Original Article

The impact of *EGFR* exon 19 deletion subtypes on clinical outcomes in non-small cell lung cancer

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Background: The study investigated the resistant pattern and clinical outcomes of epidermal growth factor receptor (*EGFR*) exon 19 deletion (19del) subtypes to tyrosine kinase inhibitors (TKIs) in non-small cell lung cancer (NSCLC).

Methods: Two hundred eight treatment naive NSCLC patients detected as *EGFR* 19del using amplification-refractory mutation system (ARMS) were included. DNA sequencing was used to detect the subtypes. Clinicopathological features as well as patients' outcomes treated with first-line EGFR-TKIs were analyzed.

Results: Thirteen *EGFR* 19del subtypes were confirmed in 181 samples (87.0%). Among these, delE746_A750 was the most frequent subtype (130/181, 71.8%). delE746_A750 and deletions starting from E746 were frequently found in female (P=0.003 and P=0.013, respectively) and never smokers (P=0.002 and P=0.014, respectively) than non-delE746_A750 and deletions starting from L747 patients, respectively. T790M was more frequently occurred in delE746_A750 than non-delE746_A750 (P=0.001) and deletions starting from E746 than L747 patients (P=0.006) after first-line EGFR-TKIs resistance. Patients harboring deletions starting from L747 with insertions had significantly shorter progression-free survival (PFS) than deletions starting from L747 without insertion (8.3 *vs.* 15.0 m, P=0.017), or all other patients (8.3 *vs.* 12.6 m, P=0.027). Different 19del subtypes with T790M mutation had similar PFS when treated with osimertinib (P=0.102).

Conclusions: Patients with *EGFR* 19del subtypes had different clinicopathological features, and resistant pattern when treated with first-line TKIs. Patients harboring deletions starting from L747 with insertions had inferior outcomes than other subtypes.

Keywords: Epidermal growth factor receptor (EGFR); exon 19 deletion (19del); non-small cell lung cancer (NSCLC)

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Introduction

Targeted therapy for epidermal growth factor receptor (*EGFR*) mutation in non-small cell lung cancer (NSCLC) developed quickly (1-5). *EGFR* exon 19 deletion (19del) was about 44% in *EGFR* mutations, and the most frequent subtype was delE756_A750, followed by delL747_P753insS, delL747_A750insP or delL747_T751 (6,7). Studies reported that the 19del subtypes could have different survival outcomes to EGFR-tyrosine kinase inhibitors (EGFR-TKIs) (8-13). Chung *et al.* found that response rate (RR) was significantly different between non-LRE (codons L747 to E749) deletions and other deletions (8), while others (10,12) did not find significant differences between the subtypes. Lee *et al.*, Kaneda *et al.* and Sutiman *et al.* found that there were significant differences in progression-free survival (PFS) or overall survival (OS) between different *EGFR* 19del subtypes (9-11), however, it was not found in other studies (8,12,13). Truini *et al.* also found that a deletion subtype starting from L747 with insertion (delL747_A750insP) had different sensitivities to different EGFR-TKIs (14). So, the association is still fuzziness and worth further study between 19del subtypes and patient clinical outcomes.

EGFR T790M mutation occurred in about 60% when were resistant to first generation EGFR-TKIs (15,16). Studies reported that the incidence was higher in *EGFR* 19del than L858R patients (17,18). Besides, T790M might also distribute differently between *EGFR* 19del subtypes when patients are resistant to EGFR-TKIs (19). Osimertinib was efficient for T790M mutation patients. Whether it had different efficacy on the patients harboring T790M mutation in different *EGFR* 19del subtypes also needed to be studied. In the retrospective study, we explored the clinical characteristics and outcomes of patients harboring different *EGFR* 19del subtypes treated with first-line EGFR-TKIs, in order to better understand the impact of mutation subtypes to patients' outcomes. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tlcr-19-359).

