Original Article

The alteration of T790M between 19 del and L858R in NSCLC in the course of EGFR-TKIs therapy: a literature-based pooled analysis

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Background: Treatment-naive epidermal growth factor receptor (EGFR) T790M mutation is more inclined to coexist with L858R than with 19 del in non-small cell lung cancer (NSCLC) patients. However, EGFR-tyrosine kinase inhibitors (EGFR-TKIs) might alter this status. We sought to compare the prevalence of T790M upon acquired resistance to EGFR-TKIs between 19 del and L858R by assembling all existing data.

Methods: Electronic databases were comprehensively searched for eligible studies. The primary endpoint was the odds ratio (OR) of T790M mutation in NSCLC co-existing with L858R mutation and 19 del upon resistance to first-generation EGFR-TKIs. A random effects model was used. Stratified analysis was performed based on study type (retrospective and prospective), race (Asians and Caucasians) and sample type (tissue and plasma).

Results: A total of 25 studies involving 1,770 patients were included. The overall T790M existent rate was 45.25%. Post-resistance T790M was more frequent in 19 del than in L858R mutated patients (53% *vs.* 36%; OR 1.87; P<0.001). All outcomes of subgroup and overall analyses were similar. In contrast, we re-analyzed the previous meta-analysis, finding that the pooled rate of pretreatment T790M was 14% and 22% in 19 del and L858R respectively (OR 0.59; P<0.001). The increase of T790M rate was 2.79-fold in 19 del and only 0.63-fold in L858R in the course of EGFR-TKIs therapy.

Conclusions: Opposite to the situation of *de novo* T790M, it was observed that T790M was more frequent in exon 19 deletion than in L858R among patients with acquired resistance to EGFR-TKIs. The difference in T790M alteration between 19 del and L858R encourages development of detection or treatment strategies for the specific resistance mechanism.

Keywords: Non-small cell lung cancer (NSCLC); T790M; L858R; exon 19 deletions; epidermal growth factor receptor (EGFR)

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Introduction

Major advances in the treatment of non-small cell lung cancer (NSCLC) in the last decade have arisen from the recognition that specific genetic alterations define subsets of NSCLC (1). Activating mutations in the gene which encode the epidermal growth factor receptor (EGFR) protein are the most extensively studied and present in 10–20% of Caucasian NSCLC cases, and 30–50% of Asian NSCLC cases (2). The most therapeutic-relevant mutations are 19 del (exon 19 deletions) and L858R mutation. Together, the two sensitive mutations occupy over 80% of EGFR mutations in NSCLC (3).

EGFR-tyrosine kinase inhibitors (EGFR-TKIs) have proven fantastic response rates and more acceptable toxicity profiles compared to traditional standard chemotherapy in patients with advanced NSCLC harboring sensitive EGFR mutations (exons 19 and 21) (4). Unfortunately, most patients with NSCLC develop acquired resistance to TKIs and experience disease progression within 12 months after the initiation of TKI therapy (5). The secondary mutation in exon 20, T790M, detected in approximately 50% of re-biopsy samples after TKI therapy, is regarded as the most common cause of acquired resistance to TKIs (6). Exon 20 insertions account for 4–9% of all EGFR mutant lung tumors before receiving TKIs, which have been shown to confer resistance to subsequent TKI therapy (7). However, if T790M mutations are selected from *de novo* T790M mutation in TKI-naïve patients as a minor clone or are acquired during TKIs therapy remains debated (8). Recently, the FLURUA study indicated the third generation TKI, Osimertinib, showed efficacy superior to that of standard first-generation EGFR-TKIs in the first-line treatment of EGFR mutation-positive advanced NSCLC, with a similar safety profile and lower rates of serious adverse events.

A previous meta-analysis suggested that T790M mutation is more inclined to coexist with L858R than with 19 del in NSCLC patients pre-TKIs [odds ratio (OR), 1.65; 95% confidence intervals (95% CIs), 1.17 to 2.32], which might be one of the reasons that 19 del was related to a better outcome than L858R with TKIs (9). However, TKIs might alter this status due to differing sensitivities of these mutations to drugs and dynamic changes associated with secondary mutations or sub-clone selection (10). To study the mechanism of resistance to TKIs in NSCLC patients and thus to develop novel treatment and rational therapy strategies, information on tumor characteristics throughout the course of the disease and therapy is essential. We sought to compare the prevalence of T790M between 19 del and L858R upon acquired resistance to TKIs by assembling all existing data.

Methods

Literature search and selection

A systematic and comprehensive literature search of online databases PubMed, Web of Science, Medline and Cochrane library was performed to identify observational studies and RCTs conducted before July 2017 that examined studies on T790M mutation for NSCLC patients.

Several terms and their variants were used, including EGFR, T790M, lung cancer, NSCLC, TKIs, and resistance. The references of identified papers, previously published systematic reviews, and meta-analysis were inspected to identify studies not included by the initial search.

We reviewed all searched results according to the PRISMA statement (11). The selection of original studies was based on the process of viewing titles, abstracts and full papers. The inclusion criteria were as follows: (I) studies that focused on patients with NSCLC; (II) data regarding 19 del and L858R with or without T790M mutations after TKIs treatment. Review articles, abstracts, case reports, editorials, and letters were excluded.

Data extraction and quality assessment

All data were recorded independently by two researchers (HR Liang and DF Chen). Any conflict was resolved by the third researcher (WH Liang). For the selected studies, information on all available variables was extracted and entered into a Microsoft Excel database. The numbers of 19 del and L858R with or without T790M mutations were extracted to compute the co-existing rate. Patients with co-existing L858R and 19 del mutations were excluded. Original data from previous meta-analysis were also extracted and re-analyzed to explore the mechanism of drug resistance during TKI therapy (9). We performed subgroup analyses according to the study design, population race, and sample types. Quality of each paper was assessed using the Joanna Briggs Institute Prevalence Critical Appraisal Tool (12). Any disagreement was resolved via discussion amongst the authors.

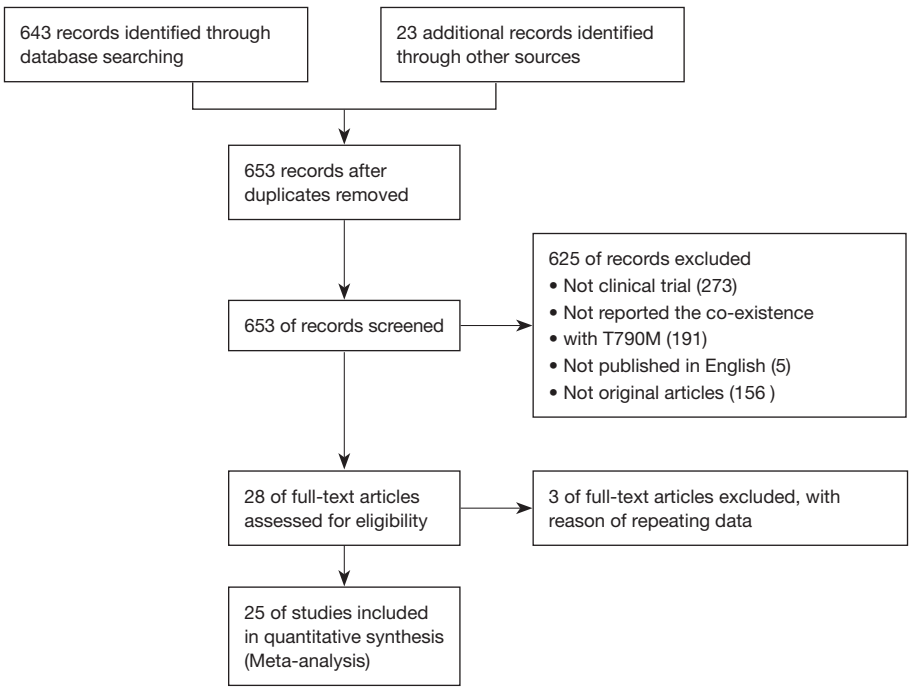


Figure 1 Flow diagram detailing the search strategy and identification of studies used in meta-analysis.

