Epidermal growth factor receptor mutations in non-small cell lung cancer patients from a single institution in Vietnam

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Summary

Objective: The purpose of this study was to evaluate the epidermal growth factor receptor (EGFR) mutations and relationship with some clinical, paraclinical characteristics in non-small cell lung cancer (NSCLC) patients in 108 Military Central Hospital, Vietnam. *Subject and method:* This is a prospective study. Tumor tissue samples were collected from 500 NSCLC patients from Jan 2015 to Jan 2018. DNA was extracted from tissue samples and examined for EGFR mutations by a peptide nucleic acid (PNA)-locked nucleic acid (LNA) polymerase chain reaction (PCR) clamp-based detection test. *Result:* The patient's mean age was 63.02 ± 9.6 years old and male/female ratio was near 4/1. Histology showed 80% of adenocarcinoma, 3.6% of squamous cell carcinoma, 0.8% of large cell carcinoma, 0.2% of adeno-squamous cell carcinoma, and 15.4% of NSCLC undefined type. In total, 35.6% were positive for presence of EGFR mutations. EGFR mutations were observed 2.2% in exon 18, 61.2% in exon 19, 34.8% in exon 21, and 1.7% in exons 20 and 21. EGFR mutations by histology were 38.2% in adenocarcinoma and 25% in other histologic types ($p<0.05$). EGFR mutations by demographic were 55.1% in female and 30.3% in male ($p<0.05$) and 44.8% in non-smoker and 30.3% in smoker ($p<0.05$). *Conclusion:* The mutation rate of EGFR in NSCLC in our hospital was 35.6%. The EGFR mutation rates were higher in adenocarcinoma vs other histologic types, in female vs male, and in non-smoker vs smoker. Their differences were statistically significant.

Keywords: EGFR mutations, non-small cell lung cancer.

1. Background

Non-small cell lung cancer (NSCLC) is the most common classification of lung cancer because it accounts for more than 80% of all lung cancer cases and it includes 2 major types: Nonsquamous cell carcinoma and squamous cell carcinoma. Currently, most NSCLC is diagnosed clinically when patients present with symptoms such as persistent cough, pain, and weight loss. Unfortunately, most patients are diagnosed when they already have advanced-stage disease [4]. To treated NSCLC was many options such as surgery, radiation therapy, chemotherapy, immunotherapy and targeted therapy [3], [4]. In select patients with advanced non-small cell lung cancer, the advent of targeted therapies has had a profound effect on the ability to control the disease, palliate symptoms, and potentially prolong life for patients with the specific molecular aberrations in their tumors that make them sensitive to these therapies. This therapy was used the drug to effect cancer cell, but not effect normal cell [3], [4]. Molecular target in NSCLC was EGFR, EML4-ALK, KRAS, BRAF… EGFR (Epidermal growth factor receptor) was transmembrane protein. The intracellular component of the EGFR protein includes a juxtamembrane domain, a region housing the TK activity and a C-terminal domain.

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Alterations in the juxtamembrane domain and C-terminal domains can influence ligand binding. More importantly, numerous tyrosine residues are present in the C-terminal domain, and phosphorylation in these sites influence protein-protein interactions that are essential for signal transduction via pathways such as those mediated by PI3K and ras GAP/KRAS. EGFR mutations related to drug response target in 4 exon from 18 to 21 and include 2 groups. Group was increased susceptibility mutations and resistant mutations [5], [6], [7]. EGFR mutations are found in approximately up to 50% of Asian patients. Clinical characteristics associated with the presence of an EGFR mutations include adenocarcinoma, little or no smoking history, female, and Asian [8]. In this study, we evaluated ratio of epidermal growth factor receptor mutations and relationship with some clinical, paraclinical characteristics in NSCLC patients treatment in 108 Military Central Hospital, Vietnam.

2. Subject and method

2.1. Subject

500 patients of non-small cell lung cancer who was examined EGFR mutations treatment in Department of Respiratory Medicine in 108 Military Central Hospital, Vietnam from Jan 2015 to Jan 2018.

2.2. Method

Study design: This is a prospective study.

Study protocol:

Clinical examination, paraclinical testing, chest X-rays, chest CT, and tumor biopsy.

Samples: Piece biopsy, tumor post operation.

To read the results of the pathology and localized cancer cells.

To test EGFR mutations.

Testing method: DNA was extracted from tissue samples and examined for EGFR mutations by a peptide nucleic acid (PNA)-locked nucleic acid (LNA) polymerase chain reaction (PCR) clamp-based detection test in Department of Molecular Biology, 108 Military Central Hospital, Vietnam.

Statistic analysis: SPSS software version 16.0 was used for all statistical computations.