Methods

Patients

From April 2016 to August 2017, stage IIIB/IV Chinese NSCLC patients at diagnosis had *EGFR/KRAS/BRAF/ALK/ROS1* gene mutation detection. All patients provided written informed consent before molecular detection. Among these, 208 patients harboring only *EGFR* 19del conducted DNA sequencing to detect the subtypes. Patients using gefitinib, erlotinib, icotinib, or afatinib as first-line treatment was conducted for subsequent analysis. Osimertinib used for patients harboring *EGFR* T790M was analyzed in this study. Clinical outcomes were followed up until April 2019. This study was approved by the Ethics Committee of Shanghai Pulmonary Hospital (K19-066Y).

Gene mutation detection

Formalin-fixed paraffin-embedded (FFPE), fine/core needle aspiration, biopsy, or pleural effusion samples were used for the detection of alterations in the five genes. The detection using amplification-refractory mutation system (ARMS) was conducted as we had reported in previous studies (20,21). *EGFR* mutation was detected by *EGFR* 29 Mutations Detection Kit (Amoy Diagnostics, Xiamen, China) as the protocol described, which covered 25 19del subtypes (*Table S1*). After patients were resistant to EGFR-TKIs, peripheral blood, fine/core needle aspiration, biopsy, or pleural effusion samples were used to detect *EGFR* T790M mutation using *EGFR* 29 Mutations Detection Kit.

Statistical analysis

All statistical analyses were performed using the SPSS v.20 software (SPSS Inc., Chicago, IL, USA). Clinicopathological features were evaluated by Pearson Chi-square or Fisher's exact test. Kaplan-Meier method and cox-regression were used for survival analysis. The two-sided significance level was set at $P<0.05$.

Results

EGFR 19del subtypes

Of the 208 patients, 13 *EGFR* 19del subtypes were confirmed in 181 patients (*Table 1*). Deletions starting from E746 occurred in 143 patients (79.0%), and starting from L747 occurred in 38 patients (21.0%). delE746_A750 was found in 130 patients (71.8%); deletion starting from E746 with insertions were found in 13 (7.2%) patients. Deletions starting from L747 without insertion were found in 16 patients (8.8%), and with insertions were found in 22 (12.2%) patients.

Table 1 *EGFR* exon 19del subtypes in NSCLC patients

No.	Subtypes	N (%) (total =181)
1	delE746_A750	130 (71.8)
2	delE746_T751insA	3 (1.7)
3	delE746_T751insI	1 (0.6)
4	delE746_S752insI	1 (0.6)
5	delE746_S752insV	8 (4.4)
6	delL747_E749	1 (0.6)
7	delL747_A750insP	7 (3.9)
8	delL747_T751insP	2 (1.1)
9	delL747_S752	1 (0.6)
10	delL747_P753insQ	1 (0.6)
11	delL747_T751	14 (7.7)
12	delL747_P753insS	11 (6.1)
13	delL747_A755insSRD	1 (0.6)

EGFR, epidermal growth factor receptor; 19del, exon 19 deletion; NSCLC, non-small cell lung cancer.

Clinicopathological features of EGFR 19del subtypes

Since deletions starting from E746 and L747 were two major kind of subtypes, and delE746_A750 was the most frequent subtype, we analyzed the clinicopathological features of the patients according to the two classifications (*Table 2*). delE746_A750 and deletions starting from E746 were frequently found in female (P=0.003 and P=0.013, respectively) and never smoking patients (P=0.002 and P=0.014, respectively). ARMS was used to detected T790M mutation after patients were resistant to first-line EGFR-TKIs. Interestingly, we found that the ratio of T790M was higher in patients harboring delE746_A750 or deletions starting from E746 (P=0.001 and P=0.006, respectively, *Table 2*). Further, we wanted to explore whether there was sample bias in T790M detecting, and found that there was no significant differences in both classifications (*Table 2*).

