ORIGINAL RESEARCH REPORT

Thoracic CT-Scan with EGFR Mutations in Pulmonary Adenocarcinoma Patients with Pulmonary Metastases at Dr. Moewardi Hospital, Surakarta, Indonesia

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ABSTRACT

Background: EGFR mutation is one of the molecular markers associated with prognosis and therapy in lung adenocarcinoma patients, including with lung metastases. The predominant imaging modality for assessing lung cancer is a chest CT scan, which correlates with prognosis. **Objective:** This study aimed to explore the association between characteristics of lung adenocarcinoma based on chest CT-Scan and EGFR mutation in lung adenocarcinoma with lung metastases. **Material and Method:** This study involved 65 lung adenocarcinoma patients in Dr. Moewardi Hospital, Surakarta, Indonesia, from January 2018-December 2020. **Result:** Chest CT-Scan and EGFR mutation were assessed in all subjects. EGFR mutation was found in 32 (49.8%) subjects. The risk of EGFR mutation was found to be higher in patients with lung adenocarcinoma who had lung metastases in a peripheral location (OR=11.56; 95%CI 3.57-37.33; p<0.001), tumor size <4 cm (OR=8.00; 95%CI 2.64-24.22; p<0.001), and semi-solid density (OR=5.21; 95%CI 1.79-15.19; p=0.002). **Conclusion:** EGFR mutation is associated with tumor location, size, and thickness based on chest CT-Scan in lung adenocarcinoma with lung metastases patients.

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Highlights

1. The thoracic CT scan can be an alternative evaluation before administering EGFR-targeting medicine to patients.
2. EGFR is now a therapeutic target for lung cancer.

BACKGROUND

Lung cancer is a malignant illness that begins in the bronchial epithelium and spreads to the lungs (Yue, et al., 2018, Lemjabbar-Alaoui, 2015). In 2018, lung cancer was the most prevalent new cancer case globally, with 2 million new cases. However, in Indonesia, it was the third most common with

30,000 new cases (de Groot et al., 2018). Lung cancer is more prevalent in males than females, and the median age at diagnosis is 71 years old. Less than 3.5% of patients diagnosed with lung cancer are younger than 45 years old (Kusumawardhani, et al., 2022). The frequency of lung cancer in Dr. Moewardi Hospital, Surakarta, Indonesia, continues to rise annually, with 92 more cases every year. In the last six months of 2016, there were 686 lung cancer patients with an average monthly rate of 155 patients (22.59%) (Grigoriu, et al., 2015). Additionally, lung cancer has the highest mortality rate of all cancers in the world and in Indonesia in 2018, accounting for 18.4% and 14% of all fatalities caused by cancer, respectively (Vivi, 2020).

Epidermal growth factor receptor (EGFR) is one of the molecular markers used in lung cancer (Torre, et al., 2016, Harrison, 2019). Increased EGFR affects the pathogenesis of lung cancer, especially in non-small cell carcinoma lung cancer (NSCLC). An elevated risk of EGFR mutations is associated with the non-small cell lung cancer subtype known as adenocarcinoma, which is a part of the NSCLC (Barta, et al., 2019). Several studies have shown that increased EGFR levels are associated with decreased life expectancy, increased lymph node metastases, and decreased patient sensitivity to chemotherapy (Guan, et al., 2016; Hasegawa, et al., 2016). As EGFR is presently being used as the therapeutic target for pulmonary adenocarcinoma, it is highly crucial to be aware of whether or not the cancer has EGFR mutations (Imai, et al., 2017; Komite Penanggulangan Kanker Nasional, 2017).

Computed tomography (CT) Chest scan is the most effective radiological modality for diagnosing pulmonary adenocarcinoma (Kumari, et al., 2019). The thoracic CT scan has the potential to be an alternate examination for assessment before medication targeting EGFR is provided to the patients. Additionally, it has the potential to be a predictor of lung adenocarcinoma. However, research on this subject is currently restricted. Currently, chemotherapy is the treatment of choice, especially in individuals with lung adenocarcinoma who also have pulmonary metastases.

OBJECTIVE

The purpose of this research was to investigate the relationship between the features of a chest CT scan and EGFR in pulmonary adenocarcinoma patients who were being treated at Dr. Moewardi Hospital, Surakarta, Indonesia, for pulmonary metastases.