3. Result

Table 1. Patient characteristics

Characteristics	Number (n = 500)	Rate %
Mean age	63.02 ± 9.6	(29 - 91)
< 60	168	33.6
≥ 60	332	66.4
Demographic		
Male	393	78.6
Female	107	21.4
Smoking		
Yes	317	63.4
No	183	36.6
Pack-year	24.13 ± 6.46	
Symptoms		
Cough	166	33.2
Coughing blood	31	6.2
Chest pain	196	39.2
Dyspnea	45	9
Other		

	62	12.4

Mean age of patient in this study was 63.02 years old, maximum 91 years old, minimum 29 years old. Male/female ratio was near 4/1. Most patients has smoking history with 24.13 pack-year. Primary of patients was hospitalized by cough and chest pain was 39.2% and 33.2%.

Table 2. Tumor characteristics

Tumor characteristics		Number (n = 500)	Rate %
Location	Right lung	277	55.4
	Left lung	223	44.6
	Peripheral	339	67.8
	Centre	161	32.2
Diameter(cm)	Mean	4.54 ± 1.8	
	Minimum	1.2	
	Maximum	12	
Staging	I + II	56	11.2
	IIIa	43	8.6
	IIIb	62	12.4
	IV	339	67.8
Marker	CEA	34.47 ± 97.3	
	Cyfra 21-1	5.45 ± 10.1	

Most patients has tumor in right lung and peripheral. The average of diameter was 4.54cm, maximum 12cm, minimum 1.2cm. Patient was hospitalized when advanced-stage disease with stage IIIb and IV was 80.2%. The average concentrations of markers CEA was 34.47 and Cyfra 21-1 was 5.45.

Table 3. Histology

Histology	Number	Rate %
Adenocarcinoma	400	80
Squamous cell carcinoma	18	3.6
Large cell carcinoma	4	0.8
Adeno-squamous cell carcinoma	1	0.2
Undefined type of NSCLC	77	15.4

Histology showed that adenocarcinoma was highest with 80%, other histology type was lower, at 15.4% of undefined type of NSCLC and 3.6% of squamous cell carcinoma, respectively. Adeno-squamous cell carcinoma was only one patient.

Bảng 4. EGFR mutations

Characteristics	Number	Rate %
Mutations		
Positive	178	35.6
Negative	322	64.4
Total	***500***	***100***

Location of mutations		
Exon 18	4	2.2
Exon 19	109	61.2
Exon 21	62	34.8
Exon 20-21	7	1.7
Total	***178***	***100***

In total, 35.6% were positive for presence of EGFR mutations and 64.4% were negative. Location of EGFR mutations: Exon 18: 2.2%, exon 19: 61.2%, exon 21: 34.8%, exon 20 and 21: 1.7%.

Table 5. EGFR mutations according to some clinical and paraclinical characteristics

			Number	Rate %	p
Demographic	Male	Positive	119	30.3	<0.05
		Negative	274	69.7	
	Female	Positive	59	55.1	
		Negative	48	44.9	
Smoking history	Smoke	Positive	96	30.3	<0.05
		Negative	221	69.7	
	Non-smoker	Positive	82	44.8	
		Negative	101	55.2	
Histology	Adenocarcinoma	Positive	153	38.2	<0.05
		Negative	247	61.8	
	Other types	Positive	25	25	
		Negative	75	75	

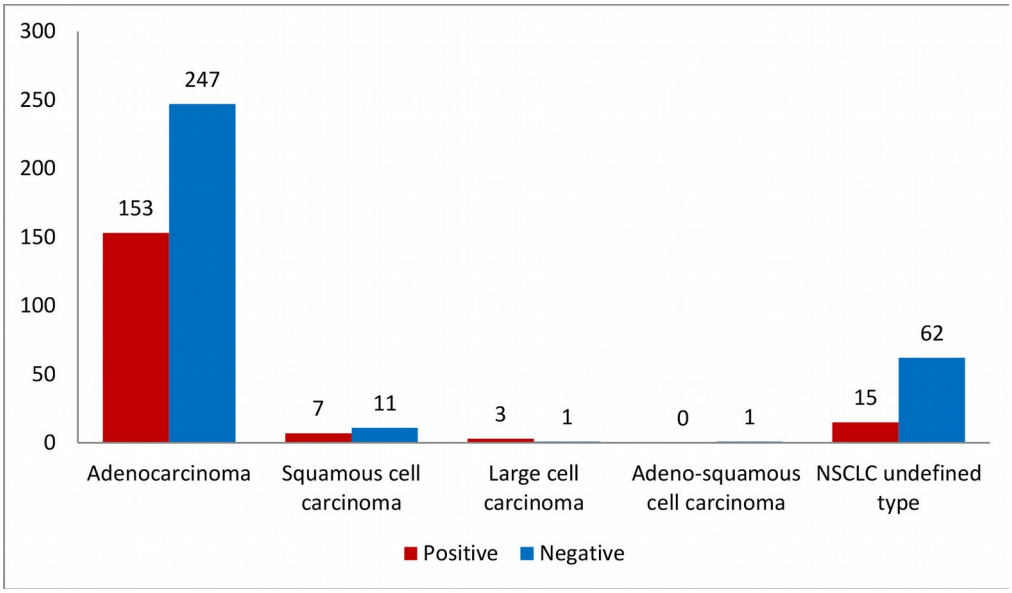

Figure 1. Positive of EGFR mutations by histology

EGFR mutations by histology were 38.2% in adenocarcinoma and 25% in other types ($p<0.05$). EGFR mutations by demographic were 55.1% in female and 30.3% in male ($p<0.05$). EGFR mutations by smoking history were 44.8% in non-smoker and 30.3% in smoker ($p<0.05$). In this study, the ratio of EGFR mutations positive in squamous cell carcinoma was 7/18 cases.

4. Discussion

In this study, ratio of male and female was near 4/1, the patient's average age was 63.02 ± 9.66, most patients was more 60 years old with 66.4%, maximum was 91 years old and minimum was 29 years old. This result according to other study in Vietnam and world wide that the higher the age is, the higher the rate of getting lung cancer is [1], [2], [8]. However, this result shows the rejuvenation of cancer aged. Essential cancer patients related smoking history with smoking ratio was 63.4% and pack-year was 24.13 ± 6.46. This result shows that smokers are at risk for lung cancer. Primary of patients was hospitalized by cough and chest pain, at 33.2% and 39.2%, respectively. Besides, symptom of other organs was 12.4%.

In our research, almost patients has tumor in right lung 55.4% and peripheral 67.8%. Mean of diameter was 4.54cm, maximum 12cm, minimum 1.2cm. Patient was hospitalized when advanced-stage disease with stage IIIb and IV was 80.2%.

Adenocarcinoma was the most common in all histology types, because it accounted for the biggest rate, at 80%. The proportion of other types were lower at 15.4% of undefined type of NSCLC and 3.6% of squamous cell carcinoma, respectively. As for the percentage of large cell carcinoma and adeno-squamous cell carcinoma, the figures were lowest, at 0.8% and 0.2%, corespondently. The same trend can be seen in other studies in Vietnam and in the world [1], [2], [4], [8].

EGFR mutations was discovered in 178 patients and the proportion was 35.6%. EGFR mutations in exon 19 and 21 was the most popular location in four exon at 61.2% and 34.8%, correspondently. Especially, we saw seven patients who had double mutations in exon 20 and 21 at T790M of exon 20. It was complicated double mutation which carrying mutations simutaneously increases susceptibility and resistance mutations. Mutations increases susceptibility was 98.3%. The percentage of EGFR mutations in our study was lower than

other researches in Vietnam. But, the rate of EGFR mutations in exon 19 and 21 in our study were higher. In 2016, the study of Nguyen Thi Lan Anh et al [1] in Bach Mai Hospital, Vietnam in 152 adenocarcinoma patients shows EGFR mutations was 39.5%. Moreover, the study of Mai Trong Khoa et al in 2016 [2] shows 204/511 patients who put on EGFR mutations and the proportion was 40.1%. Ratio of mutation in exon 19 and exon 21 was 56.4% and 37.4%, 4/211 mutations in exon 20, T790M was proportionate 1.9%. PIONEER study show rate of EGFR mutations in Vietnam was the highest at 64.2% [8], the main reason of the result was that patiens in this study included females who had adenocarcinoma and non-smoking. In our study, patiens include both male and female, all types of NSCLC, both smokers and non-smokers. Thus, our result was lower than the result of PIONEER in Vietnam.

About relationship between EGFR mutations and sex, smoking history, histology types, the ratio of EGFR mutations positive in female at 55.1% was higher than the figure of male at 30.3%, differences were statistically significant with $p<0.05$. This result according to other study in Vietnam and world wide, the presence of an EGFR mutations include adenocarcinoma, little or no smoking history, female [8]. Furthemore, the propotion of EGFR mutations positive on non-smokers at 44.8% was higher than the rate of smokers at 30.3%, differences were statistically significant with $p<0.05$. As for histology types, 38.2% of adenocarcinoma was bigger than 25% of other types, differences were statistically significant with $p<0.05$. Ratio of positive mutations on adenocarcinoma in this study was equivalent to other study in Vietnam. In 2016, the study of Mai Trong Khoa et al [2] shows the percentage of EGFR mutations positive on adenocarcinoma was 41.2%, negative was 58.8%, the rate of EGFR mutations positive on other types were 25.7%, negative were 74.3%. In this study, we met 7/18 patients who had EGFR mutations positive on squamous cell carcinoma. This result different from view that EGFR mutations on squamous cell carcinoma was very low.

5. Conclusion

Studying 500 non-small cell lung cancer patients were treated in 108 Military Central Hospital, Vietnam illustrades: The ratio of EGFR mutations was 35.6%. Major EGFR mutations occur in exon 19 and 21 which the figure at 61.2% and 34.8%, respectively. Seven patients had double mutations in exon 20 and 21 at T790M of exon 20, proportion 1.7%. The EGFR mutation rates were higher in adenocarcinoma (38.2%) vs other histologic types (25%), in female (55.1%) vs male (30.3%), and in non-smoker (44.8%) vs smoker (30.0%). Their differences were statistically significant.

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