRAS mutation and wildtype subgroups had adenocarcinoma and stage IV disease.

**Prognostic value of the KRAS G12C mutation**

Survival data were collected retrospectively for 130 KRAS mutation and 304 wildtype patients from the iCohort. In the Kaplan-Meier analysis, regardless of the KRAS mutation group or the KRAS G12C mutation subgroup, both were associated with a shorter median OS compared with wildtype tumors (15.1 vs 26.7 months, Hazard Ratio [HR]$_{KRAS} = 1.50$, $P = 0.002$; 18.3 vs 26.7 months, HR$_{G12C} = 1.66$, $P = 0.007$) (Fig. 3a, b).

To identify the prognostic values of the KRAS and KRAS G12C mutations on OS, clinical and molecular variables were included in Cox regression analysis. In the univariate analysis, age, male, smoker, stage IV disease, KRAS mutation, and KRAS G12C and non-G12C mutations were identified as independent factors for shorter OS (Table 2). In the multivariate Cox model, smoker (HR = 1.39, $P = 0.05$) and stage IV disease (HR = 2.72, $P < 0.0001$) remained as independent factors for poor prognosis. Both the KRAS mutation (HR = 1.47, $P = 0.07$) and the KRAS G12C mutation (HR = 1.23, $P = 0.07$) were borderline statistically significant.
Discussion

The frequency of KRAS mutations is much higher in Caucasian NSCLC patients, at around 30%, than in Asian patients [18]. In our study, 9.8% of the patients in the mCohort harbored KRAS mutations, similar to the rates reported by Zhou’s group [19]. EGFR and KRAS mutations are mutually exclusive, and Asian patients with NSCLC tend to have more EGFR mutations and thus fewer KRAS mutations [20]. The frequency of KRAS G12C mutations in Caucasians ranges from 35 to 45%.

### Table 1 Clinical and pathological characteristics of KRAS G12C and non-G12C mutations from the mCohort

|                      | KRAS G12C (N = 1179) | Non-G12C (N = 2819) | P-value |
|----------------------|----------------------|---------------------|---------|
| Age, mean (range)    | 63 (31–91)           | 62 (14–90)          | 0.02    |
| Sex, n (%)           |                      |                     |         |
| Male                 | 1005 (85.2%)         | 1809 (67.4%)        | ***     |
| Female               | 162 (13.7%)          | 875 (31.0%)         |         |
| NA                   | 12 (1.0%)            | 45 (1.6%)           |         |
| Pathology, n (%)     |                      |                     |         |
| Adenocarcinoma       | 1107 (93.9%)         | 2584 (91.7%)        | #       |
| Squamous carcinoma   | 23 (2.0%)            | 154 (5.5%)          |         |
| Adeno-squamous carcinoma | 9 (0.8%)         | 18 (0.6%)           |         |
| LCLC                 | 3 (0.3%)             | 13 (0.5%)           |         |
| others               | 37 (3.1%)            | 50 (1.8%)           |         |
| Stage, n (%)         |                      |                     |         |
| I                    | 37 (3.1%)            | 85 (3.0%)           | 0.24    |
| II                   | 38 (3.2%)            | 86 (3.1%)           |         |
| III                  | 125 (10.6%)          | 235 (8.3%)          |         |
| IV                   | 447 (37.9%)          | 1082 (38.4%)        |         |
| NA                   | 532 (45.1%)          | 1331 (47.2%)        |         |

# could not be computed, mCohort lung cancer patients from multiple centers, iCohort lung cancer patients from Guangdong Lung Cancer Institute, NA not available, LCLC large-cell lung cancer

![Fig. 3](image-url) 

**Fig. 3** Survival analysis of NSCLC patients with KRAS and KRAS G12C mutations. Overall survival (OS) analysis of KRAS mutation and wildtype tumors **a**. OS analysis of KRAS G12C mutation and wildtype tumors **b**. m: months; wt: wild type; HR: hazard ratio; CI: confidence interval.
In our study, 29.5% of KRAS mutations in the mCohort were of the G12C subtype, which means that nearly 3% of these Chinese NSCLC patients harbored KRAS G12C mutations. In Caucasians, KRAS mutations are more common in females and smokers [21–23]. Moreover, Dogan et al. and Osta et al. reported that G12C mutations were more common in women and those with a smoking history [17, 24]. By contrast, we found that male smokers more commonly harbored KRAS mutations, including G12C mutations, which is consistent with Guan et al. [25]. Although only a small proportion of KRAS mutation patients enrolled in the mCohort were diagnosed with stage I or II disease, KRAS mutation seems to be an early event that might drive lung cancer development [18, 21, 22, 25]. Furthermore, the KRAS G12C mutation might be a drug target in early stage lung cancer.

The prognostic role of KRAS mutations in NSCLC patients in early and advanced stages is becoming clear. Two studies enrolled surgically resected lung adenocarcinoma patients and found that those with KRAS mutation tumors had worse disease free survival and OS compared with wildtype patients [21, 22]. Even after excluding EGFR mutations, a significant survival difference persisted. A poor prognosis of KRAS mutation patients in advanced lung cancer stages has also been reported [17, 26]. Guan et al., from our institute, enrolled stage I to IV lung cancer patients. To eliminate bias of disease stage, patients were randomly paired, and KRAS mutations still predicted a poor prognosis [25]. Our results are consistent with the available data indicating a shorter OS for KRAS mutations, compared to wildtype tumors. However, the prognostic role of KRAS G12C mutations has been rarely reported. Nadal et al. showed that the KRAS G12C mutation was associated with poor outcomes in surgically resected lung adenocarcinoma and remained an independent prognostic marker for OS in multivariate analysis [22]. Svaton et al. indicated that patients with G12C mutations had shorter median OS compared to non-G12C KRAS mutation and wildtype patients (6.4 vs 10.3 vs 16.1 months, \( P = 0.01 \)) [26]. In our study, more than 80% of the NSCLC patients exhibited advanced disease. The median OS of the G12C mutation and wildtype patients was 18.3 and 26.7 months, respectively (HR = 1.66, \( P = 0.007 \)). The prognostic value of the G12C mutation was identified in Cox

