Genetic diagnostic features after failure of initial treatment with epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors among non-small-cell lung cancer patients harboring EGFR mutations

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Abstract

Background: Osimertinib, a third-generation epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI), can be used as second-line treatment for lung cancer patients harboring the T790M substitution. Although osimertinib is more effective than first-generation EGFR-TKIs used for first-line treatment, their efficacy for long-term patient survival remains unclear even upon administration of a complete sequence of EGFR-TKI therapy, and limited information is available regrading genetic diagnostic approaches after EGFR-TKI naïve treatment. This study aimed to investigate the characteristics of EGFR-mutated lung cancer patients harboring the T790M substitution resistant to EGFR-TKIs and the advantages of rebiopsy and liquid biopsy among these patients.

Methods: The medical records of patients screened for EGFR mutations were reviewed. Upon failure of naïve treatment with EGFR-TKIs except for osimertinib, single plexus COBAS version 2 was repeatedly used to detect the T790M substitution in EGFR via tissue or liquid biopsy.

Results: From April 2016 through May 2019, 113 patients harbored EGFR mutations. Sixty patients were treated with EGFR-TKIs, among which 46 underwent tissue or liquid biopsy. Twenty-nine of these 46 (63%) patients harbored the T790M substitution. In total, 141 rebiopsies were performed. The T790M substitution was detected in 24 of 43 tissue and 11 of 98 liquid biopsies. If patients displayed an EGFR exon 19 deletion, displayed a new lesion, and were administered gefitinib as first-line therapy, patients harboring an EGFR mutation were suspected to harbor the T790M substitution. Furthermore, the T790M substitution was detected through rebiopsy in patients with co-existing original mutations, brain metastases, tumor enlargement by ≥ 12 mm, or metastases at rare sites.

Conclusion: Repeated biopsy can help maximize the detection rate of the T790M substitution. Furthermore, the advantages of repeated tissue or liquid biopsy should be considered among *patients with positive T790M factors*, and these biopsies can be repeated numerous times.

Introduction

Patients with metastatic non-small-cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR)-sensitizing mutations generally receive EGFR-tyrosine kinase inhibitors (TKIs) as first-line treatment [1]. Five TKIs including first- to third-generation TKIs are available for EGFR-TKI therapy. Although most patients eventually become resistant to EGFR-TKIs, the EGFR p.Thr790Met point mutation (*EGFR* T790M) is detected in 30–50% of patients presenting with disease progression upon receiving first- or second-generation TKIs [2, 3]. These patients can be treated with osimertinib, while other patients may be treated with cytotoxic chemotherapy. Although osimertinib is generally preferred as first-line therapy because of efficacy and tolerability [4], patients with disease progression upon osimertinib treatment were administered only cytotoxic chemotherapy [5]. Recent studies have revealed numerous EGFR-TKI-based alternatives for first-line treatment. First-generation EGFR-TKIs have been used in combination with anti-VEGF antibody or with chemotherapy [6, 7, 8]. These clinical trials reported almost

the same high efficacy as that of osimertinib, despite slightly increased toxicities. In these trials, Furthermore, second-generation EGFR TKIs constitute first-line treatment alternatives for EGFR-mutated advanced NSCLC because no phase III clinical trial has compared the clinical efficacy of second-generation EGFR-TKIs and osimertinib. When NSCLC patients harboring EGFR mutations are administered EGFR-TKIs except osimertinib as first-line treatment, approximately half of the patients qualify for osimertinib therapy. For second- or third-line treatment of patients with osimertinib to maximize the treatment duration for EGFR-TKIs since April 2018 [9], it is important to maximally detect the T790M substitution. COBAS ver. 2 can be used for companion diagnostic examination (CDx) [10]. Limited information is available on maximizing the detection of the T790M substitution using this type of CDx. The purpose of this study was to investigate the characteristics of EGFR-mutated lung cancer patients harboring the T790M substitution resistant to EGFR-TKIs and the advantages of tissue rebiopsy and liquid rebiopsy among these patients.

Methods

Patients

From April 2016 to May 2019, consecutive patients screened or *EGFR* mutations were retrospectively reviewed at the National Center for Global Health and Medicine, Japan. The peptide nucleic acid-locked nucleic acid (PNA-LNA) PCR clamp method [11] was used to detect the *EGFR* mutation, using tissue biopsy specimens during the initial diagnosis of non-small non-squamous-cell lung cancer. After EGFR-mutated lung cancer acquired clinical resistance to EGFR-TKIs, the cobas® EGFR Mutation Test (Version 2; Roche Molecular Systems) [10] was repeatedly performed to detect the T790M mutation status through tissue or liquid biopsy. Clinical resistance was defined as an increase in monitoring of tumor markers, disease progression through radiological imaging, or clinical disease progression.

Rebiopsy and genetic analysis

All types of clinical rebiopsies were repeated when patients were suspected to be clinically resistant to EGFR-TKIs. If patients were likely to provide tumor tissue through a clinical procedure (e.g., bronchoscopy or CT-guided biopsy) at the time of radiographic disease progression, they underwent tissue biopsy numerous times. Otherwise, liquid biopsy was performed. After each rebiopsy, the cobas® version 2 was used. When a new T790M substitution was detected, patients were administered osimertinib; if not, they were administered treatment other than osimertinib, such as cytotoxic chemotherapy or other molecular-targeted therapy. Among patients not harboring the T790M substitution, tissue or liquid rebiopsies were repeated numerous times until the T790M substitution was detected. Cobas® version 2 is a single plexus real-time PCR procedure to detect EGFR mutations, which potentially uses unstained 5-μm-thick sections obtained from a formalin-fixed paraffin-embed (FFPE) block and mounted on slides or whole blood samples, as previously reported [10]. Mutations were analyzed at the central laboratory of LSI Medience Corporation (Tokyo, Japan).

Data collection

The following data were obtained from each patient's medical records: patient characteristics including age, sex, smoking index, smoking status, comorbidities, and Eastern Cooperative Oncology Group performance status (PS) at diagnosis, oncological data including histologic type, staging in accordance with the 8th edition of the TNM Classification of Malignant Tumors [12], tumor size of biopsy site, number of tumor lesions, metastatic organ, EGFR mutation sites detected via the PNA-LNA PCR clamp method or cobas® version 2, treatment data including surgical treatment, radiotherapy including radical or palliative radiation, pharmacotherapy (gefitinib, erlotinib, afatinib, and osimertinib) at EGFR-TKI naïve line, subsequent systemic therapies including cytotoxic chemotherapy regimens, immunotherapy, or other molecular-targeted therapy, data on the best supportive care, and tumor markers for CEA (ng/mL). Computed tomography (CT), positron-emission CT (PET-CT), and magnetic resolution imaging (MRI) were performed within one month of each biopsy for corresponding biopsy specimens. Patients harboring the T790M substitution were defined under the category of "at least one detection of T790M using single-plexus PCR through any type of clinically available biopsy."

Ethical considerations

The study was conducted in accordance with the tenets of the Declaration of Helsinki. The study protocol was approved by the certified review board of National Center for Global Health and Medicine (NCGM-G-003361-00). In accordance with the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects, we used the opt-out method. We informed the participants about this study and obtained informed consent from subjects by displaying the disclosure document in the hospital per the approval data by the appropriate review board until 31st January 2020.

Statistical analysis

The primary outcome was the identification of EGFR-mutated lung cancer patients harboring the T790M substitution having acquired clinical resistance to EGFR-TKIs. Secondary outcomes were the identification of factors inducing the T790M substitution through any type of rebiopsy among patients harboring the T790M substitution and factors inducing the T790M substitution through liquid rebiopsy.

Fisher's exact test was performed to compare the proportion of subjects with dichotomous outcomes in both groups. For continuous variables, receiver-operator characteristics (ROC) curves were analyzed using SigmaPlot version 14 software (Systat Software, Inc., San Jose CA, USA). At a p-value of <0.05 ($p < 0.05$), the optimal cutoff values of these continuous variables were set on the basis of a pre-test probability of 0.5 and cost ratio of 1.0.

Logistic regression analysis was performed to assess the aforementioned three factors among patients with EGFR-mutated lung cancer having acquired clinical resistance to EGFR-TKIs, as previously described [13]. To select a model for multivariate analysis, we identified variables with a p-value less than 0.15 on univariate analysis. Spearman's rank test and clinically clarified dependent variables were used to exclude dependent variables from the aforementioned selected variables. A correlation coefficient (ρ) of more than 0.3 as the absolute value on Spearman's rank test indicated a significant association. Some models

were constructed with only independent variables as candidates. ROC curves were used to select the best model among candidate models. In the final multivariate analysis using the simultaneous method, statistical significance was determined at a p-value of < 0.05 through a two-sided test. All analyses were performed using SPSS Statistics software version 25 (IBM, Armonk NY, USA) or Stata version 15.1 (StataCorp LLC, College Station TX, USA).

Results

Patients

From April 2016 to May 2019, 405 patients consecutively underwent the EGFR mutation test. Among them, EGFR mutations were detected in 113 patients (Figure 1). Five patients decided to undergo only best supportive care (BSC) and 48 did not experience relapse after local therapy including surgery, radiotherapy, or chemoradiotherapy. Sixty patients harbored activating EGFR mutations and 7 were administered osimertinib as TKI-naïve therapy. The remaining patients were treated with TKIs, except for osimertinib. The T790M substitution was detected in 29 of 46 (63%) patients who underwent rebiopsy. Table 1 outlines the demographic characteristics of each group. Thirteen patients presented with post-operative recurrence and 4 patients presented with post-irradiation recurrence. During the overall study period, 33 patients received chemotherapy. During TKIs-naïve treatment, 12 patients received gefitinib, 32 received erlotinib, and 8 received afatinib.

Rebiopsy outcomes

To identify patients harboring the T790M substitution, all types clinically available rebiopsies were performed numerous times (Table S1). Tissue biopsy was repeated 4 times at maximum. During the initial tissue biopsy, the detection rate was 67.8%; sensitivity, 80.8%. Thereafter, the detection rate was approximately 30%; cumulative sensitivity, 77.4–79.3%. Liquid biopsy was repeated 10 times at maximum. During the initial liquid biopsy, the detection rate was 8.1%; sensitivity, 13%. During each liquid biopsy, the median detection rate was 8.6%, ranging 0–25%, and the median cumulative sensitivity was 18.9%, ranging 16.7–20.6%. In total, we performed 141 rebiopsies, including both tissue and liquid biopsies from 46 patients (Table 2). Among these patients, 29 (63 %) harbored the T790M substitution. The T790M substitution was detected in 35 (cumulative sensitivity = 39.3%) biopsies, including 24 tissue (cumulative sensitivity = 77.4%) and 11 in liquid (cumulative sensitivity = 19%) biopsies. On detecting the T790M substitution, significant differences between tissue and liquid biopsy were observed on the Fisher's exact test (P < 0.0001).

Positive factors in patients harboring the T790M substitution

The primary outcome was to identify factors among patients harboring the T790M substitution after patients with EGFR-mutant NSCLC acquired clinical resistance to EGFR-TKIs. We performed logistic regression analyses for 53 patients treated with EGFR-TKIs other than osimertinib (Figure 1). The results of logistic regression analyses are shown in Table 3. Six variables had p-values >0.15 on univariate

analyses. Multivariate analysis indicated that significant clinical features associated with patients harboring the T790M substitution were as follows: exon 19 deletion in the original mutation, termination of TKIs owing to detection of new lesions, and gefitinib during TKI-naïve treatment.

Positive factors for the T790M substitution upon rebiopsy

One of the secondary outcomes was to identify positive factors for the T790M substitution by any type of rebiopsies among patients harboring it. Among these patients, 89 rebiopsies were performed. Logistic regression analyses revealed 16 variables with p-values <0.15 on univariate analyses. We constructed 4 sets of multivariate models comprising variables that were not correlated with each other. The best model selected through ROC curve analysis is shown in Table 4. Multivariate analysis indicated that the significant detection of the T790M substitution upon rebiopsy among patients harboring T790M were as follows: co-detection of the original mutation, co-occurring brain metastases, tumor enlargement at ≥12 mm, or involvement of rare site metastases.

Positive Factors for the T790M substitution upon liquid biopsy

Regarding the detection of the T790M substitution through liquid rebiopsy among patients harboring the T790M substitution as another secondary outcome, 58 liquid biopsies were performed. Eleven variables with p-values of <0.15 were obtained on univariate logistic regression analyses. Four sets of multivariate model candidates were constructed with each independent variable. The best model selected through ROC curve analysis is shown in Table 5. On multivariate analysis, detection of the T790M substitution via liquid biopsy among patients harboring the T790M substitution indicated the following: involvement of bone metastases or new tumor lesions ≥ 4.

Discussion

This study aimed to investigate the characteristics of EGFR-mutated lung cancer patients harboring the T790M substitution resistant to EGFR-TKIs and the advantages of rebiopsy and liquid biopsy among these patients. This study shows that repeated biopsy through single-plexus PCR revealed that 63% of EGFR-mutated NSCLC patients harbored the T790M substitution after acquiring clinical resistance to EGFR-TKIs. Tissue biopsy was superior to liquid biopsy in detecting the T790M substitution ($P < 0.0001$). Because liquid biopsy is a noninvasive biopsy modality for molecular-targeted analysis including the EGFR mutational status, using a plasma sample, it is easily reproducible. The present results indicate that liquid biopsy revealed more false-negative results in clinical practice at a limit of detection (LOD) of >100 copies of mutant DNA/ml [14]. When liquid biopsy through this test yields negative results for the T790M substitution, it is essential to undergo tissue biopsy. To identify patients harboring the T790M substitution, tissue biopsy should receive first priority because of its high sensitivity and high detection rate.

Herein, the primary outcome was to assess the clinical characteristics of patients harboring the T790M substitution. Three clinically relevant factors were detected: exon 19 deletion in the original mutation, TKI

termination owing to the detection of new lesions, and gefitinib administration during TKI-naïve treatment (Table 3). On deciding to undergo or to repeat biopsy, these 3 factors should be considered. We estimated the probability of detecting the T790M substitution and considering the number of rebiopsies.

The timing and site are important factors to consider for each rebiopsy. Positive factors for the T790M substitution through any type of rebiopsy among patients harboring the T790M substitution would provide information regarding the timing and site for the biopsy (Table 4). Based on the timing of the biopsy, patients had brain metastases and rare metastases and their tumor lesions enlarged by >12 mm. The enlarged tumor site would be better for tissue biopsy. When patients had bone metastases and harbored ≥4 new tumor lesions compared with previous tumor lesions, liquid biopsy was considered to detect the T790M substitution (Table 5).

This study has several limitations. Despite including consecutive patients herein, our study is a single-center, real-world, retrospective study. Although 405 consecutive patients were screened for the *EGFR* mutation for 3 years, these mutations were detected in only 28% of patients (Figure 1). Furthermore, our patient cohort comprised only 53 patients, thus being a small cohort for obtaining clinical data. Owing to remarkable progress in NSCLC treatment, only minor benefits would be obtained, although the clinical data were obtained over a longer duration. In clinical practice, information from real-world data would be useful for repeated molecular analyses.

Nonetheless, this study also has some strengths. The knowledge of the clinical characteristics of patients harboring the T790M substitution would help select appropriate patients who should undergo and repeat tissue or liquid rebiopsy. Because individuals with drivers receiving a matched targeted agent lived longer [15], we consider that patients with clinical characteristics of those harboring the T790M substitution should undergo repeated biopsies until the T790M substitution is detected. Furthermore, these results help select the type or timing of biopsy based on the positive factors for the T790M substitution. In addition, on testing for EGFR-mutant tumors at an LOD of >100 copies/ml, tissue biopsy still received first priority.

Conclusion

This study shows that repeated biopsy helps maximize the detection rate of the T790M substitution. On repeating the tissue or liquid biopsy, it is necessary to consider the positive factors for the T790M substitution. *If patients present these positive factors for the T790M substitution, rebiopsy should be repeated numerous times.*

List Of Abbreviations

NSCLC; non-small cell lung cancer

EGFR; epidermal growth factor receptor

TKI; tyrosine kinase inhibitor

T790M; EGFR p.Thr790Met point mutation

VEGF; Vascular Endothelial Growth Factor

CDx; Companion Diagnostic examination

PCR; Polymerase Chain Reaction

PNA-LNA PCR clamp method; Peptide Nucleic Acid - Locked Nucleic Acid PCR clamp method

PS; performance status

CT; computer tomography

PET-CT; positron emission CT

MRI; magnetic resolution imaging

ROC; Receiver-Operator Characteristics

LOD; limit of detection

Declarations

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Contributions

YT performed the analysis and wrote the article, GO, YY, MH, MS, and SI supported the article writing and analysis, YT, GO, and YY performed the analysis and proofread the article. All authors contributed to the interpretation of the data and read and approved the final manuscript.

Ethics declarations

Ethics approval and consent to participate

The study was conducted in accordance with the tenets of the Declaration of Helsinki. The study protocol was approved by the certified review board of National Center for Global Health and Medicine (NCGM-G-003361-00). In accordance with the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects, we used the opt-out method. We informed the participants about this study and obtained informed consent from subjects by displaying the disclosure document in the hospital per the approval data by the appropriate review board until 31st January 2020.

Consent for publication

Not applicable.

Competing interests

YT has received grants from Boehringer Ingelheim, Chugai Pharmaceutical, outside of this study. The remaining authors declared no competing interests for this work.

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Tables

Table 1. Patient background characteristics

Variable	Rebiopsy (+) T790M mutation Positive (n = 29)	Rebiopsy (+) T790M mutation Negative (n = 17)	Rebiopsy (-) Unknown (n = 7)
Sex			
Male	11	3	3
Female	18	14	4
Age (years)			
Median	74	72	70
Range	42 - 86	38 - 89	59 - 82
Histology			
Adenocarcinoma	27	17	7
others	2	0	0
EGFR mutation at initial diagnosis			
Exon 19 deletion	21	6	1
L858R	8	9	5
L861Q	0	1	0
Exon 20 insertion	0	1	0
Compound mutation	0	0	0
Smoking status			
Never	18	13	3
Past	8	1	2
Current	3	3	2
ECOG performance status			
0	20	12	3
1	8	5	2
2	1	0	1
3	0	0	1
Stage at initial diagnosis			
IA - IIIC	10	3	3
IVA - IVB	19	14	4
Surgical treatment			
No	13	6	3
Yes	16	11	4
Radical Radiotherapy			
No	27	16	6
Yes	2	1	1
Chemotherapy during treatment			
No	8	6	6
Yes	21	11	1
EGFR-TKIs at TKI naïve line			
Gefitinib	11	2	0
Erlotinib	16	10	6
Afatinib	2	5	1

ECOG, Eastern Cooperative Oncology Group.

Table 2. Rebiopsy outcomes

Variable	T790M mutation		
	Positive patients (n = 29)	Negative patients (n = 17)	Total patients (n = 46)
Tissue biopsy (included cytology) count	**31**	**12**	**43**
T790M positive count	**24 (77.4)**	**-**	**24 (55.8)**
With Original mutation	22	-	22
Without Original mutation	2	-	2
T790M negative count	**7 (22.6)**	**12**	**19 (44.2)**
With Original mutation	5	10	15
Without Original mutation	2	2	4
Liquid biopsy count	**58**	**40**	**98**
T790M positive count	**11 (19.0)**	**-**	**11 (11.2)**
With Original mutation	10	-	10
Without Original mutation	1	-	1
T790M negative count	**47 (81.0)**	**40**	**87 (88.8)**
With Original mutation	9	11	20
Without Original mutation	38	29	67
Total rebiopsy count	**89**	**52**	**141**

Data are number of patients (%) unless specified otherwise.

Table 3. Logistic regression analysis to identify patients harboring the T790M substitution among those with EGFR-mutated lung cancer (n = 53)

Variables	Univariate Analyses			Multivariate Analysis		
	OR	95%CI	*P-value*	OR	95%CI	*P-value*
Mutation site at initial diagnosis; Exon 19 Deletion vs. L858R	**0.17**	**0.05 - 0.51**	**0.002**	**0.04**	**0.004 - 0.34**	**0.003**
Reason for termination of TKIs;	**2.26**	**1.25 - 4.11**	**0.007**	**3.65**	**1.39 - 9.59**	**0.008**
Ongoing		**Reference**			**Reference**	
AEs	**1**	**-**	**-**	**1**	**-**	**-**
Tumor growth	**37.3**	**3.30 – 421.6**	**0.003**	**33.8**	**1.60 – 713.3**	**0.024**
New lesions	**12.4**	**1.32 – 117.0**	**0.027**	**44.9**	**2.13 – 950.9**	**0.014**
Medical Drugs at TKI-naïve line	**0.24**	**0.08 - 0.72**	**0.01**	**0.09**	**0.01 - 0.62**	**0.014**
Gefitinib		**Reference**			**Reference**	
Erlotinib	**0.18**	**0.035 - 0.95**	**0.044**	**0.49**	**0.02 – 0.99**	**0.049**
Afatinib	**0.06**	**0.007 – 0.55**	**0.012**	**0.01**	**0.0002 – 0.53**	**0.02**
Chemotherapy; absent vs. present	2.63	0.84 - 8.22	0.09		NI	
"Serum level of CEA at progression" divided by "Serum nadir level of CEA"	1.16	0.97 - 1.39	0.11	1.22	0.77 - 1.93	0.4
Serum nadir level of CEA (ng/mL)	0.97	0.95 - 1.01	0.14		NI	

Abbreviations: OR, Odds ratio; CI, confidence interval; TKI, tyrosine kinase inhibitor; AEs, adverse effects; CEA, *carcinoembryonic antigen;* Variables with a p-value < 0.15 on univariate analysis were entered into multivariate logistical analysis by a simultaneous method. NI, not included in the best multivariate logistic regression model.

Table 4. Logistic regression analysis to identify patients harboring the T790M substitution upon rebiopsy (n = 89)

Variables	Univariate Analyses			Multivariate Analysis		
	OR	95%CI	*P-value*	OR	95%CI	*P-value*
Original mutation; absent vs. present	**30.5**	**8.05 - 115.3**	**< 0.001**	**41.5**	**6.53 - 264.3**	**< 0.001**
Type of Biopsy; Liquid vs. Tissue	14.6	5.04 - 42.6	< 0.001		NI	
Detection of New tumor lesion; < 4 vs 4 ≤	5.67	2.24 - 14.4	< 0.001		NI	
Number of Tissue biopsy	5.72	2.30 - 14.2	< 0.001		NI	
Detection of New metastatic organ; 0 → 4	2.35	1.39 - 3.97	0.001		NI	
Number of tumor lesion; < 6 vs 6 ≤	5.61	2.0 - 15.7	0.001		NI	
Brain metastases; absent vs. present	**4.40**	**1.71 - 11.3**	**0.002**	**27.8**	**3.13 - 247.8**	**0.003**
Bone metastases; absent vs. present	3.94	1.55 - 9.98	0.004		NI	
Number of Liquid biopsy	0.69	0.52 - 0.90	0.006		NI	
Enlargement of Tumor size; < 12mm vs 12mm ≤	**3.47**	**1.42 - 8.49**	**0.007**	**24.5**	**2.65 - 226.7**	**0.005**
New brain metastases; absent vs. present	4.5	1.26 - 16.1	0.02		NI	
Mutation site at initial diagnosis; Exon19 Deletion vs. L858R	**3.08**	**1.06 - 8.95**	**0.04**	3.90	0.63 - 24.3	0.145
Rare site metastases; absent vs. present	**4.20**	**1.07 - 16.5**	**0.04**	**21.3**	**1.40 - 325.6**	**0.03**
New hepatic metastases; absent vs. present	3.64	0.85 - 15.7	0.08		NI	
New rare site metastases; absent vs. present	4.48	0.82 - 24.6	0.08		NI	
Hepatic metastases; absent vs. present	2.54	0.99 - 1.09	0.141		NI	

Abbreviations: OR, Odds ratio; CI, confidence interval; Variables with a p-value < 0.15 on univariate analysis were entered into multivariate logistical analysis by a simultaneous method. NI, not included in the best multivariate logistic regression model.

Table 5. Logistic regression analysis to identify patients harboring the T790M substitution through liquid biopsy (n = 58)

Variables	Univariate Analyses			Multivariate Analysis		
	OR	95%CI	*P-value*	OR	95%CI	*P-value*
Original mutation; absent vs. present	42.2	4.77 - 373.6	0.001		NI	
Bone metastases; absent vs. present	**48.8**	**5.45 - 436.4**	**0.001**	**77.9**	**5.32 - 1140**	**0.001**
Enlargement of Tumor size; < 12mm vs 12mm ≤	0.10	0.02 - 0.43	0.002		NI	
Brain metastases; absent vs. present	7.39	1.77 - 30.8	0.006		NI	
Detection of New tumor lesion; < 4 vs 4 ≤	**7.39**	**1.77 - 30.8**	**0.006**	**14.5**	**1.38 - 151.2**	**0.026**
Detection of New metastatic organ; 0 → 4	1.98	1.09 - 3.59	0.024		NI	
New rare site metastases; absent vs. present	8.44	1.21 - 58.8	0.031		NI	
Hepatic metastases; absent vs. present	5.50	0.94 - 32.2	0.059		NI	
Rare site metastases; absent vs. present	5.50	0.94 - 32.2	0.059		NI	
Mutation site at initial diagnosis; Exon19 Deletion vs. L858R	3.91	0.87 - 17.5	0.075	1.15	0.13 - 10.1	0.897
New hepatic metastases; absent vs. present	5.00	0.62 - 40.3	0.131		NI	

Abbreviations: OR, Odds ratio; CI, confidence interval; Variables with a p-value < 0.15 on univariate analysis were entered into multivariate logistical analysis by a simultaneous method. NI, not included in the best multivariate logistic regression model.

Figures

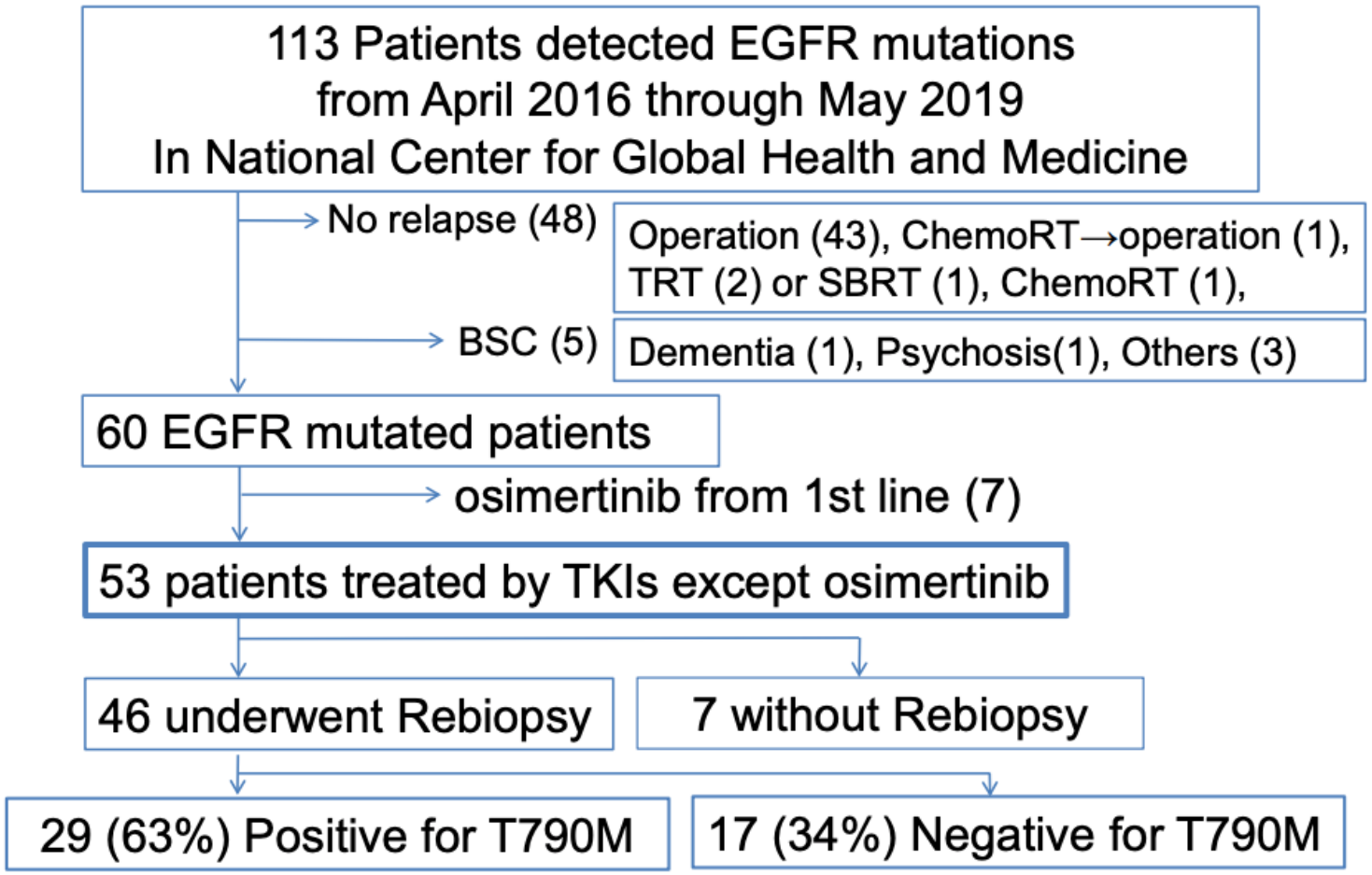

Figure 1

Study Consort Data are number of patients unless specified otherwise.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplimentarytablesBMCCancer.pdf