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Bone metastases tend to increase in non-small cell lung cancer with epidermal growth factor receptor mutation

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ABSTRACT

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BACKGROUND

Increased understanding in molecular pathology of advanced non-small cell lung cancer (NSCLC) over the past decades has led to personalized treatment approaches being advocated. Epidermal growth factor receptor (EGFR) mutation that often occurs in NSCLC can be identified using immunohistochemical examinations. Moreover, clarifying the relationship between computed tomography (CT) and EGFR mutation of NSCLC might inform therapeutic decision-making. The purpose of this study was to determine the relationship between metastatic sites on primary chest CT-scan and EGFR mutation in NSCLC lung cancer patients.

METHODS

An cross-sectional design using secondary data was conducted, involving 76 NSCLC patients. EGFR mutations were determined by immunohistochemical examination and metastatic sites by chest CT-scan with contrast. The collected metastatic sites comprised hilar and mediastinal lymphadenopathy, pulmonary nodules, and bone, liver, spleen and suprarenal metastases. A Chi square test was used to analyze the data.

RESULTS

This study revealed that the highest NSCLC stage was IVb, found in 39 samples (51.3%), while 34 (44.7%) subjects had EGFR mutation. There was no statistically significant difference between metastatic site and positive EGFR mutation, although positive bone metastases (54.8%) tend to have more numerous positive EGFR mutations compared to negative bone metastases (37.7%) ($p=0.142$).

CONCLUSIONS

Patients with positive bone metastases tend to have higher positive EGFR mutation compared to negative bone metastases in NSCLC lung cancer patients. Prospective studies evaluating patients with EGFR mutation for bone metastases should be considered. This can provide information on therapeutic decision-making to obtain good clinical outcomes.

Keywords : Chest CT-scan, EGFR mutation, bone metastasis, lung cancer



INTRODUCTION

Epidemiological studies in the world show that lung cancer is the leading cause of death, with more than half of patients diagnosed with lung cancer dying within one year of diagnosis, while the 5-year survival rate is around 17.8%.⁽¹⁾ Currently for patients with non-small cell lung cancer (NSCLC), evaluation of EGFR mutation status by immunohistochemical examination is recommended, because the presence of EGFR mutation greatly influences the choice of therapy.⁽²⁻⁴⁾ Unfortunately, this type of examination is still quite expensive and the facilities are not always available. Adequate samples must be obtained for this examination,⁽⁵⁾ but sometimes these are difficult to obtain. Therefore, the prediction of EGFR mutation from clinical characteristics and imaging tests such as chest CT-scan is important. As we know, the primary diagnostic imaging and staging of a lung mass is performed using a chest CT-scan with contrast.^(6,7)

The chest CT-scan can be used to assess the extent of the occurring metastatic process. On the chest CT-scan we can examine metastatic sites in hilar and mediastinal lymph nodes, pulmonary nodules, liver, spleen, suprarenal gland, and bone especially vertebrae. Several studies have investigated the process of metastasis in NSCLC with EGFR mutation. As is well known, bone is one of the common sites of NSCLC metastases.

Previous studies have investigated the morphological relationship between lung masses and EGFR mutations. In the studies of Hasegawa et al.⁽⁸⁾ and Qiu et al.,⁽⁹⁾ tumor size was not correlated with EGFR mutations, but Liu et al.⁽¹⁰⁾ stated that small tumors could predict the presence of EGFR mutations. In the research of Qiu et al.⁽⁹⁾ and Han et al.⁽¹¹⁾ there was a correlation between the density variable and EGFR mutations.

A retrospective study involving 57 patients with primary lung adenocarcinoma identified CT imaging-based histogram features of bone

metastases with and without EGFR mutation, which may contribute to diagnosis and prediction of EGFR mutation status.⁽¹²⁾ A systematic review and meta-analysis showed that the overall discordance rates in EGFR mutation status between primary NSCLC and distant metastatic tumors is low but varied largely between studies.⁽¹³⁾ Due to the inconsistency between several studies on metastatic tumor, the aim of the present study was to determine the relationship between NSCLC metastatic site in chest CT-scan and EGFR mutation in NSCLC patients.

METHODS

Research design

A study of cross-sectional design using secondary data was conducted in the CT-scan room of the Radiology Installation and clinical data were collected at the Pulmonology Department of dr. Saiful Anwar Malang Hospital from September 2020 to December 2020.

Study subjects

A total of 76 patients recruited into the study were taken from data forms over the time period of 2018 to 2019. The study population comprised patients diagnosed with lung cancer by a pulmonary specialist who had conducted an EGFR immunohistochemical examination and performed a chest CT-scan with contrast at the dr. Saiful Anwar Malang Hospital from January 2018 to December 2019. The inclusion criteria for this study were all male and female patients of any age with lung cancer who had already undergone an immunohistochemical examination for EGFR and chest CT-scan with contrast at the dr. Saiful Anwar Malang Hospital. The exclusion criteria were patients with lung cancer whose primary mass was not found on the chest CT-scan and patients with lung cancer who did not have a chest CT-scan at RSUD Dr. Saiful Anwar Malang.

