The Relationship between Epidermal Growth Factor Receptor (EGFR) Mutation and Computed Tomography Findings in Lung Adenocarcinoma

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The relationship between Epidermal Growth Factor Receptor (EGFR) mutation and computed tomography findings in lung adenocarcinoma

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ABSTRACT

Background: Adenocarcinoma is the highest histology subtype of lung cancer. Epidermal Growth Factor Receptor (EGFR) is a factor that can predict the prognosis or response to treatment in patients with lung adenocarcinoma. Adenocarcinomas with EGFR mutations generally have a component of Ground Glass Opacity (GGO), smaller size, oval shape, multiple nodal metastases, and distant metastases. The aim of this study was to determine the relationship between EGFR mutations and CT scan images in pulmonary adenocarcinoma patients.
Methods: This was a retrospective analytical study consisting of 92 samples, which were categorized into the mutation group (n = 62) and wild group (n = 30). This study was conducted at Dr. Soetomo General Hospital from January 2015 – December 2017. The assessed CT-Scan findings were tumor size, shape, density, lymph node size, pleural effusion, and metastasis presence. The relationship was analyzed using the chi-square test and considered significant if the p-value was < 0.05.
Results: This study found a significant relationship between EGFR mutations status with tumor size ≤ 3 cm (p = 0.02), lymph node size < 1.5 cm (p = < 0.001) and metastasis (p = 0.026). However, tumor density, tumor form, and pleural effusion did not have significant relationship with EGFR mutation.
Condusion: Tumor size ≤ 3 cm, lymph node size < 1.5 cm and presence of metastasis can be found in EGFR mutations pulmonary adenocarcinoma patients.

Keywords: CT scan, EGFR, lung adenocarcinoma
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INTRODUCTION

Lung cancer is the leading cause of death in the world and Indonesia.[1-7] In Indonesia, the total *number of* deaths caused by lung cancer reaches 30,901 and *continues to increase* every year. Lung cancer does not only attack men but also women. Adenocarcinoma is the most common histological subtype of lung cancer.[1,6,8] In diagnosing and evaluating lung cancer, imaging has an important role. The routine imaging that performed is Thoracic Computed Tomography (CT) scan with contrast.[9]

Epidermal Growth Factor Receptor (EGFR) is a biomarker that can predict the prognosis or response to treatment in patients with pulmonary adenocarcinoma.[1-5,8,10-13] Several pathology factors that have a high prevalence of EGFR mutations are women, non-smokers and East Asian races.[1,11] Before the Tyrosine Kinase Inhibitor (TKI) was discovered, patients with EGFR mutations had a worse prognosis than negative mutations due to not responding to conventional chemotherapy. Now, patients with EGFR mutations have a better response and prognosis.[1,2] Adenocarcinoma patients who have a good response to TKI are those with exon 18, 19 or 21 mutations.[1,14]

Several studies have evaluated CT-Scan in pulmonary adenocarcinoma patients with EGFR mutation when compared to the wild-type. Lung adenocarcinoma with EGFR mutation more likely to have Ground Glass Opacity (GGO) density, smaller size, oval shape, multiple nodules, and distant metastases.[1-5,8,10-13,15-17]

The aim of this study was to evaluate the relationship between EGFR mutations and CT-scan images in pulmonary adenocarcinoma patients.

MATERIAL AND METHOD

This study was an analytical retrospective study, conducted at Dr. Soetomo hospital Surabaya from January 2015 - December 2017. Patient data were taken from medical records at the pulmonary oncologic outpatient clinic, and CT Scan data were obtained from the Radio Diagnostic Installation at Dr. Soetomo Hospital. The inclusion criteria were pulmonary adenocarcinoma patients who had performed CT-Scan and cytology/histopathology examination at Dr. Soetomo Hospital and had

EGFR mutations examination. The exclusion criteria were metastatic pulmonary adenocarcinoma from other organs and mediastinal masses. The CT scan result was reviewed by two radiologists of the thorax subdivision. The reviewers were blinded from the EGFR mutation examination result.

The variables of this research were the description of thorax CT scan and EGFR mutation status in adenocarcinoma patients. The results of EGFR mutation analysis in pulmonary adenocarcinoma patients can be either positive or negative EGFR mutations (wild-type mutations). Each of the EGFR mutation subtypes was recorded and reported. The material used for EGFR mutation analysis can be from tissue (core biopsy) or cytology (FNAB). The examination was done by PCR, direct sequencing or even tissue fragment.

CT scan was performed using two types of CT scan machines, which are sixteen slices with Hitachi brand ECLOS Q1E-BW1545-1 and Siemens SOMATOM Emotion 80476. The examination performed was a thoracic CT-scan with contrast. Raw data for axial images were reconstructed with a thickness of 0.6 mm, using a matrix of 1024 x 1024 with a field of view (FOV) between 20 cm.

The radiological picture of the CT scan that will be assessed consists of six components and several components will be further divided into two groups. The six components were: (1) primary tumor size, (2) primary tumor form, (3) primary tumor density, (4) size of lymph node, (5) pleural effusion and (6) extra-nodal invasion (metastasis in the contralateral lung and extrathoracic organ).

The size of the lesion was rated as the largest diameter.[3,18] When the lesions were more than one, the lesion with the largest diameter was used. The size of the lesion was divided into two groups, namely Group 1 (size ≤ 3 cm) and Group 2 (size > 3 cm).

Shapes were categorized into two groups, which were regular or irregular. Regular consisted of round, oval or lobulated.[3,18] Round was defined as a spherical or saccular form of lesion. Oval was defined as an ellipse or egg shape, which can consist of 2 or 3 undulations. Lobulated was defined as lesions that have > 3 undulations. Irregular was defined when the lesion did not meet the criteria for round, oval, or lobulated.

Density was categorized into two groups, which are GGO and solid.[3,18] GGO was an increase in blurred density in lungs with bronchial branches and good vascular appearance in non-contrast CT scan. Solid density was a solid lesion (> 30 HU) that appeared in three dimensions.

The assessed locations of the lymphadenopathy were in the peri-bronchial, subcarinal, mediastinal, hilar, scalene, axillary, ipsilateral and contralateral axilla.[19] The size of the lymph node was grouped as < 1.5 cm (group I) and ≥ 1.5 cm (group II). The largest size was reported in patients with multifocal lymph node.[8,10]

Pleural effusion was defined as the presence or absence of fluid density in the pleural cavity. The extra-nodal invasion was the appearance or absence of metastases in the lung or other organs.

Statistical analysis was performed with SPSS software version 23. The chi-square test was used to assess the relationship. The confidence interval was set at 95% (95% CI), and a p-value of < 0.05 was considered significant.

RESULTS

A total of 92 people met inclusion criteria and were included in this study. They consisted of 55 men (59.8%) and 37 women (40.2%). Sixty-two patient (67.3%) had positive EGFR mutations, and 30 people (32.61%) had negative mutations (wild-type). The number of women with EGFR mutations was higher compared to men (89% vs. 52%). On the contrary, the number of men with wild-type was higher than women (48% vs. 11%). The age of patients was between 34 and 84 years. The highest frequency of cases was found in the 51-60-year-old age group.

As shown in Table 1, most of the samples had a tumor size > 3 cm, as many as 67 people (72.8%). All the samples had solid tumor density and irregular shape. The majority of the samples had lymph node size less than 1.5 cm (65.2%). Lymph node size less than 1.5 cm was more common in EGFR mutations group.

Pleural effusion was only found in 41 cases (44.6%), while the remaining 51 cases did not have pleural effusions (55.4%). In this study, the total number of metastatic are the same as those without metastatic. Thirty-six cases with metastasis (58%) were found in the mutation.

As shown in Table 1, there was a significant relationship between the EGFR mutation and tumor size ≤ 3 cm, lymph node size < 1.5 cm and metastases ($p < 0.05$). Whereas for tumor density, tumor form, and pleural effusion did not have a significant relationship with EGFR mutation.

DISCUSSION

The number of women with EGFR mutations was higher compared to men, and the number of men with wild-type was higher than women. This result was consistent with the previous research conducted by Hsu et al.[3] and Liu Ying et al.[1] The age of patients was between 34 – 84 years, with the

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Table 1 Distribution and analysis of EGFR mutation with CT scan

CT Scan Imaging	EGFR mutation		P - value
	Positive (N = 62)	Negative (N = 30)	
Tumor size			
≤ 3 cm	22	3	0.01
> 3 cm	40	27	
Tumor density			
GGO	0	0	-
Solid	62	30	
Shape			
Reguler	0	0	-
Irregular	62	30	
Lymph node size			
< 1.5 cm	48	12	< 0.001
≥ 1.5 cm	14	18	
Pleural effusion			
Yes	27	14	0.078
No	35	16	
Metastases			
Yes	36	10	0.026
No	26	20	

highest frequency of cases occurring in the 51 – 60 years old group. The result of this study is almost the same as the study conducted by Liu et al.[1]

The most common mass size found in this study was > 3 cm, and a size of ≤ 3 cm was more common in the positive mutation. The result of this study was consistent with Hsu et al. that found the size of ≤ 3 cm was more commonly found in patients with mutations.[3]

The mass density in this study was 100% solid and irregular. In contrast to previous studies by both Hsu et al. and Hasega et al., their study found that the case of adenocarcinoma with mutations has a picture of mass with GGO density and regular form.[3,5] However, in a study conducted by Park et al., it was found that more EGFR mutations were found with solid density (92.9%) than GGO (16.7%).[10] This may be due to concomitant mutations with other mutations such as ALK or KRAS that were not assessed in this study or because these patients were advanced stage patients.[20] Also in this study, we did not evaluate the subtypes of pulmonary adenocarcinoma.

Lymph node size less than 1.5 cm was more common in the EGFR mutations group. The results of this study are in accordance with a previous study conducted by Park et al. in 2016. This is in line with the theory of EGFR mutations naturally invading hematogenous rather than lymphatic.[10]

Patients with EGFR mutations mostly did not have effusion. This result was consistent with a study conducted by Hasegawa et al. that fewer pleural effusions were found in adenocarcinoma with the EGFR mutation.[5]

In this study, most of the mutation type had metastasis (58%). This result is consistent with the theory of the nature of adenocarcinoma EGFR mutation subtype, that stated hematogenous spread was by activating the PI3K pathway, which plays a role in cell migration and AKT enhancing angiogenesis and invasion in this subtype.

The weakness of this study is that it was a retrospective study with limited time and a relatively small number of patients compared to previous studies. Moreover, this study did not assess other factors that could influence the occurrence or absence of mutations, the presence of concomitant mutations and pulmonary adenocarcinoma subtypes.

CONCLUSION

This study showed a significant relationship ($p < 0.05$) between EGFR mutation and the size of the primary tumor, the size of the lymph node and the presence of metastasis in patients with pulmonary adenocarcinoma. Tumors sized less than 3 cm, and lymph nodes sized less than 1.5 cm are more likely to be found in adenocarcinoma lung patients with EFGR mutations.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICAL CLEARANCE

The study was approved by the ethical committee of the Health Research and Development Agency of Dr. Soetomo Hospital with ethical certificate number 0131/KEPK/III/2018.

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AUTHOR CONTRIBUTION

All authors are equally contributed to the study from manuscript preparation, data analysis, until reporting the results of study.

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