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Relationship of Various Characteristics of Lung Adenocarcinoma Patients with Status of Mutation of *Epidermal Growth Factor Receptor (EGFR)* In Haji Adam Malik Medan Hospital 2015-2017

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Abstract : Lung cancer is a major cause of malignancy in the world, reaching up to 13% of all cancer diagnoses. In addition, lung cancer also causes 1/3 of all chemotherapy caused by cancer in men. Of the types of *Non Small Cell Lung Carcinoma (NSCLC),* pulmonary adenocarcinoma is the most common. Various characteristics of patients such as age, gender, occupation, ethnicity, smoking status and *EGFR* mutation status. This study was conducted to provide an overview of the distribution and frequency of all these characteristics, and find a relationship of various characteristics of adenocarcinoma patients based on gender, ethnicity and smoking status with *EGFR* mutation status in Haji Adam Malik General Hospital Medan 2015-2017. This research is descriptive-analytic with a cross sectional approach. Data on patient characteristics are obtained from medical records and cytology / histopatology images and the results of *EGFR* mutations have been examined and the results are known. In this study most of the patients were 55-64 years old. From the analysis of the relationship between sex with *EGFR* mutation status, *p value* = 0.043, analysis of the relationship between smoking status and *EGFR* mutation status, obtained *p value* = 0.040, while the analysis between the terms and mutation status obtained *p value* = 0.11.
Keywords : Lung adenocarcinoma, *EGFR* mutation, *EGFR.*

Introduction

Globally, lung cancer is a cancer that is diagnosed most often since 1985. An estimated 1.35 million people were diagnosed with lung cancer worldwide during 2001 and 1.18 million died of lung cancer. Lung cancer has a higher incidence in men worldwide than other cancers. In women, lung cancer is the fourth most common type of cancer diagnosed. The link between smoking and lung cancer is one of the most studied

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problems in biomedical research and strong evidence has been built since the mid-twentieth century to show that smoking is a major factor for lung cancer. There is also sufficient evidence to conclude that exposure to cigarette smoke can cause lung cancer.[1] Including air pollution outside and indoors, especially the most prominent *benzopirene* carcinogens.[2]

Various treatment efforts such as surgery, radiotherapy and chemotherapy are carried out to increase the number of life skills of patients with pulmonary cancer.[3] However, 80-90% of lung cancer patients are found in stage III and IV when the first diagnosis is made.[4] Surgery and radiotherapy at this stage have been ineffective because cancer cells have spread, so treatment is based on the first choice targeting therapy system currently being carried out.[5] Treatment based on targeting therapy systems on specific proteins in cancer cells in various forms such as simple chemical compounds and antibodies is a solution that has now been developed.[6]

Two types of protein that become targeting therapy in lung cancer cases include *EGFR* and *KRAS*.[7]*EGFR* and *KRAS* proteins are two types of proteins that play an important role in controlling cell growth and death.[8] In normal cells this protein acts to regulate the way the cell growth signals regularly. But in cancer cells these two proteins experience changes characteristics due to changes in the structure of the constituent amino acids.[9]*EGFR* mutations include the type of point, deletion, and insertion mutations that occur most frequently on exons 18,29,20 and 21.[10] *EGFR* examination is one way to provide appropriate therapy for *Non Small Cell Lung Carcinoma (NSCLC)* sufferers. This makes the researchers interested in knowing the relationship between various characteristics of pulmonary adenocarcinoma patients based on gender, smoking status and ethnicity with *EGFR* mutation status.

Material and method

This research is a descriptive-analytic study with a cross sectional approach. Patient data obtained were 72 patients whose data was taken from Haji Adam Malik Medan Hospital/ Department of Anatomical Pathology from 2015-2017. The research was done after getting permission from Ethical Committee of Medical Faculty USU Medan.

Clinical data taken included age, gender, occupation, smoking status and *EGFR* mutation status. Population data taken are data of patients who have been diagnosed as pulmonary adenocarcinoma by cytology and histopathology examination and have examined *EGFR* mutations. The data obtained will then be processed statistically using the *Chi-Square* test and presented in the form of tables.

Results and Discussion

The frequency distribution of pulmonary adenocarcinoma characteristics can be seen in table one. Seventy two patients were obtained from cytology fluid (94,4%) and histopathological preparations (5,6%). Based on clinical data obtained from medical records, the majority of patients aged between 55-64 years (44,5%) and the least aged between 0-44 years (9,7%).

The sex frequency distribution of this study is mostly male (75%) and the remaining female is 25%. From the distribution of work, it was found that lung adenocarcinoma sufferers were more suffered by farmers (26,4%). For the smoking status of the data, it was found that more patients smoked (68,1%) and those who did not smoke (31,9%) . Based on the *EGFR* mutation status in this study, 24 cases of *EGFR* mutations were obtained. Most mutations were found in Exon 19 (18%) and Exon 21 (6,9%). Whereas for those without mutations / Wild type (WT) 66,7%.

Table.1. Frequency distribution characteristics of pulmonary adenocarcinoma patient.

Characteristics of patients	Total (n)	Percentage (%)
Age (years)		
- 0-44 years	7	9,7
- 45-54 years	19	26,4

- 55-64 years	32	44,5
- ≥ 65 years	14	19,4
Gender		
- Female	18	25
- Male	54	75
Occupation		
- Government employees	13	18,1
- Private employees	8	11,1
- Entrepreneur	14	19,4
- Farmer	19	26,4
- Labour	5	6,9
- Housewife	13	18,1
Ethnic		
- Jawa	20	27,8
- Batak	41	56,9
- Melayu	3	4,2
- Padang	1	1,4
- Aceh	6	8,3
- Ambon	1	1,4
Smoking Status		
- Do not smoke	23	31,9
- Smoke : - Mild	3	4,2
- Moderate	7	9,7
- Severe	39	54,2
EGFR mutation status		
- No Mutation/Wild type	48	66,7
- Mutation: - Exon 18	2	2,8
- Exon 19	13	18

- Exon 20	2	2,8
- Exon 21	7	9,7
Total	72	100

Tabel 2. Distribution of EGFR mutation status in pulmonary adenocarcinomapatients by sex, smoking status and ethnicity.

Characteristics	Mutation status				Total		Odds Ratio (OR)	*P value*
	EGFR Mutation		No Mutation					
	n	%	n	%	n	%		
Gender								
- Female	10	55,6	8	44,4	18	100		0,043
- Male	14	25,9	40	74,1	54	100	3,57	
Smoking status								
- Do not smoke	12	52,2	11	47,8	23	100		0,040
- Smoke	12	24,5	37	75,5	49	100	3,36	
Ethnic								
- Batak	10	24,4	31	75,6	41	100		0,110
- Non Batak (Jawa, Melayu, Padang, Aceh, Ambon)	14	45,2	17	54,8	31	100	2,55	

There were 72 cases of pulmonary adenocarcinoma patients who were obtained at Haji Adam Malik Hospital/Department of Anatomical Pathology, Faculty of Medicine, Universitas Sumatera Utara, Medan. In this study the most lung adenocarcinoma patients at the age of 55 to 64 years were around 44,5%, and the least age group 0 to 44 years were around 9,7%. However, in one of the studies conducted by Kasuma in 2011 at Haji Adam Malik General Hospital, it was found that the age group of patients was at most 40-60 years (59%) and the least in patients aged less than 40 years was around 10%.[11] Shigematsu et al., who also obtained data that *EGFR* gene mutations were not related to age.[12] Lung cancer has a higher incidence in men worldwide.

This is in accordance with research conducted that the highest number of pulmonary adenocarcinoma sufferers is about 75% of men. According to Melinda's study at Haji Adam Malik General Hospital Medan in 2004-2008 it was found that the sex of patients with pulmonary adenocarcinoma was male (86,1%).[13] The frequency of distribution based on work shows that the work of farmers are the highest, namely: 26,4%. Various risk factors are proven to be associated with cancer incidence, including prolonged exposure by industrial exhaust gases, chemicals and air pollution.[14] For the distribution of tribes in adenocarcinoma patients in this study shows that the Batak tribe is more about 56,9%. This has in common with the research conducted by Melindawati in Haji Adam Malik General Hospital Medan in 2004-2008 as much as 58,2%.[13] From the data on smoking habits, the results of the study showed that 68,1% and those who did not smoke were 31,9%.

Smoking is one of the risk factors for lung cancer. Specific chemicals in cigarette smoke include *polycyclic aromatic hydrocarbons (PAHs)*,*N-nitrosamine*, *aromatic amines*, *ethylene oxide* and others. Common manuscripts are exposed to *PAHs* through tobacco smoke, from the work environment, fuel (burning coal or wood).[15]In smokers, persistent and progressive genetic lesions occur which accumulate at specific

chromosomal loci. The results of genetic studies show that smokers experience a loss of heterozygosity in various alleles such as 3p14,9p21, p16 and p53.[16] The frequency distribution of pulmonary adenocarcinoma patients based on *EGFR* mutation status showed the most frequent mutations at Exon 19 (18%) and Exon 21 (9,7%). Lynch et al., The most common *EGFR* mutation was deletion in Exon 19 and point mutations in Exon 21. Shigematsu et al., Also stated that the most common *EGFR* mutations were found in the Exon 19 deletion.

From the research data the distribution of mutation status of lung adenocarcinoma patients with gender was obtained that *EGFR* mutations were more frequent in men (58,3%). Haneda et al., Stated that men with pulmonary adenocarcinoma had a higher *EGFR* mutation than those who did not, while women had no relationship.[17]

The results of the analysis of the relationship between sexes with *EGFR* mutation status obtained statistical tests with *p value = 0,043* (there is a significant relationship between gender and *EGFR* mutation status). Then the value of *OR (Odds Ratio)= 3,57* which means that the male gender suffering from pulmonary adenocarcinoma has a 3,57 times greater risk of having an *EGFR* mutation compared to female gender suffering from pulmonary adenocarcinoma. The results of statistical tests between smoking habits with *EGFR* mutation status obtained *p value= 0,040* (there was a significant relationship between smoking habits and mutation status. Then obtained values of *OR (Odds Ratio)= 3,36* means that lung adenocarcinoma patients who smoke have a risk 3,3 times more likely to experience *EGFR* mutations compared to adenocarcinoma patients who did not smoke, the data were distributed by *EGFR* mutation status with pulmonary adenocarcinoma patients with tribes obtained by statistical test *p value= 0,110* (there was no significant relationship between *EGFR* mutation status with tribe)

Conclusion

1. There is a significant relationship between sexes with *EGFR* mutation status, from the results of statistical tests showing male gender suffering from pulmonary adenocarcinoma have a greater risk of having *EGFR* mutations compared to female gender suffering from pulmonary adenocarcinoma.
2. There was a significant relationship between smoking status and *EGFR* mutation status, from the results of statistical tests showing lung adenocarcinoma patients who smoke have a greater risk of having *EGFR* mutations compared to adenocarcinoma patients who do not smoke**.**
3. There is no significant relationship between the status of the EGFR mutation and the tribe.

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