Measurements

The chest CT-scan was performed using a 128-slice Toshiba Aquilion TSX-101A CT

Scanner at the Central Radiology Installation of dr. Saiful Anwar Malang Hospital. The DICOM file was evaluated by three radiologists using the RadiAnt DICOM Viewer software version 2020.1.1. EGFR mutation was determined by immunohistochemical examination of tumor tissue specimens. Analysis of the 76 samples was carried out by the three radiologists who had more than 5 years experience in measuring metastatic sites. The assessed metastases included contralateral pulmonary nodules as seen on chest CT scan. Metastases to the liver were determined as the presence of multiple lesions that intensify after addition of contrast. With regard to other sites, nodular lesions were found in the spleen and osteoblastic or osteolytic lesions, or even mixed lesions, were found in the bones. In addition, nodules or masses may be found in the adrenals (suprarenals).

Statistical analysis

The data obtained were categorical data, so the analysis used a non-parametric Chi-Square test. All analyses used the SPSS 20 software. A p value <0.05 was considered significant.

Ethical clearance

This study has been declared ethical based on the approval letter by the Ethics and Research Commission of dr. Saiful Anwar Hospital No.400/190/K.3/302/2020.

RESULTS

The study sample consisted of 76 patients, namely 47 men and 29 women. The majority of them were in the age range of 51–60 years, totaling 25 persons (32.9%), while 37 persons (48.7%) had adenocarcinoma on histopathological examination. In this study sample, it was revealed that the highest stage was IVb, found in 39 samples (51.3%). Thirty four subjects (40.7%) had EGFR mutation. The characteristics of the samples are shown in Table 1.

There was no statistically significant association between metastatic site and EGFR mutation, but patients with positive bone

metastases (54.8%) tended to have higher EGF-positive compared to negative bone metastases (37.7%) (p=0.142). The results shown in Table 2.

DISCUSSION

Lung cancer with mediastinal lymph node metastasis is more likely to recur and metastasize after complete resection: therefore, targeted therapy is a promising treatment strategy.⁽⁸⁾ The results of the hilar and mediastinal lymphadenopathy analysis indicate that there is no significant relationship with the EGFR mutation. The samples are dominated by hilar and mediastinal lymphadenopathy. This could be due to the predominance of advanced stadium samples, so that patients with stage N tend to be numerous. Research conducted by Zhang et al.⁽¹⁴⁾ in a cohort of 280 patients with 133 men

Table 1. Demography and tumor characteristics of the study subjects (n= 76)

Variables	n (%)
Gender	
Male	47 (61.8)
Female	29 (38.2)
Age (Year)	
31-40	5 (6.6)
41-50	13 (17.1)
51-60	25 (32.9)
61-70	21 (27.6)
>70	12 (15.8)
Histopathology	
Adenocarcinoma	37 (48.7)
Adeno-squamous carcinoma	9 (11.8)
Squamous cell carcinoma	2 (2.6)
No data	28 (36.8)
Staging	
Ia	1 (1.3)
Ib	1 (1.3)
IIa	0 (0)
IIb	2 (2.6)
IIIa	6 (7.9)
IIIb	2 (2.6)
IIIc	5 (6.6)
IVa	20 (26.3)
IVb	39 (51.3)

Table 2. Relationship between metastatic site and EGFR mutation in NSCLC patients

Metastatic site	EGFR mutation		p value
	Positive EGFR Mutation (n=34) (n,%)	Negative EGFR Mutation (n=42) (n,%)	
Hilar and mediastinal lymphadenopathy			
Positive	25 (40.9)	36 (59.1)	0.184
Negative	9 (60.0)	6 (40.0)	
Metastatic pulmonary nodule			
Positive	22 (47.8)	24 (52.2)	0.502
Negative	12 (4.0)	18 (60.0)	
Bone metastasis			
Positive	17 (54.8)	14 (45.2)	0.142
Negative	17 (37.7)	28 (62.3)	
Liver metastasis			
Positive	5 (33.3)	10 (66.7)	0.321
Negative	29 (47.5)	32 (52.5)	
Spleen metastasis			
Positive	0 (0.0)	1 (100.0)	0.365
Negative	34 (45.3)	41 (54.7)	
Suprarenal metastasis			
Positive	1 (50.0)	1 (50.0)	1.000
Negative	33 (44.6)	41 (55.4)	

and 147 women showed that 120 (42.9%) patients with lung cancer had positive EGFR mutation in lymph node metastases. In contrast, the study conducted by Liu Z et al.⁽¹⁵⁾ found that the incidence of EGFR mutation in patients with lymphadenopathy was only 15.3%. This is because there are other genotypic factors besides EGFR that affect the incidence of metastatic lymphadenopathy.