MATERIAL AND METHOD

Study design and population

This research was a cross-sectional study that took data from medical records at Dr. Moewardi Hospital, Surakarta, Indonesia. Sixty-five subjects of this study were selected by consecutive sampling. The inclusion criteria of this study were adult age (>18 years), diagnosed with pulmonary adenocarcinoma by pathological anatomical examination, having pulmonary metastases, and having a chest CT scan result. The exclusion criteria for this study were no chest CT scan results before surgery, chemotherapy, or radiotherapy.

Study data

Patients' data were taken from the patient's medical records at Dr. Moewardi Hospital, Surakarta from January 2018 - December 2020. In addition to age and sex, the characteristics assessed on the CT scan were location, size, density, and tumor margin.

Statistical analysis

A chest CT scan with contrast was done using a 64-slice Toshiba CT scanner. Transthoracic needle aspiration (TTNA) samples and biopsies were analyzed for EGFR mutations. The hypothesis was examined statistically using SPSS version 25.0 and the chi-square test. When the p-value was 0.05, statistical significance was established.

RESULT

In this particular research, there were a total of 65 patients diagnosed with lung adenocarcinoma who also suffered from pulmonary metastases. The characteristics of the samples are provided in Table 1.

Based on gender, there were 34 (52.3%) males subjects and 31 (47.7%) females. The mean age of the subjects of this study was 58.9±11.7 years. As many as 32 (49.2%) subjects with pulmonary adenocarcinoma had lung metastases and EGFR mutations. Based on thoracic CT scan findings, there were 30 (46.2%) subjects with central tumor locations and 35 (53.8%) subjects with peripheral lung tumor locations. There were 32 (49.25%) subjects with tumor size >4 cm and 33 (50.8%) subjects with tumor size <4 cm. Based on tumor density, there were 37 (56.9%) subjects with solid tumor findings and 28 (43.1%) subjects with semi-solid tumors. Based on tumor margin, there were 29 (44.6%) subjects with non-spiculated tumor margins and 36 (55.4%) subjects with spiculated tumor margins.

Table 1. Sample characteristics

Variable	Amount (n)	Percentage (%)
Demographic		
Gender		
Male	34	52.3
Female	31	47.7
Age		
18-27 years	1	1.5
28-37 years	3	4.6
38-47 years	5	7.7
48-57 years	16	24.6
>58 years	40	61.6
EGFR mutations		
Positive	32	49.2
Negative	33	50.8
Thoracic CT scan finding		
Tumor location		
Central	30	46.2
Peripheral	35	53.8
Tumor size		
>4 cm	32	49.2
<4 cm	33	50.8
Tumor density		
Solid	37	56.9
Semi-solid	28	43.1
Tumor margin		
Non-spiculated	29	44.6
Spiculated	36	55.4

In patients who had metastatic pulmonary adenocarcinoma of the lung, it was found that there was a statistically significant relationship between the findings of thoracic CT scans and EGFR. These findings came in the form of tumor location, tumor size, and tumor density. This was found based on an analysis of the relationship between the characteristics of the chest CT scan and the EGFR. The peripheral area of the tumor increased the risk of positive EGFR by 11.56 times higher (OR = 11.56; 95% CI 3.57-37.33; p <0.001), tumor size <4 cm increased the risk of positive EGFR by 8 times higher (OR = 8.00; 95% CI 2.64-24.22; p <0.001), and the density of semi-solid tumors increased the risk of positive EGFR by 5.21 times higher (OR = 5.21; 95% CI 1.79-15.19; p = 0.002). In patients with metastatic pulmonary adenocarcinoma of the lung, there was no statistically significant association between tumor margins on chest CT scans and EGFR.

Table 2. Analysis of the association between characteristics of chest CT scan findings and EGFR mutations

	EGFR mutations		p-value	OR (95% CI)
	Positive	Negative		
Tumor location				
Central	26	9	<0.001	11.56 (3.57-37.33)
Peripheral	6	24		
Tumor size				
>4 cm	24	9	<0.001	8.00 (2.64-24.22)
<4 cm	8	24		
Tumor density				
Solid	12	25	0.02	5.21 (1.79-15.19)
Semi-solid	20	8		
Tumor margin				
Non-spiculated	11	18	0.102	2.29 (0.84-6.23)
Spiculated	21	15		

DISCUSSION

EGFR mutations in NSCLC, especially pulmonary adenocarcinoma, are known to have a major impact on the pathophysiology and prognosis of the patients (Guan, et al., 2016; Hasegawa, et al., 2016; Barta, et al., 2019). Attempts to identify the existence of EGFR mutations as early as feasible are to improve prognosis and extend the life expectancy of patients with lung adenocarcinoma with pulmonary metastases. This study attempted to determine the potential of a chest CT scan to predict EGFR in pulmonary adenocarcinoma patients with pulmonary metastases.

This study found that the highest age of patients with pulmonary adenocarcinoma with pulmonary metastases was in subjects aged >58, with 40 (61.6%) subjects. It is estimated that 53% of lung cancer cases occur in individuals aged 55-74 years, and 37% occur in people aged >75 years (Qiu, et al., 2019). The study by Wu, et al. (2017) showed that patients with younger age (<50 years) had a lower chance of developing an EGFR mutation in cases of pulmonary adenocarcinoma.

This study found that the number of males with metastatic pulmonary adenocarcinoma of the lung was 52.3%, and while the females was 47.7%. In general, the prevalence of lung cancer does not vary between men and women, which is assumed to be due to the continued growth in the number of women who smoke (Liu, et al., 2016). Tseng, et al., (2016) showed that gender did not affect the presence of EGFR mutations in patients with advanced pulmonary adenocarcinoma.

In this study, there were 49.2% of patients with metastatic pulmonary adenocarcinoma with positive EGFR. The study by Kumari et al., (2019) in India indicated that EGFR mutations were present in 31.6% of NSCLC patients, with 36.5% having pulmonary adenocarcinoma. A meta-analysis study by Zhang, et al., (2014) showed that the prevalence of EGFR mutations in NSCLC patients in China was 38.4%, whereas in Europe, it was only 14.1%. In the research that was carried out by Syahruddin, et al., (2018) in Indonesia, it was discovered that EGFR mutations were present in 44% of patients who had lung cancer. According to these researches, the proportion of EGFR mutations found may fluctuate, and the rates can also vary from country to country. Furthermore, no published literature examines the prevalence of EGFR mutations in lung adenocarcinoma patients with pulmonary metastases; as a consequence, the findings of this study cannot be compared directly to those of other studies.

Based on the results of this study, patients with pulmonary adenocarcinoma that has spread to other parts of the body are 11–12 times more likely to have a positive EGFR test. Location is thought to be linked to EGFR mutations in NSCLC in the pulmonary lobe, especially in the upper and lower lung lobes (Rizzo, et al., 2016).

This research suggested that patients with metastatic lung adenocarcinoma identified on chest CT scan with tumor size <4 cm had a positive EGFR risk up to 8 times greater. According by Guan, et al., (2016) showed that patients with NSCLC who had smaller tumors were at a greater risk for having the EGFR mutation. According to the research findings, NSCLC with the EGFR mutation was most often

identified in tumors measuring 3-5 cm, followed by tumors measuring 2-3 centimeters (Rizzo et al., 2016), also showing that a smaller tumor size could predict the occurrence of EGFR mutations in NSCLC patients.

In this research, semisolid tumor density was one of the chest CT findings that elevated the likelihood of EGFR positivity in patients with metastatic pulmonary adenocarcinoma of the lung. Qiu, et al., (2019) suggested that semi-solid tumor density was associated with EGFR mutases.

This study found no significant association between spiculated and non-spiculated tumor margins and EGFR in patients with metastatic pulmonary adenocarcinoma of the lung. Qiu, et al., (2019) found that specular boundaries were a risk factor for EGFR mutations in lung cancer patients. On the other hand, a study by Hasegawa, et al., (2016) showed that spicular boundaries were not associated with EGFR mutations in pulmonary adenocarcinoma subjects.

Strength and limitations

This study can contribute data for future studies, especially in analytic studies evaluating the relationship between Thoracic CT-Scan and EGFR mutations in Pulmonary Adenocarcinoma. Research on this topic is still limited. Chemotherapy is the treatment of choice, particularly for patients with lung cancer and pulmonary metastases.

CONCLUSION

This study showed that the characteristics of lung adenocarcinoma, as indicated by tumor location, size, and density based on the features of chest CT scan, has association with EGFR mutation in lung metastases patients.

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Conflict of Interest

All authors have no conflict of interest.

Ethic Consideration

This research permit was granted by the Ethics Committee of the Faculty of Medicine, Sebelas Maret State University, and Dr. Moewardi Hospital, Surakarta, no. 045 / 190 / 2021.

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Author Contribution

All authors have contributed to all processes in this research, including preparation, data gathering, analysis, drafting, and approval for publication of this manuscript.

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