Clinical outcomes of EGFR 19del patients

For the patients receiving EGFR-TKIs as first-line treatment, the objective response rate (ORR) was 85.4% (70/82) in delE746_A750 patients and 86.4% (76/88) in patients with deletions starting from E746 (*Table 2*). According to the starting codon with or without insertions, we divided *EGFR* 19del patients into four groups, and found no significant difference between them in PFS (*Figure 1A*). There was no significant difference between patients with delE746_A750 and other deletions in PFS (12.1 *vs.* 10.6 months, P=0.738, *Figure 1B*), no significant difference between patients with deletions starting from E746 and L747 in PFS (12.1 *vs.* 10.6 months, P=0.816, *Figure 1C*), and also no statistical difference between patients with or without insertions (9.5 *vs.* 12.6 months, P=0.102, *Figure 1D*). There was no significant difference between deletions starting from E746 with insertion and without insertions (*Figure 1E*). On the contrary, for patients with deletions starting from L747, those with insertions had statistical shorter PFS then those without (8.3 *vs.* 15.0 months, P=0.017, *Figure 1F*). And, patients with deletions starting from L747 with insertions had shorter PFS than all other patients (8.3 *vs.* 12.6 months, P=0.027, *Figure 1G*). Multivariate analysis showed that *EGFR* 19del subtypes had a marginal effect on PFS (P=0.051, *Table 3*). Totally, there were only 24 patients got OS data: 20 with delE746_A750, one with delL747_T751, one with del747_P753insQ, and two with delE746_S752insV. Five of the 20 (25.0%) patients harboring delE746_A750 had osimertinib treating history, and 2 of the 4 (50.0%) other patients had osimertinib treating history. Patients harboring delE746_A750 had significantly shorter OS than other patients (P=0.022, 16.7 *vs.* 28.0 months, *Figure 1H*).

Impact of different EGFR-TKIs to EGFR 19del patients

As patients with *EGFR* 19del could use different EGFR-TKIs for first-line treatment, we examined whether there were different clinical outcomes treated with different drugs. The ORR was 83.9% for gefitinib, 81.8% for erlotinib, 79.4% for icotinib and 100% for afatinib (P=0.784, *Table S2*). As there was only one patient treated with afatinib got PFS data, we did not include this patient in the following analysis. For all the other patients, there was no significant difference between different regimens in PFS (11.7 months for gefitinib *vs.* 8.5 months for erlotinib *vs.* 12.3 months for icotinib, P=0.123, *Figure 2A*). In patients with del746_A750, deletions starting from E746 with insertion, deletions starting from L747 with or without insertion, there were no significant differences between different drugs (P=0.061, P=0.156, P=0.701, and P=0.487, respectively, *Figure 2B,C,D,E*). We also investigated whether there was different resistant pattern (T790M) using different drugs, and found no significant difference (52.4% in gefitinib, 57.1% in erlotinib, and 61.5% in icotinib, P=0.837, *Table S3*). Further,

Table 2 Clinicopathological features of EGFR 19del variants

Items	delE746_A750, n (%)	Others, n (%)	P value	Deletion starting from E746, n (%)	Deletion starting from L747, n (%)	P value
Sex			0.003			0.013
Female	80 (61.5)	19 (37.3)		85 (59.4)	14 (36.8)	
Male	50 (38.5)	32 (62.7)		58 (40.6)	24 (63.2)	
Age			0.470			0.360
<60	79 (60.8)	28 (54.9)		87 (60.8)	20 (52.6)	
≥60	51 (39.2)	23 (45.1)		56 (39.2)	18 (47.4)	
Smoking status			0.002			0.014
Never	101 (77.7)	28 (54.9)		108 (75.5)	21 (55.3)	
Light/smoker	29 (22.3)	23 (45.1)		35 (24.5)	17 (44.7)	
Pathology			0.783			0.764
Adenocarcinoma	119 (91.5)	48 (94.1)		131 (91.6)	36 (94.7)	
Others	11 (8.5)	3 (5.9)		12 (8.4)	2 (5.3)	
Liver			0.224			0.749
No	125 (96.2)	46 (90.2)		136 (95.1)	35 (92.1)	
Yes	5 (3.8)	5 (9.8)		7 (4.9)	3 (7.9)	
Bone			0.991			0.583
No	84 (64.6)	33 (64.7)		91 (63.6)	26 (68.4)	
Yes	46 (35.4)	18 (35.3)		52 (36.4)	12 (31.6)	
Brain			0.908			0.983
No	113 (86.9)	44 (86.3)		124 (86.7)	33 (86.8)	
Yes	17 (13.1)	7 (13.7)		19 (13.3)	5 (13.2)	
EGFR-TKIs			0.326			0.543
Gefitinib	51 (50.0)	23 (56.1)		56 (49.1)	18 (62.1)	
Erlotinib	11 (10.8)	2 (4.9)		11 (9.6)	2 (6.9)	
Icotinib	39 (38.2)	14 (34.1)		45 (39.5)	8 (27.6)	
Afatinib	1 (1.0)	2 (4.9)		2 (1.8)	1 (3.4)	
TKI response			0.277			0.136
PR	70 (85.4)	23 (76.7)		76 (86.4)	17 (70.8)	
SD	12 (14.6)	7 (23.3)		12 (13.6)	7 (29.2)	
T790M*			0.001			0.006
Yes	32 (65.3)	2 (15.4)		33 (63.5)	1 (10.0)	
No	17 (34.7)	11 (84.6)		19 (36.5)	9 (90.0)	
Samples[#]			0.499			1.000
Blood	24 (49.0)	5 (38.5)		24 (46.2)	5 (50.0)	
Others	25 (51.0)	8 (61.5)		28 (53.8)	5 (50.0)	

*, Detected after first-line EGFR-TKIs resistance using ARMS; [#], samples used for T790M detection. EGFR, epidermal growth factor receptor; 19del, exon 19 deletion; TKIs, tyrosine kinase inhibitors; PR, partial response; SD, stable disease; ARMS, amplification-refractory mutation system.

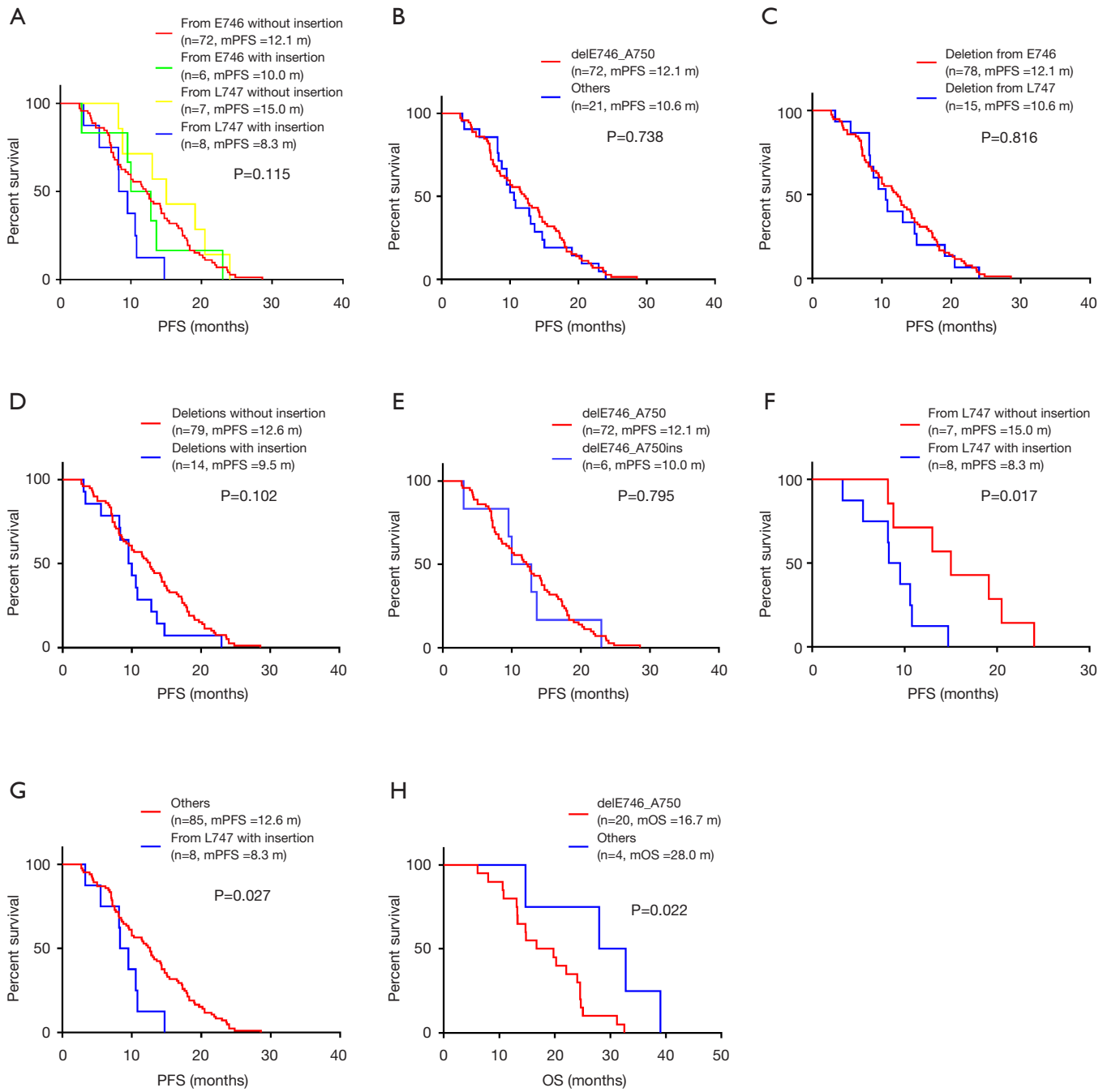

Figure 1 PFS and OS in *EGFR* 19del patients treated with first-line EGFR-TKIs. (A) PFS of patients harboring deletions starting from E746 or L747 with or without insertions; (B) PFS of patients harboring delE746_A750 or non-delE746_A750; (C) PFS of patients harboring deletions starting from E746 or L747; (D) PFS of patients harboring deletions with or without insertions; (E) PFS of patients harboring delE746_A750 with or without insertion; (F) PFS of patients harboring deletions starting from L747 with or without insertions; (G) PFS of patients harboring deletions starting from L747 with insertions or all other patients except deletions starting from L747 with insertions; (H) OS of patients harboring delE746_A750 or non-delE746_A750. PFS, progression-free survival; OS, overall survival; EGFR, epidermal growth factor receptor; 19del, exon 19 deletion; TKIs, tyrosine kinase inhibitors.

Table 3 Multivariate analysis of PFS of EGFR 19del patients treated with first-line TKIs

Items	P	HR	95% CI
Sex	0.519	0.828	0.467–1.469
Age	0.031	1.690	1.049–2.722
Smoking status	0.748	0.901	0.478–1.700
Brain metastasis	0.340	0.762	0.436–1.332
Subtypes	0.051	0.455	0.206–1.004

PFS, progression-free survival; EGFR, epidermal growth factor receptor; 19del, exon 19 deletion; TKIs, tyrosine kinase inhibitors.

the first-line PFS was not significantly different in patients harboring T790M or not when resistant to first-line EGFR-TKIs (11.5 months for T790M+, 14.7 months for T790M–, P=0.092, *Figure 2F*).

Osimertinib for EGFR 19del patients

As we showed the results in *Table 2*, *EGFR* T790M mutation distributed differently in *EGFR* 19del subtypes. Whether these patients responded differently to osimertinib was analyzed in the study. Among the patients, 25 got PFS data treated with osimertinib: 20 with delE746_A750 deletion, one with delE746_S752insV, two with delL747_T751, and two with delL747_P753insS. There was no significant difference between patients harboring delE746_A750 deletion and other mutations in PFS (4.0 *vs.* 9.5 months, P=0.102, *Figure 3A*), and also no significant difference between patients with deletions starting from E746 and L747 (5.4 *vs.* 8.0 months, P=0.102, *Figure 3B*).

Discussion

Although *EGFR* mutation patients benefitted a lot from EGFR-TKIs, studies showed that different *EGFR* mutation patients have different clinical outcomes. Patients harboring 19del could take more advantages than L858R mutation. The *EGFR* 19del subtype could also influence patient outcome. In this study, we explored T790M mutation and clinical outcomes to EGFR-TKIs in patients harboring different *EGFR* 19del subtypes.