| Table 2 Univariate and multivariate analysis of overall survival based on clinical and molecular variables |
|-----------------------------------------------|
| Variable                      | Univariate analysis | Multivariate analysis |
|-----------------------------------------------|---------------------|----------------------|
|                               | Crude HR | 95%CI       | P       | Adjusted HR | 95%CI       | P       |
| Age                            | 1.02     | 1.00–1.03   | 0.02   | 1.01        | 1.00–1.03   | 0.07    |
| Sex                            |          |             |        |             |             |         |
| Female                         | 1        |             |        | 1           |             |         |
| Male                           | 1.41     | 1.05–1.90   | 0.02   | 1.08        | 0.74–1.58   | 0.71    |
| Ever Smoking                   |          |             |        |             |             |         |
| Non-smoker                     | 1        |             |        | 1           |             |         |
| Smoker                         | 1.46     | 1.13–1.90   | 0.004  | 1.39        | 1.00–1.94   | 0.05    |
| Pathology                      |          |             |        |             |             |         |
| Adenocarcinoma                 | 1        |             |        | 1           |             |         |
| Squamous carcinoma             | 1.16     | 0.71–1.88   | 0.55   |             |             |         |
| others                         | 1.14     | 0.64–2.06   | 0.65   |             |             |         |
| Stage                          |          |             |        |             |             |         |
| I–II                           | 1        |             |        | 1           |             |         |
| III                            | 1.55     | 0.88–2.74   | 0.13   | 1.58        | 0.89–2.81   | 0.12    |
| IV                             | 2.68     | 1.60–4.47   | ***    | 2.72        | 1.62–4.56   | ***     |
| KRAS mutation                  |          |             |        |             |             |         |
| Wildtype                       | 1        |             |        | 1           |             |         |
| Mutation                       | 1.51     | 1.16–1.98   | 0.003  | 1.30        | 0.98–1.72   | 0.07    |
| KRAS mutation subtype          |          |             |        |             |             |         |
| Wild-type                      | 1        |             |        | 1           |             |         |
| G12C mutation                  | 1.65     | 1.10–2.47   | 0.02   | 1.47        | 0.97–2.23   | 0.07    |
| Non-G12C mutation              | 1.45     | 1.06–1.98   | 0.02   | 1.23        | 0.90–1.69   | 0.20    |

NSCLC non-small cell lung cancer, HR hazard ratio
regression analysis. Although the P-value reached statistical margin, this may have been due to the small sample size of KRAS mutation patients in the iCohort. Patients with KRAS mutations could receive chemotherapy as standard treatment; some could choose immunotherapy with anti-PD-1/PD-L1 blockade. No other choices were available for clinicians to prescribe for these patients. Thus, detailed information regarding the treatment is not presented in Table 2. In general, the KRAS G12C mutation was a prognostic biomarker for poor OS in Chinese NSCLC patients.

Our study included the largest sample size of NSCLC patients harboring KRAS mutations thus far. However, it had a few limitations. First, we only had clinical and pathological data for the NSCLC patients from multiple centers and lacked survival data. Thus, the prognostic role of the KRAS G12C mutation in poor OS were taken from only one of the centers, namely, the iCohort. Second, in the iCohort, there were more stage IV patients in the KRAS mutation subgroup than in the wildtype subgroup, which may have affected the results where KRAS mutations were associated with a poor prognosis (P = 0.01). However, this result has been repeated in previously published studies. Similarly, although more patients had stage IV disease in the G12C subgroup than in the wildtype subgroup, the difference in their distribution did not reach statistical significance (P = 0.10). Thus, results regarding the prognostic roles of KRAS mutations and G12C mutation were reliable. Third, racial differences in the KRAS G12C mutation should be explored further in future studies.

Conclusion
In general, our study identified that approximately 9% of Chinese NSCLC patients had KRAS mutations. Of these, nearly 30% harbored the KRAS G12C mutation subtype, which often occurred in male smokers. The KRAS G12C mutation predicted a poor OS, which could potentially be improved by specific G12C inhibitors in the future.

Abbreviations
CI: Confidence interval; EGFR-TKIs: Epidermal growth factor-receptor tyrosine kinase inhibitors; HR: Hazard ratio; LCLC: Large cell lung cancer; MEK: MAPERK kinase; NGS: Next-generation sequencing; NSCLC: Non-small cell lung cancer; OS: Overall survival

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Authors’ contributions
Conception and design of the study: Prof. Yi-Long Wu. Acquisition of clinical data: Dr. Si-Yang Liu, Dr. Jia-Ying Zhou, Dr. Guang-Ling Jie and Dr. Hao Sun. Analysis and interpretation of the data: Dr. Si-Yang Liu, Mr. Yang Shao, Mr. Xian Zhang, Mr. Jun-Yi Ye and Miss. Chun-Xiang Chen. Manuscript drafting and revision: Dr. Si-Yang Liu and Prof. Yi-Long Wu. Final approval of the manuscript: All authors.

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Availability of data and materials
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The procedures in this study were approved by the Research Ethics Committee of Guangdong Provincial People’s Hospital (2013185H). All patients provided written informed consent for the use of their NGS results.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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