Diffuse lung metastases have been reported in NSCLC with positive EGFR mutation. In a cohort study conducted by Digumarthy et al.⁽¹⁶⁾ involving 217 patients, the results showed that the finding of a primary pulmonary tumor with diffuse lung metastases in NSCLC should point to the possibility of EGFR mutation. However, it was said that this feature does not replace molecular genotyping. Research conducted by Wu et al.⁽¹⁷⁾ showed that patients who had miliary carcinomatosis had high EGFR mutation rates. The study of Hsu et al.⁽¹⁸⁾ showed that lung metastases often occur in NSCLC with EGFR mutation. After analyzing our study, we found that EGFR mutation was positive in 22 (47.8%) pulmonary nodule metastases and negative in 24

(52.2%), but the difference was statistically not significant (Table 2). Further studies are needed to find out a clear mechanism for the occurrence of pulmonary nodules metastasis with EGFR mutation.

Bone is a common site of metastasis of advanced NSCLC. Among patients with advanced lung cancer, 30–40% have bone metastases (BoM) at the time of diagnosis.⁽¹⁹⁾ Patients with bone metastatic NSCLC and EGFR mutation, when treated with EGFR tyrosine kinase inhibitors (TKIs), have a relatively long survival expectancy.⁽²⁰⁾ In our study, there was no statistically significant association between bone metastases and positive EGFR mutation, although patients with positive bone metastases (17 or 54.8%) tend to have higher positive EGFR mutation rates than do those with negative bone metastases (14 or 37.7%). A retrospective study by Shen et al.⁽¹²⁾ involving 57 patients with primary lung adenocarcinoma identified in these patients CT imaging-based histogram features of bone metastases with and without EGFR mutation, that may contribute to diagnosis and prediction of EGFR mutation status. The study

conducted by Krawczyk et al.⁽²¹⁾ found that NSCLC with EGFR mutation had more metastases to the bones than to the brain. These investigators also found that the activating mutation in the EGFR gene was significantly more frequent in adenocarcinoma bone metastases than in the primary lung adenocarcinoma. Kuijpers et al.⁽²²⁾ have confirmed that patients with positive EGFR mutation have a high incidence of bone metastases, since 54% of patients with positive EGFR mutation in stage IV NSCLC had bone metastases at diagnosis. Beypinar et al,⁽²³⁾ using a retrospective case-control study from 2013 to 2019, totaling 1085 samples, examined the site of metastases with EGFR mutation and without EGFR mutation, and found no significant association between the two. Prospective studies evaluating EGFR mutation patients for bone metastases should be considered. This can provide faster therapy to obtain good clinical outcomes.

In our study, the assessment of liver metastases showed no significant association between metastatic site and EGFR mutation. Similarly, Beypinar et al.⁽²³⁾ concluded that there was no difference in the incidence of liver metastases with and without EGFR mutation. Our study results may be due to the sample size being dominated by the presence of pulmonary metastases with positive and negative EGFR mutations of 47.5% and 52.5%, respectively. The spleen is a rare site of metastasis in NSCLC.⁽²⁴⁾ However, we also found metastases in the spleen although only in 1 sample with negative EGFR mutation which showed no significance. In the study by Mitsimponas et al.⁽²⁵⁾ on their case of spleen metastasis, also no EGFR mutation was found. Adrenal metastases in NSCLC are also frequent.⁽²⁶⁾ However, in our study we only found 2 NSCLC samples with adrenal metastases but no significant association with EGFR mutation.

The limitation of this study is the heterogeneity of the samples due to the absence of data in the interval between the time of chest CT-scan and the time of first diagnosis. The

majority of samples were at an advanced stage. For this study, it is suggested that it is necessary to detect lung cancer at an early stage to reduce the predominance of samples with an advanced stage.

CONCLUSIONS

There was no significant relationship between metastatic site and EGFR mutation in NSCLC lung cancer, based on chest CT-scan with contrast, but patients with positive bone metastases tend to have higher positive EGFR mutation compared to patients with negative bone metastases. Prospective studies should be considered evaluating EGFR mutation patients for bone metastases. This can provide faster decisions on therapy to obtain good clinical outcomes.

CONFLICT OF INTEREST

Competing interests: No relevant disclosures.

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CONTRIBUTORS

DRE, SDP, SA contributed to conception and design; RM, DRE, SDP, SA contributed to analyse and interpretation of the data; RM contributed to drafting of the article; DRE, SDP, SA contributed to revise the manuscript. All authors have read and approved the final manuscript.

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