Various *EGFR* 19del subtypes had been reported (6,7,12). Among these, delE746_A750 was the most frequent subtype, which was in accordance with our results. Deletions starting from E746 and L747 are two frequent subtypes, and the clinical features and outcomes had been compared in former studies (8,12,13). So, in this study, we applied the two classification models on these patients. It was found that delE746_A750 or deletions starting from E746 were most likely to be found in female and never smokers, indicating that even in the *EGFR* 19del patients there were still different clinical features between them.

The RR and clinical outcomes treated by EGFR-TKIs were compared between different *EGFR* 19del deletions in former studies, while the results were inconsistent. In these studies, there were mainly three methods to group the 19del patients: deletions from the starting codon E746 or L747 (8,9,12,13); deletions with or without insertion/substitution (9-11); deletions of "LRE" or "non-LRE" (8,11,12). From these studies, we speculated that the clinical outcomes could be different between NSCLC patients harboring different *EGFR* 19del subtypes, which was that patients with deletions starting from E746 had better outcomes than from L747, and a special subtype of deletion starting from L747 might influence the outcomes. In this study, we found that deletions starting from L747 with insertions had the shortest PFS. However, as the patient number was small, it was not reasonable to further specify which insertion type had the most important influence. Multivariate analysis showed that the deletion subtypes had marginal effect on PFS, indicating that patients with deletions starting from L747 with insertion could be most possibly getting inferior benefit from TKI treatment, and need large samples to confirm the results. Studies explained the relationship between 19del subtypes and outcomes of TKIs treatment in two dimensions: structural features and drug sensitivity. Truini *et al.* showed the structural features to explain their results (14). However, they mainly analyzed two 19del subtypes. More computational models of mutual interaction between deletion subtypes and EGFR-TKIs will be needed to provide a deep understanding of the interaction. Studies also explored the association from drug sensitivity, they found that delE746_A750 had the lowest IC_{50} value for target drugs, while others had relative higher IC_{50} value (22-24). However, the situation was more complicated in patients, as co-alteration of *EGFR* mutation with other genes could also influence the outcomes (25). We found that patients harboring delE746_A750 had shorter OS than others. As we know, many factors could influence patients' OS, including sample size, follow-up treatments, etc. In this study, we think the most important limitation would be the patient number—a large number of patients and their PFS and OS data are extremely needed. We will follow up the other patients and do further analysis in the future. And it

