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Professor Sai-Hong Ignatius Ou is currently the Health Science Clinical Professor of Medicine in the Department of Medicine, Division of Hematology Oncology at the University of California Irvine School of Medicine. Dr. Ou received his MD and PhD degrees from the University of Texas Southwestern Medical School and completed internship and residency in internal medicine at Duke

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Dr. Ou is one of the eight original phase 1 investigators of crizotinib, and is the senior and corresponding author of the US phase 1 dose escalation of alectinib in the US and participated in the clinical trials of lorlatinib. Dr. Ou has published close to 130 peer-reviewed articles including publication in New Journal of Medicine, The Lancet Oncology, Journal of Clinical Oncology, JAMA Oncology, and Cancer Discovery. Dr. Ou is on the scientific advisor board of TP Therapeutics which is developing the fourth generation ALK/ROS1/NTRK inhibitor that can overcome solvent front mutations. His major research interests are in targeted therapy in lung cancer and other solid malignancies that harbors actionable driver mutations in particular receptor tyrosine kinase fusions and the strategies to overcome resistance to tyrosine kinase inhibitors. Dr. Ou serves on the editorial board of Annals of Oncology, Clinical Lung Cancer, and Translational Lung Cancer research and have been ad hoc reviewer for New England Journal of Medicine, The Lancet, The Lancet Oncology and Journal of Clinical Oncology among other journals. Dr. Ou is on the scientific committee for metastatic lung cancer for the American Society of Clinical Oncology annual meeting from 2016-2018.

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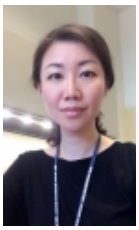

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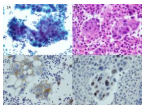

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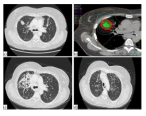

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ORIGINAL RESEARCH

Uncommon *EGFR* mutations in cytological specimens of 1,874 newly diagnosed Indonesian lung cancer patients

This article was published in the following Dove Press journal:
Lung Cancer: Targets and Therapy

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Purpose: We aimed to evaluate the distribution of individual epidermal growth factor receptor (*EGFR*) mutation subtypes found in routine cytological specimens.

Patients and methods: A retrospective audit was performed on *EGFR* testing results of 1,874 consecutive cytological samples of newly diagnosed or treatment-naïve Indonesian lung cancer patients (years 2015–2016). Testing was performed by ISO15189 accredited central laboratory.

Results: Overall test failure rate was 5.1%, with the highest failure (7.1%) observed in pleural effusion and lowest (1.6%) in needle aspiration samples. *EGFR* mutation frequency was 44.4%. Tyrosine kinase inhibitor (TKI)-sensitive common *EGFR* mutations (ins/dels exon 19, L858R) and uncommon mutations (G719X, T790M, L861Q) contributed 57.1% and 29%, respectively. Approximately 13.9% of mutation-positive patients carried a mixture of common and uncommon mutations. Women had higher *EGFR* mutation rate (52.9%) vs men (39.1%; $p<0.05$). In contrast, uncommon mutations conferring either TKI responsive (G719X, L861Q) or TKI resistance (T790M, exon 20 insertions) were consistently more frequent in men than in women (67.3% vs 32.7% or 69.4% vs 30.6%; $p<0.05$). Up to 10% *EGFR* mutation–positive patients had baseline single mutation T790M, exon 20 insertion, or in coexistence with TKI-sensitive mutations. Up to 9% patients had complex or multiple *EGFR* mutations, whereby 48.7% patients harbored TKI-resistant mutations. One patient presented third-generation TKI-resistant mutation L792F simultaneously with T790M.

Conclusion: Routine diagnostic cytological techniques yielded similar success rate to detect *EGFR* mutations. Uncommon *EGFR* mutations were frequent events in Indonesian lung cancer patients.

Keywords: *EGFR* mutations, lung cancer, treatment naive, T790M, tyrosine kinase inhibitor, Indonesia, cytology

Introduction

Lung cancer in Indonesia ranks the fourth most common of all cancers.[1] Majority of lung cancer cases are found in late stages and cytological specimens are common sources of diagnostic practices in tertiary hospitals.[1] In addition to valuable diagnostic tools, cytological specimens are useful sources of epidermal growth factor receptor (*EGFR*) mutation testing. Specific guidelines of *EGFR* mutation testing in cytological specimens have been issued and adopted widely.[2,3] However, there are considerable concerns regarding *EGFR* testing failure rates that may delay timeline of treatment decisions. Few or lack of tumor cells, improper fixation procedures, poor extracted DNA quality, and/or absence of or generation of nonspecific polymerase chain reaction (PCR) products have led to testing failures.[3]

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Indonesian health authority has published national formulary to reimburse expenses of tyrosine kinase inhibitors (TKI) as first-line treatment for lung cancer patients bearing *EGFR* mutation. In 2014, we had described common *EGFR* mutations associated with first-generation TKI (erlotinib and gefitinib) sensitivity mainly in exons 19 (insertions/deletions) and 21 (L858R) obtained from cytological specimens using Sanger sequencing.[4] However, the prevalence and clinical pathology associations of rare or uncommon *EGFR* mutations such as G719S/A/C (collectively G719X), T790M, and L861Q had not been described extensively in Indonesia. These uncommon mutations are sensitive to second and third generations of *EGFR* TKI, namely afatinib and osimertinib.[5] Specifically, T790M mutation rate is thought to be low in treatment-naïve patients, but it contributes up to 50% of patients who are resistant to first-generation TKI.[6–8]

In this real-world *EGFR* mutation testing of treatment-naïve lung cancer patients, we had employed combination of PCR high-resolution melt (HRM) and restriction fragment length polymorphism (RFLP) to screen for common *EGFR* mutations (exon 19 insertions/deletions and L858R mutation in exon 21 of *EGFR* gene) to improve *EGFR* genotyping sensitivity.[9,10] PCR HRM allowed rapid screening for genetic mutations due to differential melting properties of wild-type and mutant alleles PCR products.[11] Both PCR HRM and RFLP methods have demonstrated superior sensitivity to Sanger sequencing.[12] We also described the impact of various cytological sampling techniques to successful testing rate and evaluated frequency of individual mutation subtypes as well as their clinical pathology associations.

Patients and methods

Patients

Since the initial introduction of *EGFR* testing a few years ago, Indonesian clinicians and pathologists had been routinely using cytological specimens as primary testing sources as practical approach. Such routine practices cited successful *EGFR* testing from cytological samples by a reputable Southeast Asian laboratory.[13] Moreover, tissue resection or surgical biopsies were not commonly performed by most clinicians (personal communications). Consequently, there were no formalin-fixed paraffin-embedded (FFPE) tissue specimens being received by our *EGFR* testing facility. Cytological specimens of 1,874 consecutive newly diagnosed lung cancer patients were received and tested for *EGFR* mutation by Kalbe Genomics Laboratory from September 2015 to April 2016. Cytological specimens along with pathology reports describing sex, age, cytopathology, and diagnostic sampling methods were received from 44 cities in Indonesia. However, fixative procedures of cytological specimens were not described in the *EGFR* testing request forms, except for 175 samples that arrived as FFPE blocks.

Kalbe Genomics is an ISO15189 accredited laboratory for *EGFR* mutation testing and has demonstrated consistent satisfactory performance in *EGFR* proficiency testing organized by European Molecular Genetic Quality Network and UK NEQAS annually since 2011. Ethic committees of Faculty of Medicine Universitas Airlangga, Soetomo General Hospital, Surabaya, and Persahabatan Hospital, Jakarta, approved this study. The study was performed in accordance with the 1964 Helsinki Declaration and its later amendements. Patient identities were anonymized. The approving ethics committees waived the need for informed consent because the study was based on existing administrative records and clinical data.

EGFR mutation screening program in Indonesia

During the study period, Astra Zeneca Indonesia (AZI) and Roche Indonesia (RI) invited physicians to test for *EGFR* mutation in newly diagnosed lung cancer patients and covered the costs for any patients diagnosed with lung adenocarcinoma or any non-small-lung cancers, respectively. The program stipulated no obligation in any kind of prescription in compliance with both AZI and RI ethical code of conducts. Test results were sent directly from the laboratory to the physicians.

DNA extraction

Genomic DNA was isolated from tumors using the QIAamp DNA Micro kit (Qiagen, Hilden, Germany) following the manufacturer's protocol. DNA from each sample was eluted in 50 μL of AE buffer (included in the kit).

Mutation analysis

EGFR exons 19 and 21 mutation screenings were performed using PCR HRM analysis. PCR cycling and HRM analyses were performed on Rotor-Gene Q (Qiagen) using intercalating dye SYTO9 (Thermo Fisher Scientific Inc., Waltham, MA, USA) as described.[9] Samples were denatured with an initial hold of 95°C for 30 s and a melting profile from 79°C to 90°C rising at 0.2°C. HRM data were presented as derivative graph to observed "split peak" indicating presence of mutated alleles (Figure 1) using Rotor-Gene Q software (Qiagen). Split peak pattern was observable in low percentage of mutant alleles, that is, less than 25%, a percentage that was usually not detect-

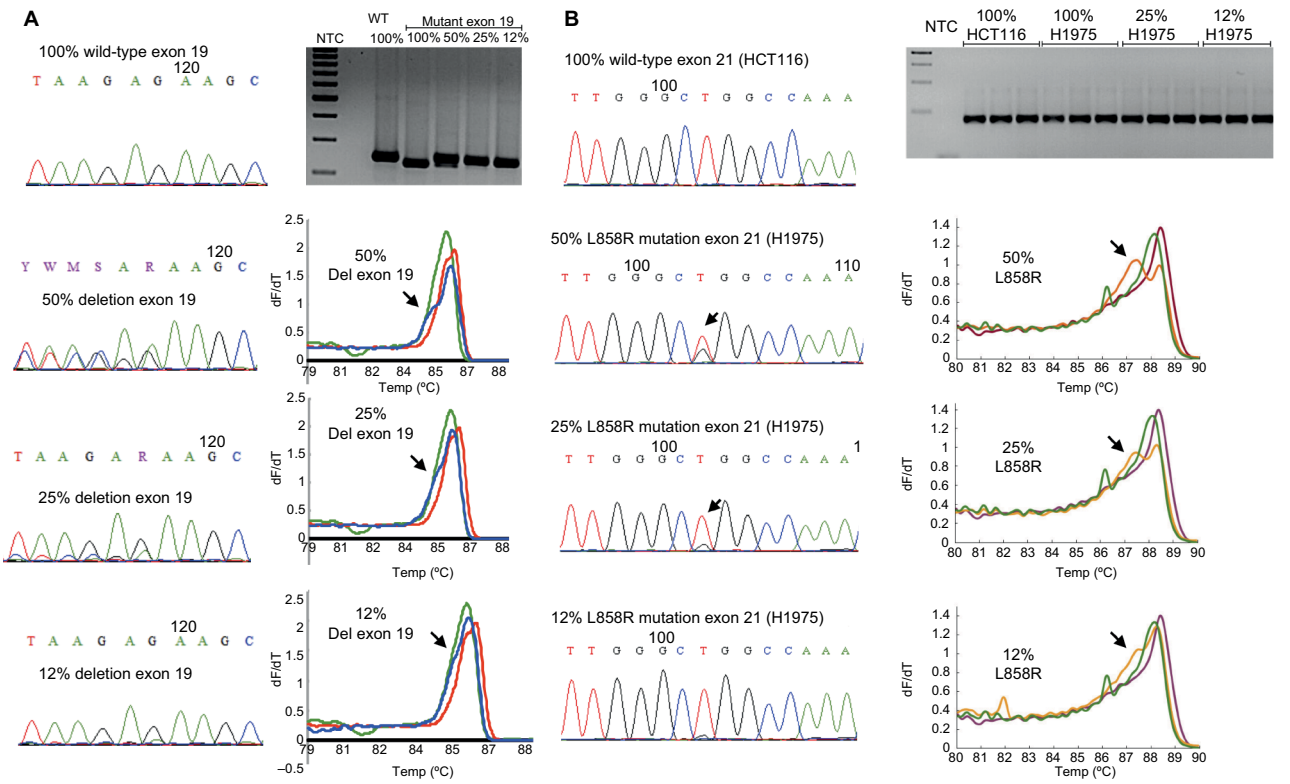

Figure 1 Analytical sensitivity of PCR high-resolution melt (HRM) derivative graph of melt pattern (right panel) in comparison to direct sequencing (left panel) and fragment sizing to screen for insertion/deletion mutations in EGFR gene exon 19 (**A**) and point mutation L858R in exon 21 (**B**).

Notes: Sequencing tracing images in left panel shows the descending ratio of mutant to total alleles (wild-type and mutant alleles) ranging from 12% to 100%. Upper right panel shows the specificity of PCR product. Lower right panels show the melt pattern of PCR HRM graph in various ratios of mutant to wild-type alleles. Arrows show "split peaks" indicating the presence of mutations. HCT116 and H1975 are cell lines carrying wild-type and EGFR L858R mutant alleles, respectively.

Abbreviations: PCR, polymerase chain reaction; EGFR, epidermal growth factor receptor.

able using direct sequencing method. PCR RFLP method was then used to follow up suspected mutation suggested by presence of "split peak" pattern. Genotyping of *EGFR* L858R and L861Q hotspot mutations in exon 21 was performed using PCR RFLP that had been shown to detect 1% mutant allele.[10]

Mutations in *EGFR* exons 18 (namely to detect G719X) and 20 (T790M and insertions) were analyzed using Sanger sequencing. Primer pairs for *EGFR* exon 18 were designed with primer-BLAST software and for *EGFR* exon 20 was described previously.[14] Some samples carrying mutation in exon 20 T790M were retested using Therascreen *EGFR* RGQ PCR kit (Qiagen, Manchester, UK) and/or AmoyDx *EGFR* 29 mutations detection kit (AmoyDx, Xiamen, China), according to the manufacturer's instructions.

Direct sequencing

PCR amplification products were purified using the ExoSAP-IT PCR Product Cleanup (Affymetrix/USB, Santa Clara, CA, USA) according to the manufacturer's protocol. Sequencing analysis was performed on an Applied Biosystem 3500 Genetic Analyzer. Nucleotide sequences of primers are available upon requests.

Statistical analysis

Fisher's exact test was used to analyze associations between the presence of *EGFR* mutations and clinical pathology characteristics. Significance was set at $p<0.05$ (two-sided).

Results

Utility of melting peak PCR HRM to screen *EGFR* mutations

Direct sequencing method generally could not detect the presence of mutations when there were less than 25% as shown in left panels of Figure 1A (exon 19 mutations) and 1B (exon 21 mutations). To improve our capability to detect *EGFR* mutations, we employed PCR HRM to screen for the presence of *EGFR* mutations in exons 19 (Figure 1A right panel) and 21 (Figure 1B right panel) and observed different forms of melt pattern between PCR amplicons containing normal/wild-type *EGFR* and mutant *EGFR* samples when

presented in derivative graph mode (Figure 1). As shown in Figure 1A, melt pattern (pointed by arrow) of wild-type exon 19 PCR amplicon (green trace line) showed single peak, while samples (red and blue trace lines) with PCR amplicons bearing mutational exon 19 insertions or deletions (ins/dels) demonstrated split peaks.

Similar split peak patterns were also observed in L858R sample (orange trace line, Figure 1B), while normal or wild-type samples showed single peak (green and brown trace lines). Unlike exon 19, however, split peak patterns shown in samples having mutations in exon 21 were due to single base substitution instead of multi PCR amplicons. Agarose electrophoreses of exon 21 PCR amplicon also confirmed the presence of single PCR product amplicon (Figure 1B upper panel). Therefore, split peak pattern strongly suggested the presence of mutant alleles.

To determine the analytical sensitivity of HRM approach, we tested using serial dilution of artificial DNA method. As shown in right panels of Figure 1A and 1B, threshold of detection limit indicated by the presence of split peak corresponded to 12% and 6% of mutant alleles in exons 19 and 21, respectively.

Impact of cytological techniques to *EGFR* testing

Clinical pathology characteristics of consecutive 1,874 newly diagnosed lung cancer patients drawn from 44 Indonesian cities are described in Table 1.

Male patients (61%) were more frequent than female patients (39%). Median age was 57 years with a range between 19 and 92 years.

Most cytological specimens were adenocarcinoma (94%), obtained as malignant pleural effusion (MPE, 26%), as well as from fine needle aspirations (FNA, 20%), bronchoscopies (17%), and transthoracic needle biopsies (20%).

Out of the 1,874 consecutive samples, 95 (5.1%) samples failed *EGFR* testing. Failures were divided into preanalytical and analytical failures. Seventy-four (3.9%) samples were rejected outright (preanalytical failure), because the numbers of tumor cells were too few (<100 cells) or absent altogether.

MPE specimens showed the highest preanalytical failure rate (6.6%) and FNA specimens demonstrated the least (1.6%) (Table 2). Upon passing preanalytical step, there were only 11 samples that failed to generate specific amplicons after repeated PCR attempts at least twice. Out of the 11 samples, 7 were formalin-fixed while 4 were direct smear samples. Therefore, formalin fixation had higher frequency of PCR failure (2.4%; 4 out of 164 FFPE samples) than direct smear preparations (0.4% or 7 out of 1,626 samples; p=0.0019).

Table 1 Demography and clinical pathology characteristics (N=1,874 patients)

Characteristics		N	(%)
Patients in major islands of Indonesia (44 cities)			
	Jawa, Bali	1,386	74
	Sumatera	332	18
	Sulawesi	88	5
	Kalimantan	68	4
	Papua	0	0
Sex			
	Male	1,145	61
	Female	729	39
Age (years)			
	Range	19–92	
	Median	57	
	Average	57.1	
Sampling methods			
	Malignant pleural effusion	486	26
	Fine needle aspiration biopsy	378	20
	Bronchoscopies	319	17
	Transthoracic biopsy	366	16
	Not specified	325	21
Cytopathology			
	Adenocarcinoma	1,753	94
	Adenosquamous carcinoma	40	2
	Squamous carcinoma	21	1
	Nonsmall-cell carcinoma	24	1
	Bronchoalveolar carcinoma	13	1
	Other	23	1

EGFR mutation frequency and clinical pathology associations

Overall *EGFR* mutation frequency was 44.5% (95% CI: 42.09–46.71). Approximately 57.1% and 29% of *EGFR* mutation–positive patients had common TKI-sensitive mutations (exon 19 ins/dels and L858R) and uncommon mutations (G719X, T790M, exon 20 insertions, and L861Q), respectively. The remaining 29% of patients harbored mixture of common and uncommon *EGFR* mutations (G719X, T790M, and L861Q) (Table 3).

Most patients harbored single mutations (80.5%). However, 19.5% of patients had multiple or complex mutations involving more than one mutation subtypes. Furthermore, first-generation TKI-resistant T790M mutations were found as single (3.4%) and complex (4.2%) TKI-sensitive mutations. The proportion of T790M in complex mutations (48.7%) was higher than in single mutations (9.6%, Table 3). Moreover, complex mutation cases of T790M/L858R (30%)

Table 2 Impact of cytological samples on EGFR testing failure rates

Cytological sampling methods	Total samples submitted for testing (%)	Overall failures (%)	Administrative rejection[a] (%)	Preanalytical step			Analytical step	
				QNS (%)	Evaluable (%)	*p*-value[b]	PCR failures (%)	PCR successful (%)
MPE	486 (25.9)	37 (7.6)	10 (0.5)	32 (6.6)	454 (93.4)	0.0018	3 (0.7)	451 (99.3)
FNA	378 (20.2)	6 (1.6)		6 (1.6)	372 (98.4)		0 (0)	372 (100)
BOC	319 (17.0)	19 (6.0)		15 (4.7)	304 (95.3)		1 (0.3)	303 (99.7)
TTB	366 (19.5)	18 (4.9)		9 (2.5)	357 (97.5)		0 (0)	357 (100)
NS	325 (17.3)	15 (4.6)		12 (3.7)	313 (96.3)		7 (2.2)	306 (97.8)
Total	1,874 (100)	95 (5.1)		74 (3.9)	1,800 (96.1)		11 (0.6)	1,789 (99.4)

Notes: [a]Administrative rejection includes unmatched patient-sample identity and wrong testing indication; [b]number of tumor cells were too low, typically <100 cells in entire slide.

Abbreviations: EGFR, epidermal growth factor receptor; MPE, malignant pleural effusion; FNA, fine needle aspiration; BOC, bronchoscopy; TTB, transthoracal biopsy; NS, not specified; QNS, quantity not sufficient; PCR, polymerase chain reaction.

Table 3 Breakdown of EGFR mutation types and rates

EGFR mutation subtypes	Mutation frequency per total evaluable patients			Frequency per mutation positive patients	
Total evaluable patients (N=1,779)	N	Ratio	Percent	Ratio	Percent
Total EGFR mutation positive	791	791/1,779	44.5	791/791	100
Common mutations (exon 19 ins/dels, L858R)	452	452/1,779	25.4	452/791	57.1
Uncommon mutations (G719X, exon 20 ins, T790M, L861Q)	229	229/1,779	12.9	229/791	29.0
Mixture of common and uncommon	110	110/1,779	6.2	110/791	13.9
EGFR single mutations	637	637/1,779	35.8	637/791	80.5
Common mutations; TKI sensitive					
Exon 19 ins/dels	227	227/1,779	12.8	227/637	35.6
Exon 21 (L858R)	209	209/1779	11.7	209/637	32.8
Uncommon mutations; TKI sensitive					
Exon 18 (G719X)	18	18/1,779	1.0	18/637	2.8
Exon 21 (L861Q)	121	121/1,779	6.8	121/637	19.0
Uncommon mutations; TKI resistance					
Exon 20 insertion	1	1/1,779	0.1	1/637	0.2
Exon 20 (T790M)	61	61/1,779	3.4	61/637	9.6
EGFR complex or compound mutations	154	154/1,779	8.7	154/791	19.5
Common TKI sensitive (L858R and exon 19 ins/dels)	16	16/1,779	0.9	16/154	10.4
Uncommon TKI sensitive (G719X and L861Q)	8	8/1,779	0.4	8/154	5.2
Common and uncommon TKI sensitive	44	44/1,779	2.5	44/154	28.6
TKI sensitive and resistance T790M	75	75/1,779	4.2	75/154	48.7
TKI sensitive and resistance exon 20 ins	10	10/1,779	0.6	10/154	6.5
TKI sensitive, T790M, exon 20 ins	1	1/1,779	0.1	1/154	0.6

Abbreviations: EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

were found more frequently than T790M/exon 19 ins/del (9%).

When stratified according to gender, *EGFR* mutations were higher in women (52.9%) than in men (39.1%, $p<0.05$). Furthermore, adenocarcinoma patients had higher rate of *EGFR* mutations (45.1%) than nonadenocarcinoma (34.3%, $p=0.028$) (Table 4).

Common mutations (exon 19 ins/dels, L858R) conferring sensitivity to TKI were more prevalent in female (54.9%) than in male patients (45.1%). In contrast, uncommon *EGFR* mutations conferring either sensitivity (G719X, L861Q) or resistance to TKI (T790M, exon 20 insertions) were more frequent in male (64.9%) than in female patients (35.1%) (Table 4).

EGFR T790M mutation

Using Sanger sequencing, we found that majority of T790M mutations were heterozygous as shown in a typical sequencing result (Figure 2A upper panel), which we confirmed using real-time PCR (Figure 2B). Examination of T790M-positive cases revealed that up to 16% showed mutant allele specific imbalances (MASI) due to overrepresentation of mutant alleles (Figure 2A lower panel). To detect probable presence of germline mutation, DNA was isolated from adjacent

Table 4 Associations between clinicopathology and types of EGFR mutations

Parameters	N	EGFR				*p*-value	Common mutations		Uncommon mutations			
		Normal		Mutation			TKI sensitive		TKI sensitive		TKI resistant	
		n	%	n	%		n	%	n	%	n	%
Overall	1,779	988		791			452		191		148	
Gender												
Female	696	328	47.1	368	52.9	0.0001	248	54.9	67	35.1	53	35.8
Male	1,083	660	60.9	423	39.1		204	45.1	124	64.9	95	64.2
Age												
>57 years	872	469	53.8	403	46.2		235	52.0	88	46.1	80	54.1
≤57 years	894	510	57.0	384	43.0	0.18	214	47.3	102	53.4	68	45.9
Unspecified	13	9		4			3					
Cytopathology												
Adenocarcinoma	1,671	917	54.9	754	45.1	0.0282	427	94.5	186	97.4	142	95.9
Nonadenocarcinoma	108	71	65.7	37	34.3		25	5.5	5	2.6	6	4.1
Squamous	18	12	66.7	6	33.3		3	0.7	0	0.0	0	0.0
Adenosquamous	38	24	63.2	14	36.8		11	2.4	1	0.5	0	0.0
Bronchioalveolar	9	4	44.4	5	55.6		2	0.4	2	1.0	0	0.0
Not specified NSCLC	43	31		12					2			

Abbreviations: NSCLC, non small cell lung carcinoma; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

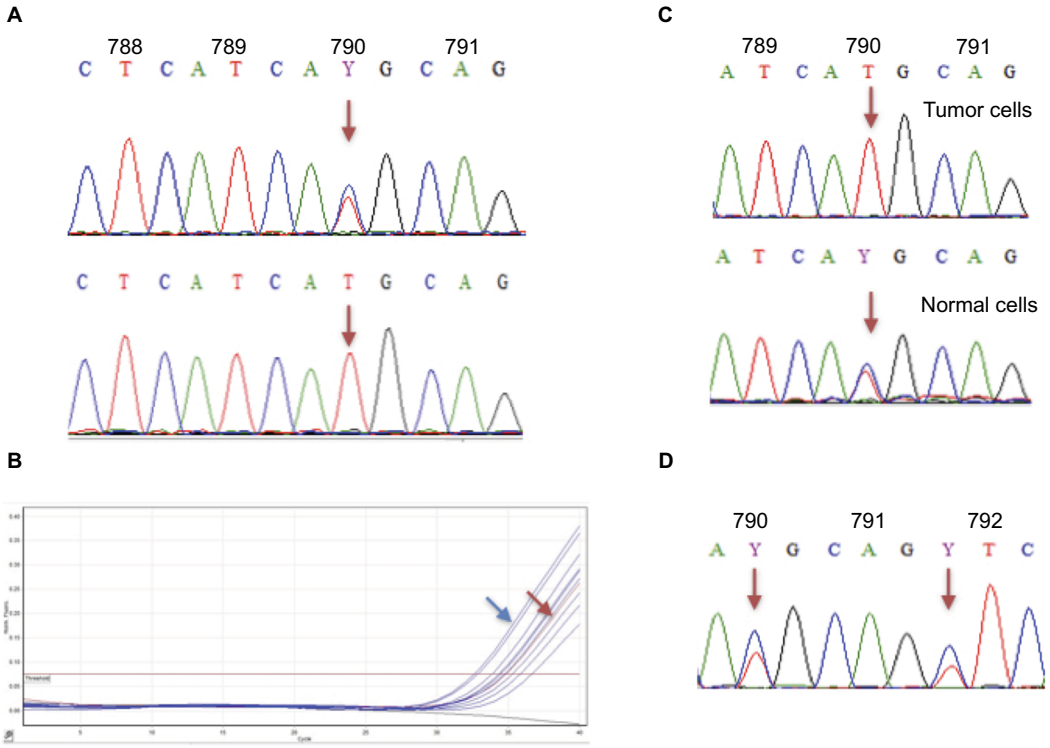

Figure 2 Representative T790M detection in cytological samples using direct sequencing.
Notes: (**A**) Upper panel shows the case of heterozygous T790M mutation and lower panel shows the case of homozygous T790M mutation indicating mutant allele-specific imbalance (MASI). (**B**) Real-time PCR-independent confirmation of T790M detection. Red arrow points to T790M control positive specimen. Blue arrow points to specimens showing positive T790M signal. (**C**) T790M MASI in DNA of tumor cells and heterozygous T790M in DNA of normal cells scraped from the same cytological smears. (**D**) Complex mutation of T790M and L792F in treatment-naïve patient. Red arrow points to mutations.
Abbreviation: PCR, polymerase chain reaction.

normal cells. In 1out of 5 randomly selected MASI cases, a heterozygous T790M mutation was detected (Figure 2C) in normal cells indicating germline mutation. Confirmation in peripheral blood was not done because the patient died before the initiation of this study. In the other 4 cases, T790M mutations were absent in normal cells supporting the relatively

rare frequency of T790M germline mutation. Last, we found that 1 out of 136 patients had concomitant T790M and L792F mutations, a putative resistance marker to second- and third-generation TKI (Figure 2D).

Discussion

We reported that the overall failure rate of *EGFR* mutation testing in real-world population was 5.1%, with MPE showing the highest (7.6%) and FNA the lowest (1.6%). MPE failure rates were combination of rejection during preanalytical step (6.6%) and PCR failures (1%) during analytical step. In addition, improper formalin fixation protocol performed at the referring hospitals to our laboratory might contribute to PCR failure. For instance, fixation time may affect the integrity of pre-PCR DNA template.[15] However, an FFPE specimen failure rate of 2.4% obtained in our cohort was still lower than that of 11.4% obtained by the recent RING diagnostic trial involving 13 laboratories.[16] Taken as a whole, our experience in receiving cytological specimens had similar success rate (94.9%) to previous descriptive review analyzing 19 publications of *EGFR* mutation testing in cytology samples stating an overall success rate of ~95%.[3]

The rate of total *EGFR* mutation in our population (44.5%) using cytological specimens was also similar to what laboratories in neighboring Southeast Asian countries had reported using either cytological[13] or tissue specimens.[17,18] Notably, the *EGFR* mutation rate was higher than our previous study (29%) when Sanger sequencing was used.[4] The current study used PCR HRM and RFLP that had higher analytical sensitivity than Sanger sequencing and covered 4 exons (18–21) instead of just 2 exons (19 and 21). In addition, others and we had described the utility of split peak pattern of PCR HRM previously to screen for *RAS* and *EGFR* mutations rapidly.[19,20]

Most *EGFR* mutations in our current cohort were also detected as single mutations and the remaining 19.5% was complex mutations (containing more than one mutation). Our complex mutation rate was slightly higher than that demonstrated by other studies varying between 7% and 14%.[21–24] Using massive parallel sequencing, the complex mutation rate is increased to 26%[25] and has been associated with poor prognosis.

Most *EGFR* mutation studies to date reported major tyrosine kinase sensitizing mutations such as exon 19 insertions/deletions and L858R substitution mutations in exon 21. These common mutations generally comprised 80%–90% of total *EGFR* mutations, while the remaining mutations or uncommon mutations contributed 10%–20%.[26,27] However, our population had high rates of uncommon mutations (composed of G719X, exon 20 insertions, T790M, and L861Q) contributing up to 43% of total *EGFR* mutations. High proportion of uncommon *EGFR* mutations to total *EGFR* mutations has been reported in European population (50%)[28] and Chinese regions of Yunnan Province (70%).[29]

The reasons of variations in *EGFR* mutation subtypes may be attributed to geographical differences, ethnic backgrounds,[30] and environmental exposures (coal burning, wooden smoke, cigarette smoking).[29,31] Although information about smoking history was not available within our cohort, Indonesian lung cancer smoking attributable fractions in males is as high as 87% and in females 12%.[32] This is consistent with the high prevalence of smoking among Indonesian males (65%), which ranks third in the world.[33] Our data showed that male patients (65%; $p<0.05$) had higher rate of *EGFR* uncommon mutations than female patients (35%), which may be partly explained by recent descriptive studies suggesting putative association between uncommon mutations (G719X and L861Q) and smoking history.[34,35] Therefore, future studies are needed to clarify definite association between *EGFR* uncommon mutations and smoking history in Indonesian lung cancer patients.

Among uncommon *EGFR* mutation types, T790M mutation has generated diagnostic as well as clinical interests. Up to 50% of common *EGFR* mutant patients would develop resistance to first-generation TKI due to acquired T790M mutations. TKI-naïve patients are not expected to harbor T790M mutations as confirmed by insensitive detection method such as Sanger sequencing with frequency typically less than 5%.[6] Using Sanger we did find significant portion of T790M mutations in treatment-naïve patients (7.6%) having slightly higher frequency than what other studies have reported.[8,36] T790M prevalence in complex mutation contributed up to 48.7% and mostly coexisted with L858R that is consistent with recent meta-analysis study of baseline T790M.[37]

Although Sanger sequencing is not as sensitive as amplification-refractory mutation system PCR, it may yield certain advantages. We were able to discern the extent of MASI by comparing the relative sequencing tracer heights of mutant allele vis a vis normal allele.[38] We found that the rate of MASI in T790M mutations was similar to other mutations such as L858R and exon 19 insertions/deletions (26%–37%).[39,40]

Clinical significance of baseline T790M with or without MASI was not clear. However, presence of baseline T790M has been correlated with good prognosis,[41] while others have demonstrated shorten progression free survival (PFS)[42] and median overall survival.[8] Nevertheless, current clinical

practice does not exclude prescription of first-generation TKI to patients harboring concurrent T790M and TKI sensitive mutations.[6] Interestingly, recent clinical trial subjecting 60 *EGFR* mutated patients (5 of whom harbored T790M mutations) to osimertinib as first-line treatment demonstrated an objective response rate of 77%[43] and a PFS of 19.3 months, a significant extension of historical PFS of 10–13 months.[44] Therefore, population with significant numbers of baseline T790M mutations like ours may benefit from using osimertinib as first-line treatment.

Furthermore, we had explored the potential presence of T790M germline mutations in some specimens. Out of the 5 specimens showing T790M MASI, we found 1 specimen having heterozygous T790M mutation in normal cells from the same slide. Unfortunately, we were not able to confirm mutation in the blood because the patient died at the time of our study. To our knowledge, this was the first study to demonstrate the utility of cytological specimens to screen for potential germline mutation. Germline mutation T790M has been an interest due to associated risk to develop lung cancer in family members having inherited the identical mutant alleles. Due to relatively rare mutation of T790M, the extent of germline T790M mutation may be as high as 50% of patients with somatic mutations.[45] However, in general population, prevalence of germline T790M mutation has been estimated to be 1 in 7,500.[46] We were not able to compare the proportion of germline T790M within our cohort, because majority of cytological slides whose tumor cells had been scraped during routine *EGFR* mutation testing were not available. Lastly, we also found one specimen having L792F mutation in complex with T790M mutation. L792F mutation has been proposed as putative resistant marker to second-generation (afatinib)[47] and third-generation (osimertinib) TKI.[48] L792F-acquired mutations had been shown in plasma of 3 patients who were resistant to osimertinib[48] but not in pretreatment samples. Therefore, we found evidence that resistance marker to third-generation TKI may exist prior treatment albeit with extremely low frequency.

Conclusion

We used PCR HRM "split peak" melt pattern to screen and analyze *EGFR* mutation in real-world testing of Indonesian lung cancer samples obtained from major cities using routine cytological specimens. We found high rates of uncommon *EGFR* mutations (G719X, L861Q) in Indonesian male lung cancer patients, potential germline T790M mutation, and L792F next-generation TKI resistance *EGFR* mutation in cytological samples of untreated patients. These patients may benefit from first-line treatment using second- and third-generation TKIs.

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Disclosure

The authors report no conflicts of interest in this work.

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Unit/Instansi : DEPARTEMEN PULMONOLOGI & KEDOKTERAN RESPIRASI
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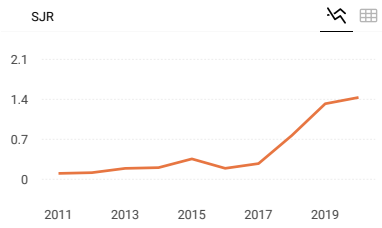
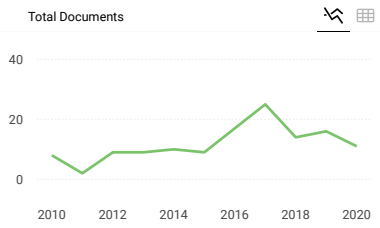
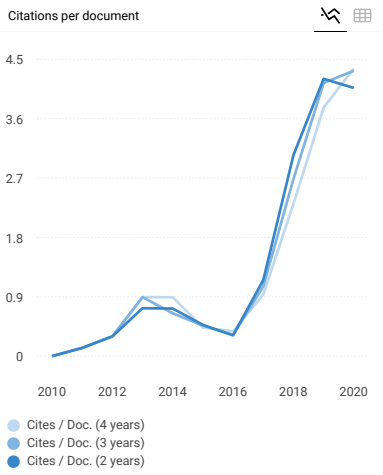
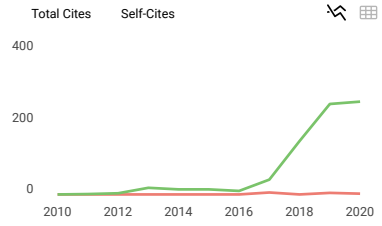
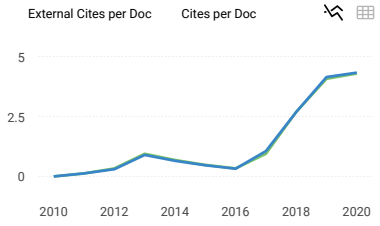
90% similarity	**86%** similarity	**85%** similarity	**81%** similarity	**72%** similarity

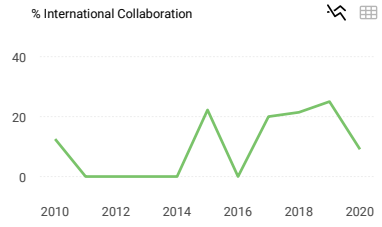


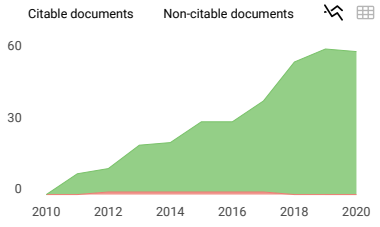


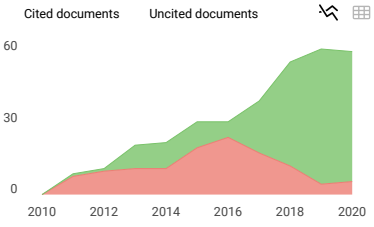












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