Statistical analysis

OR with its 95% CIs were computed to compare the prevalence of T790M between 19 del and L858R. We used Cochran's I^2 test and X^2 to examine the heterogeneity among included studies. Statistical heterogeneity among studies was defined as I^2 statistic greater than 50% (13). Random effects model was preferred owing to the heterogeneity among studies (14). Single-arm and re-analysis were also performed to evaluate the co-existence of T790M with 19 del or L858R in our study and previous meta-analysis. Statistical significance was settled as two-sided P<0.05. The analysis was conducted with STATA 12.0.

Results

Study selection and quality assessment

A total of 643 records were screened from the previously mentioned online databases with the search cutoff of June 30th 2017. After excluding duplicates, a manual search and inspection of the reference lists and existing reviews identified 23 additional relevant studies. Further review according to inclusion criteria led to the final selection of the 25 papers considered in this analysis (*Figure 1*) (10,15-38). The contextual details and the results of the quality assessment of each study were summarized in *Tables 1,2*. The detailed quality score of each enrolled study is shown in the *Table S1* (quality score of each enrolled study).

The studies were conducted in 7 different countries and the period ranged from 2010 to 2017. Ten articles were prospective studies and the others were retrospective. A total of 25 studies involving a total of 1,770 patients were included. The overall T790M detection rate of post-TKIs was 45.25%. All studies gained 8 to 10 stars in study quality assessment on a scale of 0 to 10.

Primary outcome

In single-arm synthesis, the co-existence rate of T790M was 53% (95% CI, 47% to 59%) and 36% (95% CI, 30% to 42%) in 19 del and L858R, respectively. Post-TKIs T790M was significantly more frequently co-existing with 19 del than L858R mutated patients (OR 1.87; 95% CI, 1.38 to 2.54; P<0.001). Statistical heterogeneity was moderate among studies (I^2 =42.6; P=0.014) (*Figure 2*).

Subgroup analysis

We performed subgroup analysis stratified by the study design, population race and sample types. The relative

Table 1 Characteristics of the included studies in the meta-analysis

Author	Year	Period	Region	Design	TKI type	Age	Female (%)	Smoker (%)	IIIb, IV (%)
Yoshida *et al.*	2017	2002–2016	Japan	Retro	Gefitinib, erlotinib, afatinib	64	70.00	68.00	78.00
Ke *et al.*	2017	2010–2014	China	Retro	Gefitinib, erlotinib, afatinib	NG	54.46	23.21	NG
Zhang *et al.*	2016	2004–2014	China	Retro	Gefitinib, erlotinib	58	62.70	15.70	100.00
Wang *et al.*	2016	2014–2015	China	Retro	Gefitinib, erlotinib, icotinib	NG	49.07	34.26	97.22
Tseng *et al.*	2016	2014–2016	China	Retro	Gefitinib, erlotinib, afatinib	NG	62.20	24.50	NG
Takahama *et al.*	2016	2014–2015	Japan	Pro	Gefitinib, erlotinib, afatinib	NG	70.00	27.30	78.80
Aragane *et al.*	2016	2011–2012	Japan	Pro	afatinib	NG	65.52	36.21	NG
Nosaki *et al.*	2016	2013–2014	Japan	Retro	Gefitinib, erlotinib, afatinib	63	61.00	36.70	NG
Matsuo *et al.*	2016	2005–2015	Japan	Retro	Gefitinib, erlotinib, afatinib	67	78.08	23.29	NG
Ko *et al.*	2016	2002–2014	Japan	Retro	Gefitinib, erlotinib, afatinib	64	72.00	28.00	NG
Re *et al.*	2016	NG	Italy	Retro	Gefitinib, erlotinib	NG	60.06	33.30	97.00
Otsuka *et al.*	2015	2010–2014	Japan	Retro	Gefitinib, erlotinib, afatinib	64	75.00	29.00	NG
Chen *et al.*	2015	2010–2015	China	Pro	Gefitinib, erlotinib, icotinib	NG	NG	NG	NG
Reguart *et al.*	2014	2008–2010	Spain	Pro	erlotinib	60	64.00	36.00	96.00
Li *et al.*	2014	2011–2013	China	Pro	Gefitinib, erlotinib, icotinib	51.2	46.30	12.96	NG
Kuiper *et al.*	2014	2006–2013	Netherlands	Retro	Erlotinib, gefitinib	54	79.00	46.00	NG
Sun *et al.*	2013	2010–2012	Korea	Pro	Gefitinib, erlotinib	NG	74.00	20.00	NG
Ji *et al.*	2013	2007–2010	Korea	Retro	Gefitinib	60	61.54	NG	NG
Hata *et al.*	2013	2008–2012	Japan	Retro	Gefitinib, erlotinib	NG	31.00	33.00	NG
Uramoto *et al.*	2012	NG	Japan	Retro	Gefitinib	67.6	73.68	10.53	57.89
Yano *et al.*	2011	NG	Japan	Pro	Gefitinib, erlotinib	59.5	70.00	15.00	NG
Sequist *et al.*	2011	NG	USA	Pro	Gefitinib, erlotinib	NG	59.50	NG	NG
Oxnard *et al.*	2011	1999–2009	USA	Pro	Gefitinib, erlotinib	NG	65.00	34.00	NG
Nakamura *et al.*	2011	2000–2009	Japan	Retro	Gefitinib, erlotinib	65	57.10	36.70	100.00
Onitsuka *et al.*	2010	NG	Japan	Pro	Gefitinib	65.7	70.00	20.00	50.00

Pro, prospective studies; Retro, retrospective studies; TKIs, tyrosine kinase inhibitors; NG, not given.

effects were consistently significant in most subgroups except in Caucasians (OR 1.48; P=0.244) and in studies using plasma (OR 1.68; P=0.062), but the trend remained the same. No significant heterogeneity was found among studies in any of the subgroups (*Table 3*).

Comparison with the previous meta-analysis

We re-analyzed the previous meta-analysis and made a single-arm meta-analysis (9), finding that the pooled rate of pre-TKIs T790M was 14% (95% CI, 10% to 17%) and 22% (95% CI, 16% to 27%) in 19 del and L858R respectively. Pre-TKIs T790M was significantly less frequently co-existing with 19 del than L858R mutated patients (OR 0.59; 95% CI, 0.44 to 0.80; P<0.001) with no heterogeneity (I^2 =0; P=0.788), while the co-existing rate of T790M mutation became 53% (95% CI, 47% to 59%) and 36% (95% CI, 30% to 42%) in 19 del and L858R after TKI resistance in our pooled analysis. The increase of the T790M co-existing rate was 2.79-fold in 19 del but only

Table 2 Characteristics of the included studies in the meta-analysis

Author	Year	19 del		L858R		Detection method	Sample type	EGFR (mt)	T790M (mt)	Detection rate of T790M (%)	Quality score
		T790M+	T790M–	T790M+	T790M–						
Yoshida *et al.*	2017	8	20	9	13	NG	Tissue	50	17	34.00	10
Ke *et al.*	2017	70	69	31	54	PCR	Tissue	224	101	45.09	10
Zhang *et al.*	2016	13	18	5	15	ARMS	Tissue	51	18	35.29	10
Wang *et al.*	2016	31	39	14	19	ddPCR	Plasma	103	45	43.69	10
Tseng *et al.*	2016	36	22	15	21	PCR	Tissue	94	51	54.26	9
Takahama *et al.*	2016	48	79	24	98	ddPCR	Plasma	249	72	28.92	8
Aragane *et al.*	2016	16	15	7	20	MBP-QP	Plasma	58	23	39.66	9
Nosaki *et al.*	2016	85	74	56	52	NG	Tissue	267	141	52.81	9
Matsuo *et al.*	2016	26	15	12	20	PCR	Tissue	73	38	52.05	10
Ko *et al.*	2016	9	28	9	10	PCR, ARMS	Plasma + tissue	56	18	32.14	10
Re *et al.*	2016	14	6	8	2	ddPCR	Plasma	30	22	73.33	9
Otsuka *et al.*	2015	3	1	3	12	PCR	Tissue	19	6	31.58	9
Chen *et al.*	2015	5	4	1	2	PCR	Tissue	12	6	50.00	10
Reguart *et al.*	2014	4	11	3	7	NG	Plasma	25	7	28.00	9
Li *et al.*	2014	13	9	10	9	ARMS	Tissue	41	23	56.10	10
Kuiper *et al.*	2014	28	19	6	8	PCR	Tissue	61	34	55.74	9
Sun *et al.*	2013	30	12	6	17	PCR	Tissue	65	36	55.38	9
Ji *et al.*	2013	8	8	3	7	PCR	Tissue	26	11	42.31	10
Hata *et al.*	2013	17	25	8	25	PCR	Tissue	75	25	33.33	10
Uramoto *et al.*	2012	6	1	2	10	PCR	Tissue	19	8	42.11	9
Yano *et al.*	2011	8	3	2	7	PCR	Tissue	20	10	50.00	10
Sequist *et al.*	2011	13	7	4	11	PCR	Tissue	35	17	48.57	9
Oxnard *et al.*	2011	44	26	14	9	PCR	Tissue	93	58	62.37	9
Nakamura *et al.*	2011	5	4	2	3	PCR	Tissue	14	7	50.00	9
Onitsuka *et al.*	2010	5	0	2	3	PCR	Tissue	10	7	70.00	9

ARMS, amplified refractory mutation system; ddPCR, droplet digital PCR; MBP-QP, mutation-biased PCR and quenching probe PCR; Mt, mutation; NG, not given.

0.63-fold in L858R (*Figure 3*).

Discussion

Newly acquired resistance in sensitive EGFR mutation positive NSCLC patients after first-generation TKI therapy is a tough problem. The T790M mutation can be detected in nearly 50% patients at time of acquiring TKI-resistance (39). The results of a previous meta-analysis reported that pre-TKIs T790M is less frequent in patients harboring 19 del compared to those carrying the L858R mutation (14% *vs.* 22%; OR 0.59; P<0.001) (9). The trend of our study differed from the previous study in that T790M was more frequent in exon 19 deletion than in L858R among patients with acquired resistance to TKIs (53% *vs.* 36%; OR 1.87; P<0.001). In subgroup analyses by

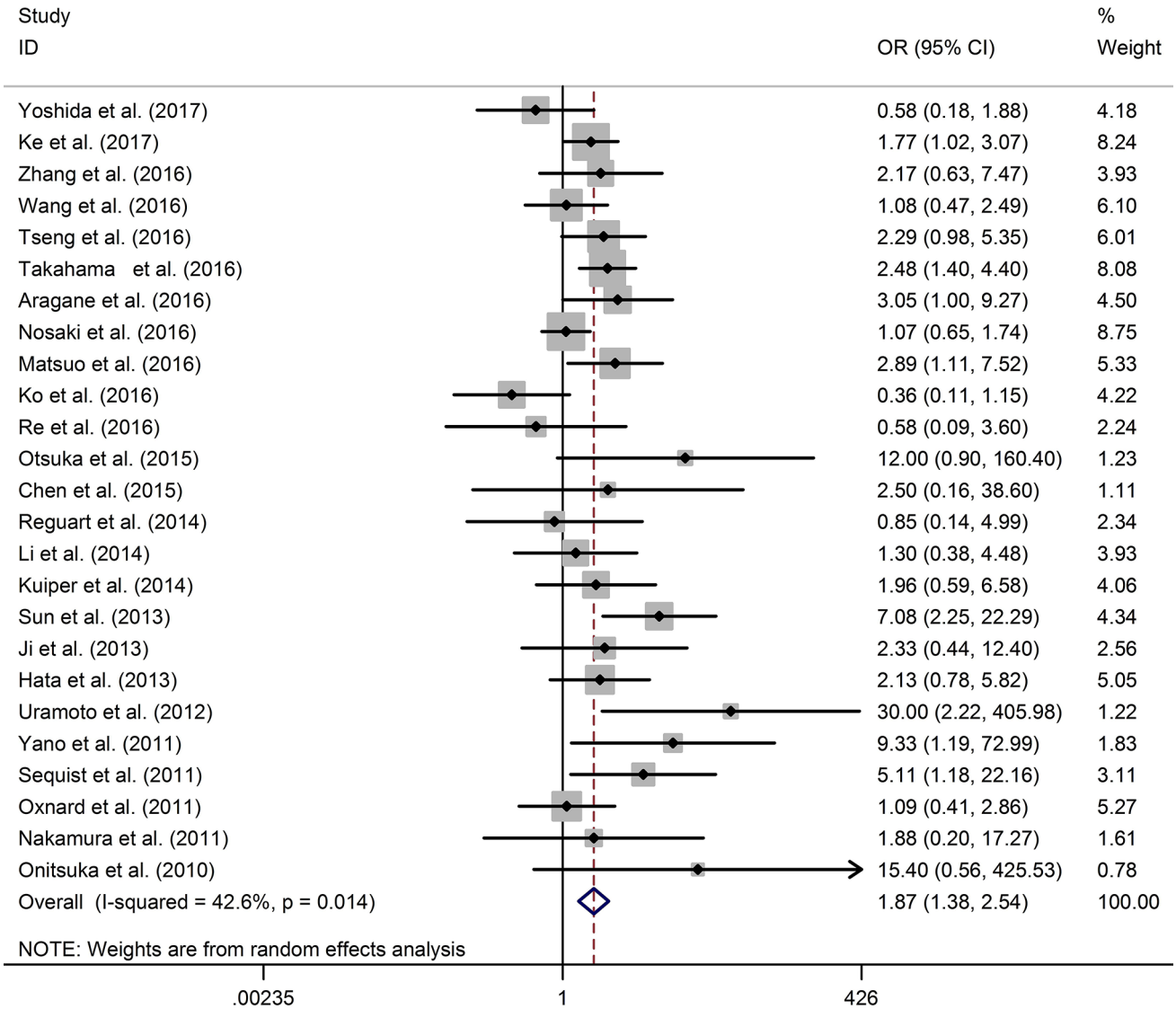