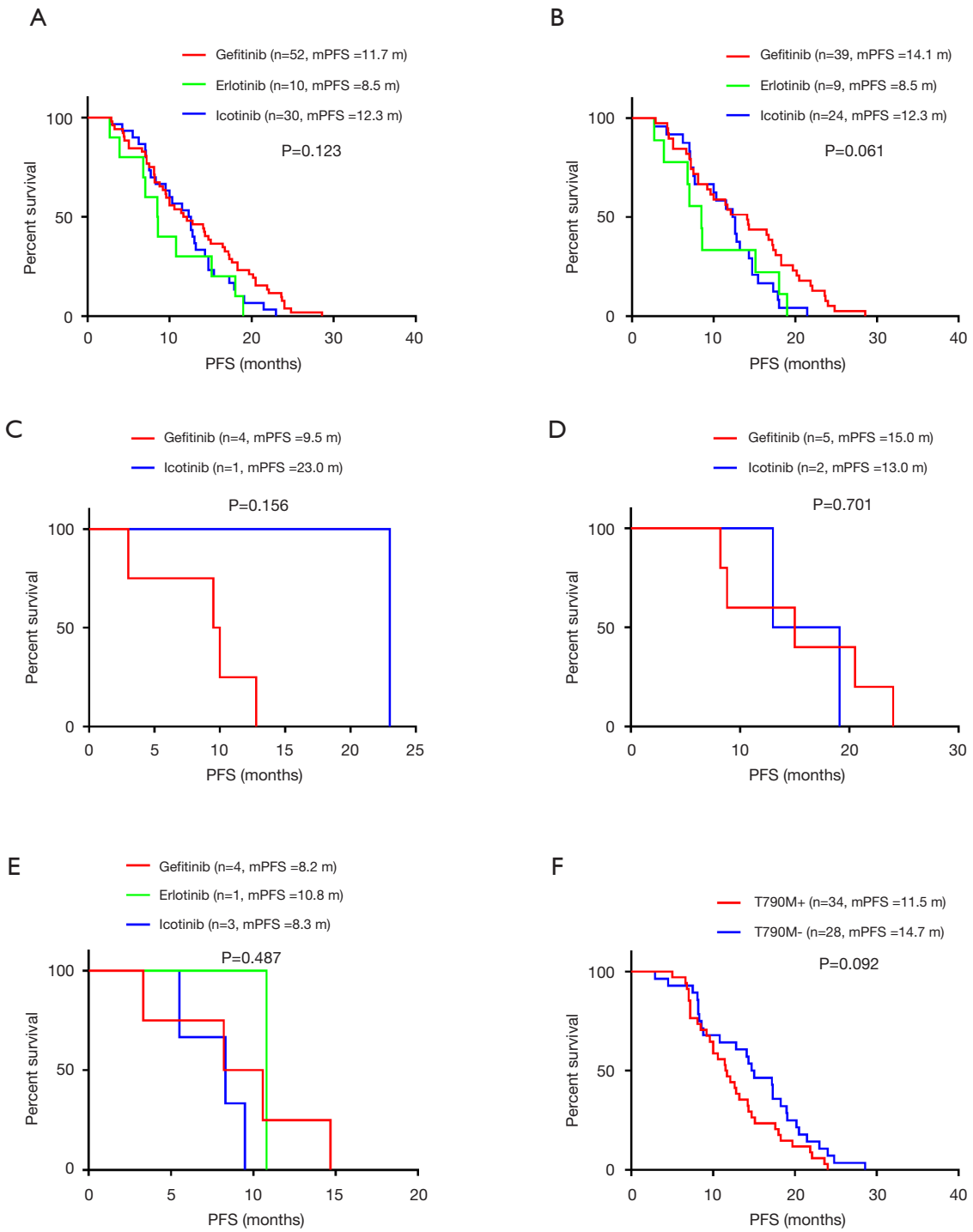

Figure 2 Impact of different EGFR-TKIs to patient PFS. (A) The impact of first-line gefitinib, erlotinib or icotinib to patient PFS; the impact of different drugs to delE746_A750 (B), deletions starting from E746 with insertions (C), deletions starting from L747 without insertions (D), and deletions starting from L747 with insertions (E); (F) PFS of patients harboring T790M (T790M+) or not (T790M–) when treated with first-line EGFR-TKIs. EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; PFS, progression-free survival.

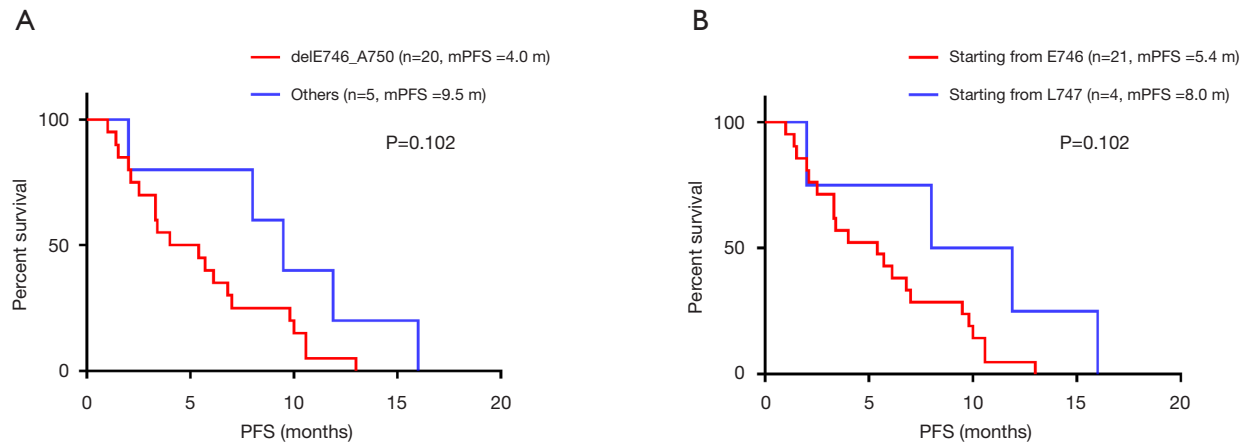

Figure 3 PFS of T790M positive patients treated with osimertinib. (A) PFS of patients harboring delE746_A750 or non-delE746_A750; (B) PFS of patients harboring deletions starting from E746 or L747. PFS, progression-free survival.

also would be better to know comprehensive gene mutation spectrum (e.g., co-alteration or passenger gene mutations) of the patients to understand the impact of 19del subtypes to patient outcomes.

