

Re-biopsy status among Chinese non-small-cell lung cancer patients who progressed after icotinib therapy

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Objective: Acquired T790M mutations account for 50%–60% of tyrosine kinase inhibitor (TKI)-resistant mechanisms in *EGFR* mutation-positive (m+) non-small-cell lung cancer (NSCLC) patients, and re-biopsy is recommended to detect these mutations. We investigated the re-biopsy status and the T790M incidence rate in patients after treatment with icotinib, which is the first-generation *EGFR*-TKI widely used in China.

Patients and methods: Target patients had *EGFR*m+NSCLC, who were progressed after icotinib therapy. The primary end point was the re-biopsy rate (number of cases in which re-biopsies were performed successfully/total number of patients progressed after icotinib therapy). Secondary end points included the T790M mutation incidence rate, differences between the first biopsy and re-biopsy, and details of why re-biopsy was not performed in relevant patients.

Results: A total of 77 adenocarcinoma patients were evaluated (median age, 58 years). Tissue re-biopsy was successful in 41 patients (53.2%). Compared with the first biopsy, percutaneous tissue biopsies increased from 51.2% to 70.7% ($P=0.008$), while bronchoscopy biopsies and the surgical rate decreased from 19.5% to 14.6% ($P<0.001$) and 17.1% to 7.3% ($P<0.001$), respectively. Primary lung lesions were more common in the first biopsy than in re-biopsy (80.5% vs 65.9%, $P=0.008$), but metastatic lesions were more often selected for re-biopsy (14/41 [34.1%], including metastases in the bone, lymph nodes, and liver). The incidence rate of T790M was 56.1% (23/41). The reasons for not performing re-biopsies included lesion sizes and/or locations unsuitable for biopsy ($n=17$), a positive circulating tumor DNA (ctDNA) result ($n=3$), patient unwillingness ($n=7$), older age or severe comorbidity ($n=4$), and poor health ($n=5$). No severe complications were found.

Conclusion: In this real-world study, the re-biopsy rate was 53.2% and the incidence rate of T790M mutations was 56.1%. Further efforts are needed to increase the re-biopsy rate in patients who progress after icotinib therapy.

Keywords: re-biopsy, T790M mutation, resistant mechanism, *EGFR*-TKI, icotinib, non-small-cell lung cancer

Introduction

Lung cancer is the leading cause of cancer death worldwide,¹ and the treatment guidance based on genetics has brought great benefits to patients. Some lung cancers are associated with mutations, including *EGF* gene (*EGFR*) mutations which are the most common in the Eastern non-small-cell lung cancer (NSCLC) population. Patients who harbor *EGFR* mutations account for ~50% of NSCLC cases² and are sensitive to *EGFR* tyrosine kinase inhibitor (TKI) therapy, with the first-generation *EGFR*-TKI treatment shown to achieve control in around 1 year.^{3,4} However, subsequent treatment depends on the mechanism of drug resistance. Acquired T790M mutations account

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for 50%–60% of the resistance mechanisms and are targeted by the third-generation EGFR-TKIs.^{5–7} These include osimertinib, which achieved a progression-free survival (PFS) of 10.1 months and an overall response rate (ORR) of 71% in T790M mutation patients.⁸ To predict whether patients can benefit from osimertinib treatment, it is critical to identify T790M mutations in TKI-resistant patients.

Suitable specimens for *EGFR* mutation detection include tissue and plasma. Tissue analysis remains the gold standard for the identification of *EGFR* mutations, with blood used as an effective alternative when tissue specimens are not available.⁹ However, the rate of re-biopsy to obtain tissue samples is very low in China; hence, more efforts are needed to improve the status of re-biopsy.

The most commonly used first-generation EGFR-TKIs outside China are gefitinib and erlotinib. Icotinib is a widely used Chinese first-generation EGFR-TKI with independent intellectual property rights whose non-inferiority to gefitinib was previously established in the ICOGEN study.¹⁰ It is thought to have similar resistance mechanisms to other EGFR-TKIs, but this has not been proven.

This retrospective study analyzed the re-biopsy and T790M mutation statuses of NSCLC patients with *EGFR* mutations, who were progressed after icotinib therapy between July 2015 and July 2017.

Patients and methods

Patients

Patients with histologically or cytologically determined advanced-stage (stage IIIB or IV) NSCLC with an activating *EGFR* mutation or patients with a documented prolonged partial response or stable disease (>24 weeks) to icotinib (according to Response evaluation criteria in solid tumors [RECIST] criteria¹¹), who were progressed after icotinib therapy between July 2015 and July 2017 and who had a complete medical record, were retrospectively analyzed. Patients with de novo T790M mutations were excluded.

Details of biopsies, including those performed prior to TKI treatment (pre-TKI biopsy) and/or after TKI treatment (post-TKI biopsy), were collected. Reasons not to perform a post-TKI biopsy were obtained from medical records or by telephone follow-up. The quality of the post-TKI biopsy and the method of mutation detection were determined from the pathological report. Demographic data and details of prior TKI treatments (including time to progress and response to treatment) were collected from medical records.

Biopsies underwent histological assessment using H&E staining. A successful re-biopsy was defined if the number

of tumor cells in the specimens exceeded 100 to meet the needs of detecting *EGFR* mutations.

Methods and results of *EGFR* mutation detection (especially T790M) were collected from medical records or the pathological department.

For those patients whose plasma circulating free DNA (cfDNA) was analyzed to detect T790M mutations, detailed information about the methods and results of cfDNA analysis was also collected from medical records. This study was approved by the institutional review board of Peking Union Medical College Hospital (approval No. S-K374). The patient consent was not required for this retrospective study, since the subjects cannot be identified directly or through identifiers linked to the subjects.

Data and statistical analyses

RECIST 1.1 criteria were used for response evaluation.¹¹ Survival curves were constructed using the Kaplan–Meier method. Survival data were compared using the log-rank test. The primary end point was the re-biopsy rate (number of cases in which re-biopsies were performed successfully/total number of patients who progressed after icotinib therapy). Secondary end points included the incidence rate of T790M mutations, differences between the first biopsy and re-biopsy as determined by the chi-squared test, and details of why re-biopsy was not performed in relevant patients. IBM SPSS Statistics for Windows software (version 19.0; IBM Corporation, Armonk, NY, USA) was used for statistical analyses.

Results

Patient characteristics

Figure 1 shows the flowchart of patients' recruitment. A total of 77 adenocarcinoma patients who progressed after icotinib therapy between July 2015 and July 2017 were evaluated (Table 1). The median age was 58 years (range, 36–81 years); 48 patients (62.3%) were females, and 20 (26%) were smokers.

Initial *EGFR* mutation status of patients

Initial biopsy specimens were analyzed for primary *EGFR* mutations by the Scorpion amplification refractory mutation system (ARMS; Qiagen NV, Venlo, the Netherlands) in 75 patients. No tissue biopsy was obtained from the remaining two patients during the initial diagnoses, and their *EGFR* mutation status was determined by digital PCR of plasma cfDNA (AmoyDx, Xiamen, China).

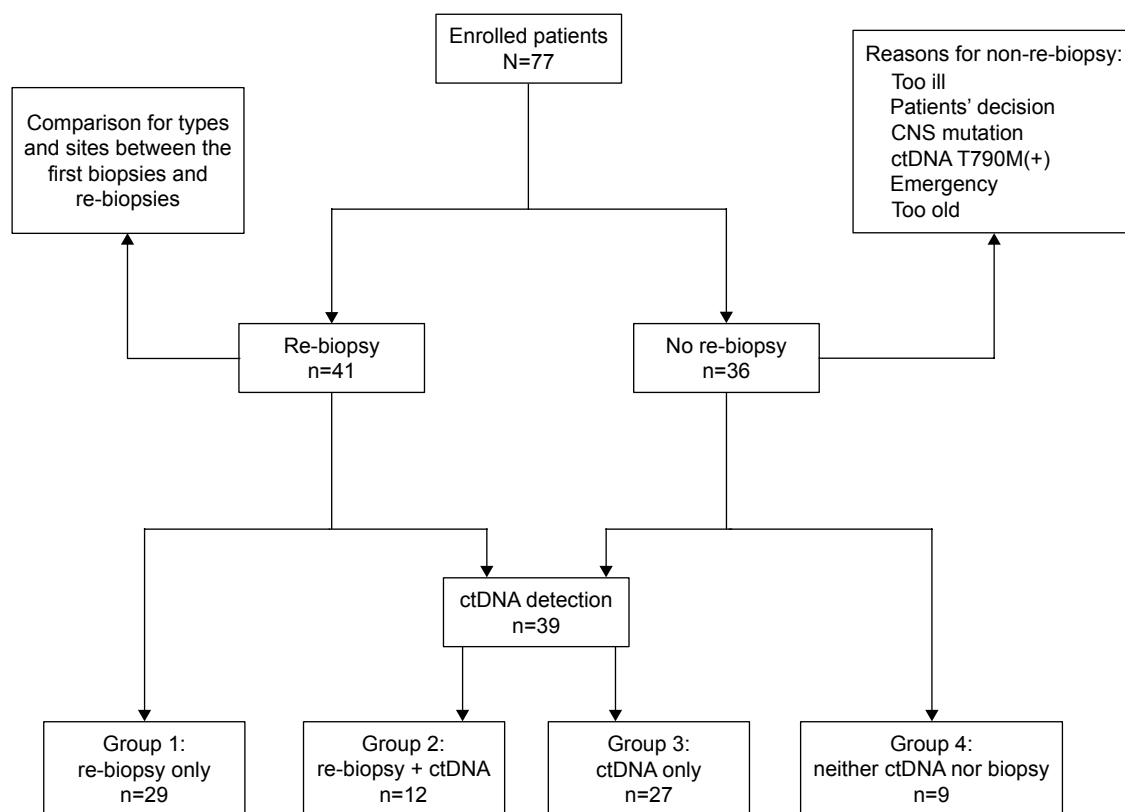


Figure 1 Flowchart of patients' recruitment.

Abbreviations: CNS, central nervous system; ctDNA, circulating tumor DNA.

According to the initial detection, 33 (42.9%) patients had an exon 19 deletion, 40 (51.9%) had an L858S mutation, and two had uncommon mutations (one had the L861 mutation, and the other had a complex mutation of L861Q+G719X).

Icotinib treatment and its efficacy in patients

Icotinib was used as the first-line therapy in 72 (93.5%) patients, as the second-line therapy in four patients (whose prior first-line therapy was pemetrexed plus cisplatin/carboplatin), and as the third-line therapy in one patient (treated by vinorelbine plus cisplatin as the first-line therapy and pemetrexed as the second-line therapy).

The median PFS of icotinib in the full set of patients was 13.3 months (95% CI: 10.6–16.0 months), the ORR was 57.1% (95% CI: 45.8%–68.4%), and the disease control rate was 97.4% (95% CI: 93.8%–101.0%).

Re-biopsies after progress from icotinib

The general status of re-biopsy is shown in Figure 2. Tissue re-biopsies were successful in 41 patients (41/77, 53.2%), and plasma analysis was successful in 39 patients (39/77, 50.6%).

Tissue re-biopsies and plasma analysis were concurrently successfully performed in 12 patients (15.6%). However, nine (11.7%) patients underwent neither tissue re-biopsy nor plasma analysis.

The median interval duration from icotinib progression to first re-biopsy was 1.0 months (range, 0.1–6.0 months). Only two patients accepted chemotherapy before re-biopsies.

Differences in the types and sampling sites of both pre-TKI biopsies and post-TKI re-biopsies in 41 patients are summarized in Table 2. Compared with pre-TKI biopsies, percutaneous tissue biopsies increased from 51.2% to 70.7% ($P=0.008$), while bronchoscopy biopsies and the surgical rate decreased from 19.5% to 14.6% ($P<0.001$) and 17.1% to 7.3% ($P<0.001$), respectively.

Regarding the site of biopsy, primary lung lesions were more common for pre-TKI biopsies than re-biopsies (80.5% vs 65.9%, $P=0.008$), and metastatic lesions outside the lung were more often selected for re-biopsies (14/41, 34.1%), including metastases in the bone, lymph nodes, and liver.

No severe re-biopsy-associated complications were found. Only one patient had mild hemoptysis, and one patient

Table 1 Patients' characteristics (N=77)

Characteristics	n	Percentage
Age, years		
Mean	58	
Range	36–81	
Sex		
Female	48	62.3
Male	29	37.7
ECOG PS (before icotinib therapy)		
0–1	73	94.8
2–3	4	5.2
ECOG PS (after icotinib therapy)		
0–1	67	87.0
2–3	10	13.0
Smoking		
Yes	20	26.0
No	57	74.0
Initial EGFR mutation		
L858R	33	42.9
L858R	40	51.9
Uncommon mutation ^a	2	2.6
Line of prior EGFR-TKI		
First line	72	93.5
Second line	4	5.2
≥Third line	1	1.3

Note: ^aUncommon mutation includes the following: one with 21L861Q mutation and the other with complex mutation of L861Q+18 exon G719X.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; TKI, tyrosine kinase inhibitor.

had mild pneumothorax after percutaneous puncture; both of these were reversible.

ARMS methods (Qiagen NV) were used in 39 patients, and next-generation sequencing (NGS) was used in two patients.

Reasons for unsuccessful tissue re-biopsy

Re-biopsies were unsuccessful after progress after icotinib therapy in 36 patients. The reasons for no re-biopsy included lesion size and/or an unsuitable location for biopsy (n=17), positive circulating tumor DNA (ctDNA) result (n=3), patient unwillingness (n=7), older age or severe comorbidity (n=4), and poor health (n=5).

Plasma cfDNA analysis

The plasma of 39 patients was analyzed for T790M mutations. In 36 non-re-biopsy patients, 27 had their plasma cfDNA analyzed for *EGFR* mutations instead.

Regarding the methods of cfDNA analysis, droplet digital PCR (ddPCR) technology was used in 22 patients (56.4%), Scorpion ARMS in 14 (35.9%), and NGS in three (7.7%).

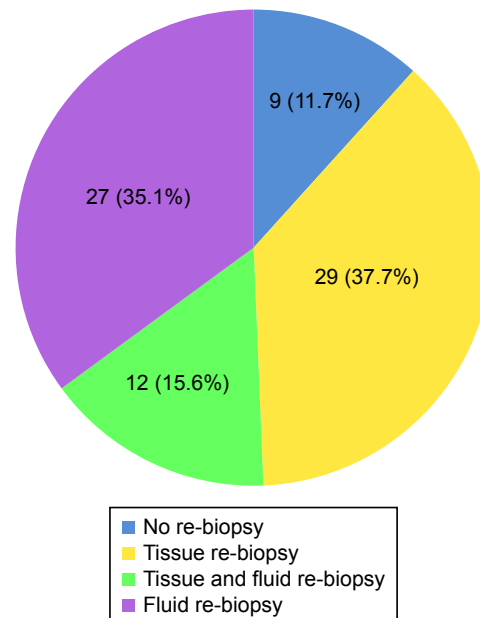


Figure 2 Re-biopsy status of patients: T790M mutations were not detected in 11.7% of patients.

Note: A total of 41 (53.3%) patients underwent tissue re-biopsies, and 39 (50.7%) patients underwent plasma analysis, with 12 patients underwent both tissue re-biopsies and plasma analysis.

T790M mutation status according to tissue/plasma analysis

The results of T790M mutation detection are summarized in Table 3.

Table 2 Comparison of the types and sites between first biopsies and re-biopsies

Type of biopsy	Total initial biopsy (N=75)	Initial biopsy (N=41)	Re-biopsy (N=41)
CT-guided percutaneous biopsy	34 (45.3%)	21 (51.2%)	29 (70.7%)
Lung	34	21	23
Liver	0	0	2
Bone	0	0	1
Chest wall	0	0	1
Adrenal gland	0	0	1
Pelvic parenchyma	0	0	1
Thoracentesis	8 (10.7%)	5 (12.2%)	3 (7.3%)
Bronchoscopy biopsy	20 (26.7%)	8 (19.5%)	6 ^a (14.6%)
Surgery	13 (17.3%)	7 (17.1%)	3 (7.3%)
Lung	9	5	0
Lymph node	3	2	2
Bone	1	0	1

Note: ^aTissues of two patients were re-biopsied through EBUS-TBNA at mediastinal lymph node.

Abbreviation: CT, computed tomography; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration.

Table 3 The situation of T790M mutation according to tissue and/or plasma analysis

	Plasma T790M+	Plasma T790M-	No plasma	Total
Tissue T790M+	7	1	15	23
Tissue T790M-	2	2	14	18
No tissue	13	14	9	36
Total	22	17	38	77

Twenty-three of 41 patients were found to have acquired T790M mutations according to tissue re-biopsy. The incidence rate of T790M was 56.1%. Initial *EGFR* mutations were identified in all re-biopsied tissues.

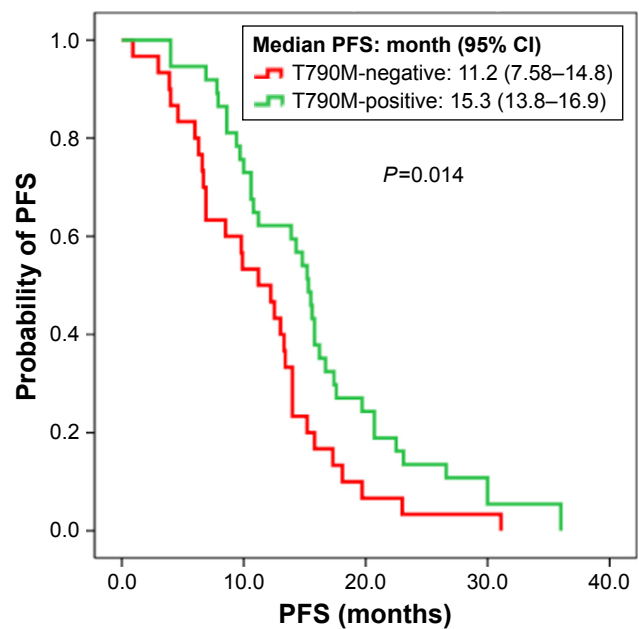
According to plasma analysis, T790M mutations were found in 22 (56.4%) patients together with their initial *EGFR* mutation. Initial *EGFR* mutations conferring sensitivity to EGFR-TKIs were found in cfDNA without T790M mutations in 14 patients. Three patients showed neither initial *EGFR* mutations nor acquired T790M mutations in their cfDNA.

The total incidence rate of T790M mutations according to both tissue and plasma analysis was 55.9% (38/68).

Among the 12 patients who underwent both tissue re-biopsy and plasma cfDNA analysis, nine had consistent results of T790M mutation status, while three had inconsistent results. Two patients were T790M(-) in their tissue re-biopsy but T790M(+) in plasma analysis. Tissues of both patients were re-biopsied after progression from icotinib, and both were shown to be 19del(+), which is consistent with their initial *EGFR* mutation status, but T790M(-). Both were then treated with chemotherapy, one with pemetrexed plus cisplatin and avastin, and one with gemcitabine plus cisplatin. Their cfDNA was then analyzed at 10 months and 15 months after icotinib progression, respectively, and shown to be T790M(+). They were both administered osimertinib, and both achieved partial remission. The third patient was shown to be T790M(-) in plasma analysis, then, T790M(+) in tissue re-biopsy 6 months later.

Correlation analysis between T790M mutations and clinical characteristics

Kaplan–Meier analysis showed that the median PFS of prior icotinib therapy in patients with acquired T790M mutations was significantly longer than in patients without acquired T790M mutations ($P=0.014$; Figure 3). No other clinical characteristics, including sex, age, smoking status, type of initial *EGFR* mutation, ORR, and disease control rate of icotinib, were found to be associated with the acquired T790M mutation status.

**Figure 3** PFS in patients with prior icotinib therapy.

Note: PFS was significantly longer in the T790M-positive group than in the T790M-negative group (15.3 vs 11.2 months, respectively, $P=0.014$).

Abbreviation: PFS, progression-free survival.

Subsequent therapy of patients with acquired T790M mutations

All 38 patients with acquired T790M mutations were treated by a third-generation EGFR-TKI: three received axitinib and 35 received AZD9291 (some labeled and some unlabeled). The efficacy could not be calculated because of the diversity of treatment.

Discussion

Acquired T790M mutations in *EGFR* exon 20 account for around 50%–70% of the mechanism of EGFR-TKI resistance. According to the AURA3 trial, osimertinib had a significantly greater efficacy than platinum therapy plus pemetrexed in patients with T790M(+) advanced NSCLC in whom disease had progressed during the first-line EGFR-TKI therapy.⁸ Therefore, it is important to detect T790M mutations when patients progress from the first-generation TKIs.

T790M mutation detection relies mainly on tissue specimens, although plasma cfDNA detection can also be efficient.¹² Indeed, plasma T790M(+) patients showed similar curative effects to tissue-positive patients in the AURA3 trial.⁸ However, cfDNA detection can give false-negative results, so patients who could potentially benefit from the third-generation TKIs might be missed. Therefore, tissue sample analysis remains the standard method of detecting T790M mutations to guide further treatment,¹² although plasma cfDNA detection has rapidly increased in recent

years. However, the rate of successful re-biopsy is very low in real-world China.

Among our *EGFR*-mutated NSCLC patients treated with icotinib, re-biopsies were successful in more than half. Feasibility and safety are the core problems associated with re-biopsy. Patients with recurrence often develop new metastatic lesions outside the thorax or in the peripheral regions of the lung, which are more suited to percutaneous needle biopsy than bronchoscopic mucosal biopsy.¹³ Even in Japan where bronchoscopies are more widely used for biopsies, their role is being reduced.¹⁴ The success of re-biopsy can also be influenced by the heterogeneity of the cancer or prior therapy which may affect the lesions through fibrosis or scarring. In such cases, positron emission tomography–computed tomography (CT) or contrast CT could be helpful for re-biopsy.

In terms of safety, no biopsy-related deaths occurred in our patients, and no serious adverse effects were observed, including mass pneumothorax or large hemoptysis causing unstable hemodynamics. Nevertheless, careful evaluation of the method, site, and safety of re-biopsy was required before it was conducted.

Plasma cfDNA was analyzed for T790M mutations in half of our patients. The accuracy of NGS in China is unsatisfactory because of developments in other detection technologies, so we used ARMS and ddPCR more often than NGS. Both methods showed a good positive rate, which supported the previously reported high accuracy of ddPCR for *EGFR* mutation detection in plasma and its clinical usefulness in selecting patients who progressed during the first-line *EGFR*-TKI therapy for treatment with the third-generation TKIs.^{15,16}

A retrospective study that conducted cfDNA analysis on over 200 samples from patients treated with osimertinib from the AURA study found 70% sensitivity for detecting the T790M mutation.¹⁷ Outcomes in patients whose plasma proved positive for T790M were equivalent to those seen in patients with positive tissue tests. The study also suggested that, upon the availability of validated plasma-based T790M assays, some patients could avoid a tumor biopsy for T790M genotyping.¹⁷ However, the 30% false-negative rate of plasma genotyping indicates that those patients with T790M(–) plasma results still need a tumor biopsy to determine the T790M mutation status. Moreover, pooled AURA extension and AURA2 data demonstrated that the plasma test did not detect the T790M mutation in plasma ctDNA of approximately 40% of patients with a T790M(+) tissue test result.¹⁸ A recent study compared T790M mutation detection rates in cfDNA and circulating tumor cells (CTCs) against biopsies in 40 patients. The T790M mutation was found in 75% of biopsies, 70% of CTC samples, and 80% of ctDNA

samples, so it was concluded that the various detection methods give similar results.¹⁹ Thus, for patients progressing from prior icotinib, cfDNA analysis for T790M mutations could be used first because it is more convenient and non-invasive.²⁰ However, for plasma T790M(–) patients, tissue re-biopsy should be performed as often as possible.

We identified two patients who were negative for tissue T790M mutations but positive for plasma T790M mutations at a later stage. Chemotherapy was administered to both patients during the period from tissue re-biopsy to plasma analysis, so we hypothesized that the observed increase in T790M positivity after chemotherapy might reflect tissue heterogeneity.²¹ This also indicated that further detection of the T790M mutation status could be helpful in patients shown to be T790M(–) by re-biopsy to identify those with “delayed” T790M mutations. Moreover, cfDNA analysis may be better for dynamic detecting.

Li et al found that patients with secondary T790M mutations at the time of gradual or local progress after acquired resistance to *EGFR*-TKI benefit more from *EGFR*-TKI treatment beyond progress compared with those without T790M mutations.²² Our study found a significantly longer prior PFS in T790M(+) patients than in T790M(–) patients. This indicated that acquired T790M mutations might be associated with an improved response to icotinib. However, this should be confirmed in a larger sample size.

The main limitation of this study is its retrospective nature. In addition, we did not include an evaluation of other resistance mechanisms in our re-biopsies, such as *MET* and *HER2* amplifications, mutations in *Ros-1*, *K-ras*, *BRAF*, and *PIK3CA*, and epithelial-to-mesenchymal transitions,^{5,6,23,24} thereby limiting our conclusion. Moreover, although T790M mutations were detected in some patients, their subsequent therapies were varied, so the relationship between therapeutic findings and the T790M mutation status could not be properly analyzed.

Conclusion

The re-biopsy rate was 53.2% in this real-world Chinese study, and the incidence rate of T790M mutations was 56.1% in these patients after icotinib therapy. More efforts are needed to increase the re-biopsy rate.

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Disclosure

The authors report no conflicts of interest in this work.

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