Figure 2 Forest plot for pooled estimation of the co-existence rate of T790M between 19 del and L858R.

study design, sample size and race, we found results were similar to overall analyses.

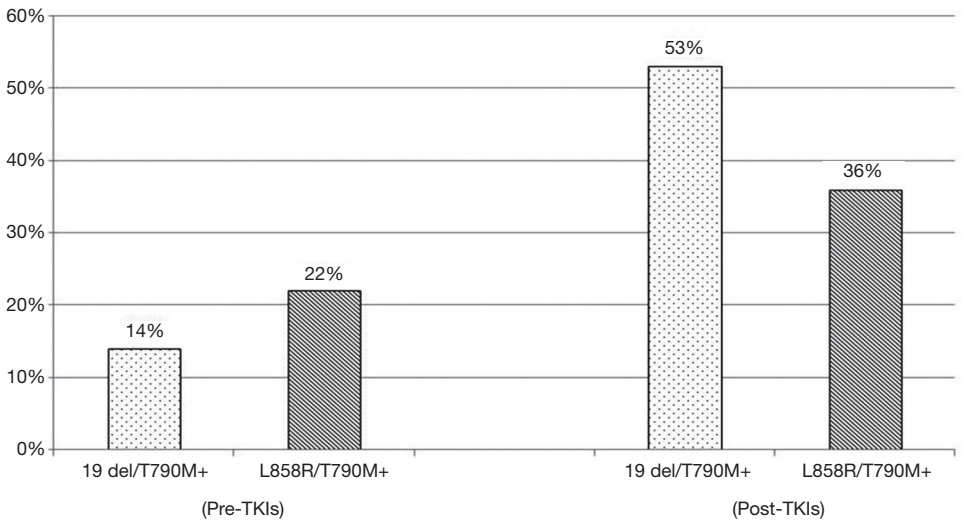
Much debate exists regarding the "selection" or "acquisition" of the T790M mutation formation process. This mutation was initially thought to be acquired only after exposure to TKIs because T790M was lacking in pre-progression samples. However, T790M has been identified in TKI treatment-naive NSCLC samples using standard sequencing methods, which indicated T790M is a common mutation in some TKI-naive tumors, and this alteration are picked by following TKI treatment (40). One of the interpretations to explain the "reversal" of T790M prevalence between 19 del and L858R in the course of TKI therapy might be patients with 19 del mutation are more sensitive to TKIs (41), thus the sub-clone of T790M mutation in 19 del patients are more likely to be selected and enriched.

The median survival of late stage NSCLC patients is less than 2 years after the emergence of T790M mutation (42). Recently, third-generation TKIs, such as AZD9291 (Osimertinib), have emerged as a potential therapeutic option to fight against the EGFR T790M-positive tumors (43). However, there is a great number of patients harboring the T790M mutation that are

Table 3 Outcomes of subgroup analysis

Subgroups	Number	Effect size (95% CI)	Heterogeneity I^2 (%)
Study design			
Prospective study	10	OR 2.61 (1.62,4.19); P=0.000	I^2=26.7; P=0.198
Retrospective study	16	OR 1.61 (1.10,2.25); P=0.014	I^2=44.1; P=0.030
Sample type			
Tissue	20	OR 2.22 (1.56,3.17); P=0.000	I^2=39.9; P=0.034
Plasma	5	OR 1.68 (0.97,2.91); P=0.062	I^2=29.4; P=0.226
Race			
Caucasian	5	OR 1.48 (0.77,2.86); P=0.244	I^2=15.2; P=0.317
Asian	21	OR 2.05 (1.44,2.91); P=0.000	I^2=49.4; P=0.006

OR, odds ratio; CI, confidence interval.



	Studies	Patients	19 del/T790M+	19 del/T790M–	L858R/T790M+	L858R/T790M–
Pre-TKIs [Chen *et al.* (9)]	18	2,874	193	1,449	174	1,058
Post-TKI (Our study)	25	1,770	545	515	256	454

Figure 3 Alternation of T790M prevalence between 19 del and L858R in the course of TKIs therapy (9). TKI, tyrosine kinase inhibitor.

either unavailable to re-biopsy or of which the mutation has not been detected and thus unable to receive these treatments. Besides, the sensitivity of plasma detection is not satisfactory, thus these patients who are detected as negative T790M mutation via plasma may be also potentially benefited from Osimertinib. Our study suggested that patients harboring the 19 del mutation may be more likely to gain profit from Osimertinib than those with L858R if they attempt treatment when it is not clearly indicated.

Even so, there is still a subset of patients who will receive repeat first-generation TKIs as salvage treatment after initial failure. To date, no satisfying biomarkers have been found to indicate which patients may receive benefit from the continuation of first-generation TKI therapy. One study found that T790M positive patients had better prognosis with both longer PFS and OS than those without the mutation, and, therefore, claimed patients with acquired T790M

mutation at the time of progression may benefit more from TKI re-challenge (30). But another study reported that survival outcomes of secondary TKIs did not differ significantly between T790M-positive and T790M-negative groups; this indicated that T790M might not predict the clinical outcomes in first-generation TKI re-challenge (16). These findings suggested there is heterogeneity in predictive effect on TKI therapy and a difference in the prognosis of 19 del and L858R patients. TKIs are more effective in 19 del patients, and our pooled analysis observed the acquired resistance as a result of the T790M mutation is more likely attributed to 19 del than L858R. Thus, we speculate that it might be the proportion of L858R-T790M mutation, not the T790M mutation alone, that could predict the outcome of first generation TKI re-challenge and suppose the continuation of first-generation TKIs in patients harboring 19 del might be less recommended.

In addition, different prognostic effects were observed in pre- and post-TKI T790M positive NSCLC patients. A meta–analysis demonstrated that pre-TKI T790M positive NSCLC patients were associated with a worse outcome in either PFS or OS, while newly acquired T790M mutation after TKI therapy seemed to be a good prognostic factor (44). Another meta-analysis also linked the pre-TKI T790M mutation with a negative impact on the PFS for NSCLC patients (45). The worse outcomes correlated with the assumption that pre-TKI T790M mutation might be a result of the decreased sensitivity of T790M positive cell to TKIs, while the better prognosis of T790M positive patients after TKI therapy could be explained by the indolent biologic behaviors of T790M positive cells (46). There is evidence that patients who had exon 19 deletions had statistically significant longer PFS than those with L858R(47). Our study suggested that the proportion of patients with coexisting 19del and T790M mutations might obtain better survival.

We acknowledge several limitations to our study. First, not all of the included studies were prospective randomized comparisons, which increase the risk of potential selection and reporting bias. Second, though moderate, heterogeneity among studies (I^2 =42.6; P=0.014) still existed. Different baseline characteristics, differing sensitivities of detection methods, and small populations in each study might explain the heterogeneity. Third, the data we used are based on the published literature rather than primary data as we were unable obtain unpublished data. Last, though we observed more T790M mutations co-existing with 19 del post-TKIs, we do not know the state of T790M abundance in 19 del and L858R.

Conclusions

Unlike the situation of *de novo* T790M, an opposite trend that T790M was more frequent in exon 19 deletion than in L858R among TKI acquired resistance patients was observed. The resistance lead by T790M mutation is more likely attributed to 19 del than L858R, which indicated that re-challenge of first-generation TKIs may be less recommended in patients harboring 19 del. Our study also suggested that patients who harbored 19 del mutation may be more likely to gain profit from Osimertinib than those with L858R if they attempt treatment when it is not clearly indicated. In all, our results encouraged developing detection or treatment strategies in L858R and 19 del patients, respectively, for the specific resistance mechanism.

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Footnote

Conflict of Interest: The authors have no conflicts of interest to declare.

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Supplementary

Table S1 Quality score of each enrolled study

Author	Year	Score	Study type	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11
Takayuki Takahama	2016	8	Pro	1	1	1	1	0	1	1	0	1	0	1
0oko Sueoka-Aragane	2016	9	Pro	1	1	1	1	0	1	1	1	1	0	1
Yoshiro Nakahara	2016	9	Pro	1	1	1	1	0	1	1	1	1	0	1
Qi Chen	2015	10	Pro	1	1	1	1	1	1	1	1	1	0	1
Noemi Reguart	2014	9	Pro	1	1	1	1	0	1	1	1	1	0	1
Wei Li	2014	10	Pro	1	1	1	1	1	1	1	1	1	0	1
Seiji Yano	2011	10	Pro	1	1	1	1	1	1	1	1	1	0	1
Lecia V. Sequist	2011	9	Pro	1	1	1	1	0	1	1	1	1	0	1
Takamitsu Onitsuka	2010	9	Pro	1	1	1	1	0	1	1	1	1	0	1
Qiuyi Zhang	2016	10	Retro	1	1	1	1	1	1	1	1	1	1	
Wenxian Wang	2016	10	Retro	1	1	1	1	1	1	1	1	1	1	
Kaname Nosaki	2016	9	Retro	1	1	1	1	1	1	0	1	1	1	
Ryo Ko	2016	10	Retro	1	1	1	1	1	1	1	1	1	1	
Marzia Del Re1	2016	9	Retro	1	1	1	1	1	1	0	1	1	1	
Kyoko Otsuka	2015	9	Retro	1	1	1	1	1	1	0	1	1	1	
Patients J. L. Kuiper	2013	9	Retro	1	1	1	1	1	1	0	1	1	1	
Akito Hata	2013	10	Retro	1	1	1	1	1	1	1	1	1	1	
Hidetaka Uramoto	2012	9	Retro	1	1	1	1	1	1	0	1	1	1	
Hidetaka Uramoto	2011	9	Retro	1	1	1	1	1	1	0	1	1	1	
Geoffrey R. Oxnard	2011	9	Retro	1	1	1	1	1	1	0	1	1	1	
Tomomi Nakamura	2011	9	Retro	1	1	1	1	1	1	0	1	1	1	
Hidetaka Uramoto	2010	9	Retro	1	1	1	1	1	1	0	1	1	1	

Pro, prospective study; Retro, retrospective study.