T790M mutation is the main reason for first/second generation EGFR-TKI resistance. Studies already showed that the incident rate of T790M mutation was higher in *EGFR* 19del patients than L858R patients (17,18). Huang *et al.* also reported that T790M mutation had a higher prevalence in delE746_A750 than other 19del subtypes (19), which was in accordance with our results. Besides, we found that it was higher in deletions started from E746 than from L747. We used ARMS PCR to detect T790M for two reasons. Firstly, it is widely and commercially used in China for its convenience and fast speed. Secondly, we only analyzed the data detected by this method to reduce data bias brought by different detecting methods. From former studies (14,22-24), it seemed that delE746_A750 was more sensitive to EGFR-TKI than deletions starting from E746 with insertions. But for deletions starting from L747, it was complicated. They had similar or higher IC_{50} than dellE746_A750. It seemed that the more intensive affinity between drugs and EGFR mutants, the less incidence of mutation in the same gene would occur-T790M in this study. Evolution theory, mutation tendency or other theories may be included to clarify the mechanism in the future. Although they had similar outcomes when treated with osimertinib, patients harboring deletions starting from L747 had longer PFS, indicating these patients could more possibly benefit from osimertinib, and also the optimal treatment of osimmertinib or first/second generation TKIs for different 19del subtypes. We will follow up the outcomes of other patients to find if there would be significant difference, and also the outcomes of 19del patients using osimertinib for first-line therapy.

Conclusions

In conclusion, different *EGFR* 19del subtypes of NSCLC patients have different clinical features and outcomes, the mutant rate of T790M after EGFR-TKI resistance could be higher in delE746_A750 or deletions starting from E746 patients, but do not significantly influence outcomes of patients harboring different 19del subtypes when treated with osimertinib.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Ethics Committee of Shanghai Pulmonary Hospital (K19-066Y).

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Supplementary

Table S1 *EGFR* 19del subtypes detected by the kit

No.	Subtypes
1	delE746_A750
2	delL747_P753insS
3	delE746_T751insI
4	delE746_T751
5	delE746_T751insA
6	delE746_S752insA
7	delE746_S752insV
8	delE746_S752insD
9	delL747_A750insP
10	delL747_T751insQ
11	delL747_E749
12	delL747_T751
13	delL747_S752
14	delL747_A750insP
15	delL747_P753insQ
16	delL747_T751insS
17	delL747_T751
18	delL747_T751insP
19	delL747_T751
20	delL747_S752insQ
21	delL747_A750insP
22	delL747_K754insQL
23	delE746_K754insEQHL
24	delL747_S752insQ
25	delL747_A755insSRD

EGFR, epidermal growth factor receptor; 19del, exon 19 deletion.

Table S2 RR of *EGFR* 19del patients to different EGFR-TKIs

Items	TKIs				P
	Gefitinib, n (%)	Erlotinib, n (%)	Icotinib, n (%)	Afatinib, n (%)	
TKI response					0.784
PR	52 (83.9)	9 (81.8)	27 (79.4)	2 (100.0)	
SD	10 (16.1)	2 (18.2)	7 (20.6)	0	

RR, response rate; EGFR, epidermal growth factor receptor; 19del, exon 19 deletion; TKIs, tyrosine kinase inhibitors; PR, partial response; SD, stable disease.

Table S3 T790M mutation after different EGFR-TKIs treatment

Items	TKIs			P
	Gefitinib, n (%)	Erlotinib, n (%)	Icotinib, n (%)	
T790M mutation				0.837
Positive	22 (52.4)	4 (57.1)	8 (61.5)	
Negative	20 (47.6)	3 (42.9)	5 (38.5)	

EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors.