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Epidermal Growth Factor Receptor Mutation in Newly Diagnosed Lung Adenocarcinoma

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Abstract

Introduction: Studies of EGFR mutation frequency in patients with non-small cell lung cancer (NSCLC) or lung adenocarcinoma were limited to clinical trials, convenient sample, retrospective studies of archived samples or studies involving advanced lung cancer only.

Methods: A cross sectional, single center, prospective study of EGFR mutation status among patients with newly diagnosed lung adenocarcinoma attending University Malaya Medical Center over a 4-year-period.

Results: Of 394 patients with adenocarcinoma, 166 (42.1%) were tested EGFR mutation-positive while the remaining 228 (57.9%) had EGFR wild-type tumour. Exon 19 deletion mutation was the most common EGFR mutation subtype (96 (24.4%)), followed by exon 21 L858R point mutation (64 (16.2%)). On univariate analysis, gender, smoking status and smoking pack-years ($p<0.001$) were significantly associated with EGFR mutation status. Multivariate logistic regression analysis identified smoking status and smoking pack-year ($p<0.001$) as independent predictive factors for EGFR mutation positivity. EGFR mutation frequency was significantly higher in never smokers (OR, 7.12; 95% CI, 3.79 – 13.38; $p<0.001$) and previous smokers (OR, 2.45; 95% CI, 1.18 – 5.09; $p=0.016$). Compared to current or previous smokers of more than 50 pack-years, those who smoked less than 10 pack-years (OR, 7.70; 95% CI, 2.06 – 28.74; $p=0.002$) and 10-20 pack-years (OR, 3.42; 95% CI, 1.02 – 11.50; $p=0.047$) had significant higher frequency of EGFR mutation.

Conclusion: EGFR mutation is common in Malaysian patients with lung adenocarcinoma. A never smoking status is a robust independent predictor of EGFR mutation positivity. EGFR mutation rate was inversely related to the amount of smoking, and is significantly lower in patients who smoked >20 pack-years.

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Introduction

Lung cancer is the leading cause of cancer-related death worldwide [1], with 85% of lung cancer being of non-small cell lung cancer (NSCLC) variety [2]. In recent years, adenocarcinoma has replaced squamous cell carcinoma as the commonest histological subtype of lung cancer in many parts of the world, including in Malaysia [3].

Presence of activating mutation in the epidermal growth factor receptor (EGFR) of NSCLC predicts clinical response to gefitinib, an oral first-generation reversible EGFR-tyrosine kinase inhibitor (EGFR-TKI) [4,5]. EGFR is a transmembrane glycoprotein that is coded by a gene located at the short arm of chromosome 7. Mutation in EGFR causes continuous tyrosine kinase activities that can lead to uncontrolled cellular proliferation, differentiation, migration and survival, which ultimately leads to lung cancer development [6]. The frequency of EGFR mutation has been found to be high among East Asian, women, non-smoker and adenocarcinoma subtype of NSCLC [7-9].

Several phase 3 clinical trials have demonstrated the superiority of EGFR-TKI over cytotoxic chemotherapy as first-line treatment in patients with EGFR mutant advanced NSCLC or adenocarcinoma in terms of response and progression-free survival [10-16]. Clinical guidelines recommend EGFR-TKI as first-line treatment in patients with EGFR-mutant advanced NSCLC [17,18]. As EGFR mutation testing is costly, understanding independent predictive factor of EGFR mutation become very important in prioritizing patients for this investigation. This is particularly true at the area with limited laboratory support and financial resources.

Up to date, there are many epidemiology studies looking at the frequency of EGFR mutation and its predictor factors. Nevertheless, most of these studies are very selective. These include clinical trials that focus on selected patients with favorable demographic and clinical characteristic [10,19], epidemiology studies that use convenient sample involving patients who could afford EGFR-TKI treatment [20,21], or retrospective studies that analyzed archived tissue sample [9,22]. The result of these studies might not represent the true EGFR mutation rate in real-world NSCLC or adenocarcinoma populations.

A prospective, molecular epidemiology study of mutations in Asian patients with advanced NSCLC of adenocarcinoma histology (PIONEER) was the first multinational epidemiology study that investigated EGFR mutation frequency in stage IIIB and IV lung adenocarcinoma [23]. Malaysia with a multiethnic population consisting of 54.6% Malay, 24.6% Chinese, 7.3% Indian and 13.5% ethnic minorities was not included in the PIONEER study [24]. Therefore, we have decided to conduct a 4-years prospective study in the University Malaya Medical Center (UMMC) to determine the EGFR mutation frequency in all patients with newly diagnosed lung adenocarcinoma irrespective of the disease stage. UMMC is a community-based teaching hospital located in Kuala Lumpur, the capital of Malaysia.

Methods

Study design and patients

This is a cross-sectional, single-center, prospective study of EGFR mutation frequency in Malaysian patients with newly diagnosed lung adenocarcinoma of all stages. Universal sampling method was used to enroll patients as EGFR mutation testing was a reflex investigation for every patient with newly diagnosed NSCLC in UMMC. The primary objective was to determine the EGFR mutation frequency, while the secondary objective was to correlate EGFR mutation status with demographic and clinical characteristic of the patients. Patients analyzed were aged 18 years and above, with histologically confirmed lung adenocarcinoma. Patients were excluded if their tumor biopsy samples were inadequate or not feasible for EGFR mutation testing. This study was approved by the hospital's ethics committee with the reference number of MECID NO. 201412-871 and adhered to the Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practice. We obtained written informed consent from every patient prior on recruitment for study.

Procedure

An online data collection template was created prior to the initiation of the study. Adequate tissue samples were obtained from the primary tumor or metastatic site of every patient suspected of having lung cancer either through computed tomography (CT)-guided needle biopsy, bronchoscopic endobronchial or transbronchial biopsy or excisional biopsy. All tissue samples obtained were examined by the pathologists in the Department of Pathology, UMMC within a week. Upon histological confirmation of lung adenocarcinoma, patients were interviewed for their demographic and clinical data. This information was keyed into the online data collection template.

Patients were categorised as never-smokers if they had not smoked more than 100 cigarettes in their lifetime, previous smokers if they had smoked more than 100 cigarettes in their lifetime and had ceased smoking for more than a year, and current smokers if they had smoked more than 100 cigarettes in their lifetime and were still smoking or had ceased smoking less than a year. The patient's functional status at diagnosis was graded based on Eastern Cooperative Oncology Group (ECOG) performance status (EPS). Every patient had a baseline CT scan of thorax, abdomen and pelvis (CT-TAP) and brain (if the patient had neurological symptoms or signs) with contiguous slices of 10 mm. The lung adenocarcinoma was staged based on 2009 International Staging System for Lung Cancer [25].

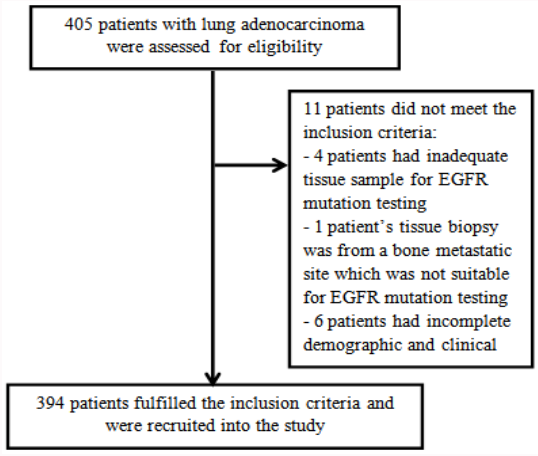

Figure 1: 394 of 405 patients with histologically confirmed lung adenocarcinoma were recruited for the study.

Formalin-fixed paraffin embedded (FFPE) tissue blocks of patients' tumor samples were prepared by the pathologists of UMMC and sent to the designated centers for EGFR mutation testing. From August 01, 2010 to May 31, 2012, EGFR mutation was tested at the Pathology Laboratory of Subang Jaya Medical Center (SJMC) using QIAGEN EGFR RGQ PCR Kit (QIAGEN, Manchester Ltd, UK). From June 01, 2012 to April 31, 2013, EGFR mutation was tested at the Pathology Laboratory of Tuanku Mirzan Army Hospital (HAT TM) using cobas® EGFR Mutation Test (cobas®, Roche Molecular System Inc, USA). From May 01, 2013 to December 31, 2014, EGFR mutation was tested at the Pathology Laboratory of SJMC again using PNAClamp™ EGFR Mutation Detection Kit (PANAGEN, Daejon, Korea). DNA extraction from FFPE tissue blocks was performed per standard procedure stated in the kits manufacturer instruction. The number of somatic mutations that can be detected by QIAGEN, cobas® and PNAClamp™ kits were 29, 42 and 42, respectively. These somatic mutations included exon 19 deletion mutation, exon 21 L858R point mutation, exon 18 G719X mutation, exon 20 S7681 mutation, exon 20 insertion, exon 20 T790M mutation and exon 21 L861Q mutation.

Statistical analysis

Results for continuous variables are expressed as mean ± standard deviation (SD), median or range depending on normality of the variable distribution; while results for categorical variables are expressed as percentages.

Differences between patients with EGFR-mutant and EGFR wild-type lung adenocarcinoma were tested for significance by using the chi-squared test or Fisher's exact test whichever was appropriate for categorical variables, and Student's t-test for continuous variables, taking two-sided p values of less than 0.05 as statistically significant. For statistically significant results, odds ratios (ORs) were obtained via binary logistic regression tests of univariate variables with p values

Table 1: Demographic and clinical characteristics of the patients.

Demographic and clinical characteristics	Population (n=394)	Percentages (%)
Age, mean (± SD)	394	63.0 (± 11.6)
Gender, n (%)		
Male	223	56.6
Female	171	43.4
Ethnicity, n (%)		
Chinese	289	73.4
Malay	83	21.1
Indian	21	5.3
Other	1	0.3
Smoking status, n (%)		
Never smoker	219	55.6
Previous smoker	86	21.8
Current smoker	89	22.6
Pack-years of smoking, n (%)		
0	218	55.3
>0-10	19	4.8
10-20	29	7.4
20-30	41	10.4
30-40	26	6.6
40-50	27	6.9
>50	33	8.4
Stage of disease, n (%)		
IA	7	1.8
IB	7	1.8
IIA	2	0.5
IIB	1	0.3
IIIA	23	5.8
IIIB	19	4.8
IV	335	85
ECOG PS, n (%)		
0	71	18
1	211	53.6
2	59	15
3	35	8.9
4	18	4.6
Real time PCR EGFR testing methods, n (%)		
QIAGEN	167	42.4
cobas®	81	20.6
PNAClamp™	146	37.1
EGFR mutation status, n (%)		
Wild-type	228	57.9
Positive	166	42.1
Type of EGFR mutation:		
Exon 19 deletion	96	24.4
Exon 21 L858R point mutation	64	16.2
Exon 18 G719X	3	0.8

Exon 20 T790M	1	0.3
Exon 20 S768I	4	1
Exon 20 insertion	1	0.3
Exon 21 L861Q	3	0.8
No. of mutations, n (%)		
Single mutation	160	40.6
Two mutations	5	1.3

Table 2: EGFR mutation based on the testing platform.

EGFR mutation testing method	QIAGEN (n=167)	cobas® (n=81)	PNAClamp™ (n=146)	p value of x^2 test
EGFR mutation status, n (%)				
Wild-type	102 (61.1)	47 (58.0)	79 (54.1)	0.46
Positive	65 (38.9)	34 (42.0)	67 (45.9)	
Exon 19 deletion	44 (26.3)	14 (17.3)	38 (26.0)	0.123
Exon 21 L858R point mutation	22 (13.2)	17 (21.0)	25 (17.1)	
Exon 18 G719X	0 (0)	2 (2.5)	1 (0.7)	
Exon 20 T790M	1 (0.6)	0 (0)	0 (0)	
Exon 20 S768I	0 (0)	2 (2.5)	1 (0.7)	
Exon 20 insertion	0 (0)	0 (0)	1 (0.7)	
Exon 21 L861Q	1 (0.6)	1 (1.2)	2 (1.4)	
No. of mutations, n (%)				
Single mutation	62 (37.1)	32 (39.5)	66 (45.2)	
Two mutation	3 (1.8)	4 (4.9)	1 (0.7)	

of less than 0.20 or considered significant in other studies. Statistical analyses were performed using the software package, Statistical Package for the Social Sciences (SPSS for windows version 21.0, SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

Four hundred five patients were diagnosed of lung adenocarcinoma from January 01, 2010, to December 31, 2014. Only 394 patients were included in this study, with the selection algorithm (Figure 1) as demographic and clinical characteristics of the patients are summarized in Table 1.

The mean age of the patients was 63.0 (+ 11.6) years (range 27 to 92 years). There was slightly more male patients (223 (56.6%)). Nearly three-quarter of the patients were of Chinese ethnicity (289 (73.4%)). The majority of the patients were never smokers (218 (55.3%)), had good EPS of 0-1 (282 (71.6%)) and presented with advanced stage disease of IIIB-IV (354 (89.8%)).

EGFR mutation analysis

The tumors of 166 (42.1%) patients were tested EGFR mutation positive (Table 1). Exon 19 deletion mutation was the most common EGFR mutation subtype (96 (24.4%)), followed by exon 21 L858R point mutation (64 (16.2%)). Eleven (2.8%) patients had rare sensitizing mutations, and only 1 (0.3%) patient had de novo exon 20 T790M resistant mutation. Only 5 (1.3%) patients had multiple mutations.

The EGFR mutation rate was highest among those patients tested with the PNAClamp™ platform (67 out of 146 (45.9%)), followed by the cobas® platform (34 out of 81 (42.0%)) and the QIAGEN platform (65 out of 167 (38.9%)) (Table 2). Exon 19 deletion mutation was the most common EGFR mutation subtype found in PNAClamp™ and QIAGEN platform; while exon 21 L858R point mutation was the most common EGFR mutation subtype found in cobas® platform.

Association of EGFR mutation with demographic and clinical characteristics

Gender, smoking status and smoking pack-years ($p<0.001$) were significantly associated with EGFR mutation status based on chi-square test (Table 3). Nevertheless, these characteristics could be influenced by other factors and need further analysis with multivariate logistic regression. EGFR mutation was significantly more common in female patients (96 out of 171 (56.1%)) than male patients (70 out of 223 (31.4%)).

EGFR mutation frequency was significantly higher in never smokers (125 out of 216 (57.9%)) than previous smoker (27 out of 86 (31.4%)) or current smoker (14 out of 89 (15.7%)). Previous or current smokers of 10 pack-years and below had similar EGFR mutation frequency as never smoker (11 out of 19 (57.9%)). Previous or current smoker of 10-20 pack-years had lower EGFR mutation frequency of 37.9% (11 out of 29). Those who smoked more than 20 pack-years had significantly lower EGFR mutation frequency of only 17.6% (range 7.7% to 22.2%).

The majority of patients with EGFR mutant tumors were Chinese (123 out of 166 (74.1%)). Indian patients had the highest EGFR mutation rate of 52.4% (11 of 21), followed by the Chinese (123 of 289 (42.6%)) and Malay of (32 of 83 (38.6%)) ($p=0.054$). EGFR mutation frequency was slightly higher in patients with advanced stage lung adenocarcinoma 42.9% (152 of 354) compared to those with early stage disease 35.0% (14 out of 40) ($p=0.335$). There was no difference in the mean age or ECOG PS of patients with EGFR mutant tumors versus those with EGFR wild-type tumors. The EGFR mutation

Table 3: Correlation between EGFR mutation status and demographic and clinical characteristics.

Demographic and Clinical Characteristics	EGFR mutation (n=394)		p value of x^2/fisher's exact/ student t-test	p value of univariate analysis	p value of multivariate analysis
	Positive (n=166)	Wild-type (n=228)			
Age, mean (± SD)	62.6 (± 11.6)	63.3 (± 11.60	0.734	0.635	0.845
Gender, n (%)					
Male	70 (42.2)	153 (67.1)	<0.001	0.35	0.361
Female	96 (57.8)	75 (32.9)			
Ethnicity, n (%)					
Chinese	123 (74.1)	166 (72.8)	0.554	0.998	-
Malay	32 (19.3)	51 (22.4)			
Indian	11 (6.6)	10 (4.4)			
Others	0 (0)	1 (0.4)			
Smoking status, n (%)					
Never smoker	125 (75.3)	93 (41.2)	<0.001	<0.001	<0.001
Previous smoker	27 (16.3)	59 (25.9)			
Current smoker	14 (8.4)	75 (32.9)			
Smoking pack-years n (%)					
0	125 (75.3)	93 (41.2)	<0.001	<0.001	<0.001
>0-10	11 (6.6)	8 (3.5)			
10-20	11 (6.6)	18 (7.9)			
20-30	6 (3.6)	35 (15.4)			
30-40	2 (1.2)	24 (10.5)			
40-50	6 (3.6)	21 (9.2)			
50	5 (3.0)	28 (12.3)			
Staging, n (%)					
IA	3 (1.8)	4 (1.8)	0.062	0.452	-
IB	2 (1.2)	5 (2.2)			
IIA	1 (0.6)	1 (0.4)			
IIB	1 (0.6)	0 (0)			
IIIA	7 (4.2)	16 (7.0)			
IIIB	2 (1.2)	17 (7.5)			
IV	150 (90.3)	185 (81.1)			
EPS, n (%)					
0	37 (22.3)	34 (14.9)	0.389	0.531	-
1	85 (51.2)	126 (55.3)			
2	25 (15.1)	34 (14.9)			
3	13 (7.8)	22 (9.6)			
4	6 (3.6)	12 (5.3)			
EGFR testing methods, n (%)					
QIAGEN	65 (39.2)	102 (44.7)	0.46	0.395	-
cobas®	34 (20.5)	47 (20.6)			
PNAClamp™	67 (40.4)	79 (34.6)			

testing method did not have a significant effect on EGFR mutation positivity.

Multivariate logistic regression identified smoking status (p<0.001) and smoking pack-years (p<0.001) as the only 2 significant independent predictors for EGFR mutation positivity while age and gender were found not to be significant. Compared to current smoker, EGFR mutation frequency was significantly higher in never smoker (OR, 7.12; 95% CI, 3.79 – 13.38; p<0.001) and previous smoker (OR, 2.45; 95% CI, 1.18 – 5.09; p=0.016). Similarly, compared to current or previous smoker of more than 50 pack-year, those who smoked less than 10 pack-years (OR, 7.70; 95% CI, 2.06 – 28.74; p=0.002) and 10-20 pack- years (OR, 3.42; 95% CI, 1.02 – 11.50; p=0.047) had significantly higher EGFR mutation rates.

Association of common EGFR mutation subtypes with demographic and clinical characteristics

Student t-test showed that patients with exon 19 deletion mutation were significantly younger than those with exon 21 L858R point mutation (mean age, 60.6 versus 64.7 years, p=0.036) (Table 4). Otherwise, there was no significant differences in gender, ethnicity, smoking status, stage of disease, ECOG PS and EGFR mutation testing methods between patients with exon 19 deletion mutation and those with exon 21 L858R point mutation.

Table 4: Association of common EGFR mutations with demographic and clinical characteristics.

Demographic and Clinical Characteristics	EGFR mutation (n=154)		p value of x^2/fisher's exact/ student t-test	p value of univariate analysis	p value of multivariate analysis
	Exon 19 deletion (n=94)	Exon 21 L858R point mutation (n=60)			
Age, mean (± SD)	60.6 (± 12.6)	64.7 (± 10.1)	0.036	0.221	0.087
Gender, n (%)					
Male	43 (45.7)	21 (35.0)	0.187	0.053	0.172
Female	51 (54.3)	39 (65.0)			
Ethnicity, n (%)					
Chinese	68 (72.3)	48 (80.0)	0.557	0.68	-
Malay	20 (21.3)	9 (15.0)			
Indian	6 (6.4)	3 (5.0)			
Others	0 (0)	0 (0)			
Smoking status, n (%)					
Never smoker	73 (77.7)	44 (73.3)	0.828	0.879	-
Previous smoker	13 (13.8)	10 (16.7)			
Current smoker	8 (8.5)	6 (10.0)			
Smoking pack-years n (%)					
0	72 (76.6)	44 (73.3)	0.516	0.976	-
>0-10	8 (8.5)	3(5.0)			
10-20	6 (6.4)	3 (5.0)			
20-30	2 (2.1)	4 (6.7)			
30-40	1 (1.1)	1 (1.7)			
40-50	2 (2.1)	3 (5.0)			
50	3 (3.2)	2 (3.3)			
Staging, n (%)					
IA	3 (1.8)	0 (0)	0.372	0.999	-
IB	2 (1.2)	2 (3.3)			
IIA	1 (0.6)	0 (0)			
IIB	1 (0.6)	0 (0)			
IIIA	7 (4.2)	3 (5.0)			
IIIB	2 (1.2)	1 (1.7)			
IV	150 (90.3)	54 (90.0)			
EPS, n (%)					
0	22 (23.4)	14 (23.3)	0.123	0.09	0.069
1	56 (59.6)	23 (38.3)			
2	8 (8.5)	15 (25.0)			
3	5 (5.3)	5 (8.3)			
4	3 (3.2)	3 (5.0)			
EGFR testing methods, n (%)					
QIAGEN	42 (44.7)	19 (31.7)	0.46	0.093	0.09
cobas®	14 (14.9)	16 (26.7)			
PNAClampTM	38 (40.4)	25 (41.7)			

Multivariate logistic regression adjusted for mean age, gender, ECOG PS and EGFR mutation testing methods showed that none of these factors were independent predictor of exon 19 deletion or exon 21 L858R point mutation.

Discussion

Midha et al. [26] had reported the global mapping of EGFR mutation among patients with lung adenocarcinoma (mutMapII) based on a systemic review of 151 reported articles (Table 5) [26]. The overall EGFR mutation rate of 42% in our study population was similar to that reported in Asia-pacific region(overall 47%, range 20% to 76%) and significantly higher than EGFR mutation rate reported in Europe region (overall 39%, range 7% to 37%) or North America region (overall 19%, range 14% to 23%) [26]. When compared to

Table 5: EGFR mutation frequency among patients with lung adenocarcinoma.

Country	Number of patients with EGFR mutation/total study population	EGFR mutation frequency (%)	EGFR mutation range (%)
Asia Pacific region	5958/12819	47	20-76
China	1403/2949	48	27-66
Hong Kong	312/585	53	47-58
Japan	2069/4619	45	21-68
Korea	1248/2884	43	20-56
Malaysia	272/599	45	39-47
Thailand	63/117	54	N/A
Vietnam	77/120	64	N/A
Singapore	57/142	40	39-43
Philippines	34/65	52	N/A
Europe	1527/10464	15	06-41
North America	1638/7396	22	03-42
Indian subcontinent	278/1090	26	22-27
South America	250/686	36	09-67
Oceania	69/570	12	07-36
Africa	29/137	21	N/A

other Southeast Asian countries, the EGFR mutation rate of our population was similar to that reported in Singapore (40%, range 39% to 43%) [22,27]. This was likely due to similar ethnic composition of the populations in both countries. Other neigh boring countries such as Vietnam, Thailand and Philippines have slightly higher EGFR mutation rate (52% to 64%) than Malaysia [23]. The EGFR mutation rate of 52% in our Indian subgroup was doubled of that reported in the Indian sub continental region of 26% (22% to 27%) [28,29]. This discrepancy might have been due to the small number of Indian patients in our study (n=21) that had led to study bias. The EGFR mutation rate reported in another convenient sample study in Malaysia was marginally lower (39.5%) than ours [20]. QIAGEN EGFR mutation testing kit that detected 29 somatic mutations was used in that study. On the other hand, cobas® or PNAClamp™ EGFR mutation testing kits that able to detect 42 somatic mutations were used in 48% of the patients in our study which potentially could have resulted in a higher EGFR mutation detection rate of 42% to 46% [26].

It has been widely reported that East Asian, women, young age and non-smokers have higher frequency of EGFR mutation [7-9,23]. Our study also showed that women and non-smoker were significantly associated with presence of EGFR mutation. The EGFR mutation rate of 56% in our female sub group and 58% in our non-smoker subgroup was slightly lower than that reported in Asia-Pacific region (overall 60%, range 46% to 69%, and overall 64%, range 47% to 73% respectively) [26]. On the other hand, the EGFR mutation rate of our female subgroup was significantly higher than that reported in Europe (22%, range 11% to 33%) and United States of America (28%) [26,30]. Similar finding was observed in our never smokers compared to that reported in Europe region (overall 35%, range 23% to 50%) and United States of America (47%) [26]. These findings highlight that East Asia population had higher EGFR mutation rates than Western population. The high prevalence of EGFR mutation among the male (31%) and ever-smoker (27%) in our study indicated that EGFR mutation testing should become a routine investigation in every Malaysia patient with newly diagnosed lung adenocarcinoma.

Our study showed than EGFR mutation rate was inversely related to the amount of smoking. There was a sharp decline in EGFR mutation rate among those smoked above 20 pack-years. Those who smoked less than 10 pack-years and 10-20 pack-years had significantly higher EGFR mutation rate. One study in mainland China had reported the similar mutation pattern, in which EGFR mutation rate was significantly reduced once the smoking amount reached more than 10 pack-years [31]. Surprisingly, our study also shows that previous smokers have significantly higher EGFR mutation rate than current smokers. In practical point of view, our study demonstrated that either reduced amount of smoking earlier cessation of smoking would increase the likelihood of EGFR mutation positivity in lung adenocarcinoma.

We tried to demonstrate the different in EGFR mutation rate between patients with early and advances stage lung adenocarcinoma. Such outcome was hardly considered in other epidemiology studies. Nevertheless, our study showed that stage of lung adenocarcinoma might have no impact of EGFR mutation status.

The main limitation of this study was due to the different EGFR mutation testing platforms used. Ideally, a uniform EGFR mutation testing platform that could detect a maximum number of somatic mutations should be used. EGFR mutation testing using plasma cell-free tumor DNA was not performed in our patients and will be of our interest in a future study.

Conclusion

This study showed than EGFR mutation was common in Malaysian patients with lung adenocarcinoma irrespective of demographic and clinical characteristics. EGFR mutation testing should become a routine investigation for every patient with newly diagnosed lung adenocarcinoma. Being a non-smoker is an independent predictor of EGFR mutation positivity. EGFR mutation rate was inversely related to amount of smoking and was significantly reduced in patients smoked >20 pack-years.

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