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By Tiara Aninditha

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Diagnosis of brain metastasis due to lung cancer and affecting factors at "Dr. Cipto Mangunkusumo" General Hospital

Tiara Aninditha[1], Ansi Rinjani[1], Gurmeet Singh[2], Rahmad Mulyadi[3], Rini Andriani[1], Nadia Ayu Mulansari[2]

[1]Department of Neurology Faculty of Medicine, Universitas Indonesia – "Dr. Cipto Mangunkusumo" General Hospital, Jakarta, Indonesia.

[2]Department of Internal Medicine Faculty of Medicine, Universitas Indonesia – "Dr. Cipto Mangunkusumo" General Hospital, Jakarta, Indonesia.

[3]Department of Radiology Faculty of Medicine, Universitas Indonesia – "Dr. Cipto Mangunkusumo" General Hospital, Jakarta, Indonesia

Corresponding author:
Tiara Aninditha
E-mail: t.aninditha@ui.ac.id

ABSTRACT

Background and objectives. The incidence of brain metastases is higher than primary brain tumors, with lung cancer as a common etiology at "Dr. Cipto Mangunkusumo" General Hospital. Delay in diagnosis can cause brain herniation, resulting in disability and death. We aimed to investigate the compatibility between daily clinical practice and clinical practice guidelines for diagnosing brain metastases due to lung cancer at Cipto Mangunkusumo General Hospital while also examining factors that might influence the duration of the diagnosis.

Materials and methods. We conducted a retrospective cohort study to determine the conformity between the duration of diagnosis of metastatic brain tumors due to lung cancer in daily clinical practice with clinical practice guidelines. Secondary data was obtained from medical records from November 2021 until June 2022.

Results. Twelve subjects (30%) were diagnosed with brain metastases from lung cancer within two weeks with a median duration of 18.5 days (IQR 12-34 days). The duration of 7 days (IQR 4-11 days) was required to obtain a lung mass, 8 days (IQR 4.5-13 days) to perform a biopsy, and 6 days (IQR 3.5-7 days) to obtain t pathology results. No statistically

significant relationship exists between the variables assessed and the duration of diagnosis.

Conclusions. The clinical practice guidelines at "Dr. Cipto Mangunkusumo" General Hospital for diagnosing brain metastases from lung cancer within two weeks could only be carried out in 30% of subjects in this study. Collaboration between departments is needed to make the diagnosis faster.

Keywords: brain metastases, diagnosis, duration, lung cancer

Abbreviations:

IQR	Interquartile Range
MRI	Magnetic Resonance Imaging
CT Scan	Computed Tomography Scan
GCS	Glasgow Coma Scale
KPS	Karnofsky Performance Status
NRS	Numeric Rating Scale
NSCLC	Non-Small Cell Lung Cancer

INTRODUCTION

Metastatic brain tumor increases the morbidity and mortality of patients with malignancy. Brain metastases are the most common intracranial tumors with an incidence of 3-10 times higher than primary brain tumors. Recently, the incidence of metastatic brain tumors has been increasing because of population aging, advances in diagnostic tests such as MRI, and increased life expectancy of cancer patients due to the improvement of therapeutic modalities.[1,2] Lung cancer is the most common primary tumor that causes brain metastases.[3] Data at Cipto Mangunkusumo General Hospital also found lung cancer as the most common cause of brain metastases, covering 36.5%.[4] However, about 2-14% of patients with brain metastases came to the hospital without history of previous primary tumors.[3] Brain metastases with an unknown primary tumor have aggressive metastatic spread, obscure response to chemotherapy, and poor prognosis. Technological advances have increased the likelihood of finding brain metastases with previously unknown primary tumors.

Diagnosis of metastatic brain tumors needs to be determined from the beginning of the admission because it will have a remarkably different approach from primary brain tumors. Patients usually present to the hospital with increased intracranial pressure, because brain metastases are usually multiple lesions with extensive edema. Therefore, delay in diagnosis will lead to brain herniation and could result in death. Longerprocess of

establishing an adequate diagnosis and treatment will lead to more complex symptoms and worse patient quality of life..[5]

To date, data regarding time to diagnosis of brain metastasis due to lung cancer er at Cipto Mangunkusumo General Hospitalis not yet available. . This topic received little attention in previous studies. This topic is clinically important because it will help patients with brain metastases from lung cancer have a more accurate diagnosis, begin treatment sooner, and have a better prognosis. Thus, we aimed to investigate the compatibility between daily clinical practice and clinical practice guidelines for diagnosing brain metastases due to lung cancer at Cipto Mangunkusumo General Hospital while also examining factors that might influence the duration of the diagnosis.

MATERIALS AND METHODS

We conducted a retrospective cohort study. We used secondary data obtained from the medical records at "Dr. Cipto Mangunkusumo" General Hospital Jakarta from November 2021 until June 2022. Samples were taken by total sampling in the target population that met the inclusion and exclusion criteria. The inclusion criteria were patients aged 18 years or older without a history of previous cancer (including lung cancer), who had a CT scan/MRI of the head with contrast and had lung malignancy based on histopathological results. Medical record data that were incomplete or could not be traced were excluded from the study. We identified 182 patients with brain metastases and 101 patients had a non-pulmonary primary tumor. A total of 41 patients who had not met the criteria were excluded from the study leaving a final of 40 patients (Figure 1).

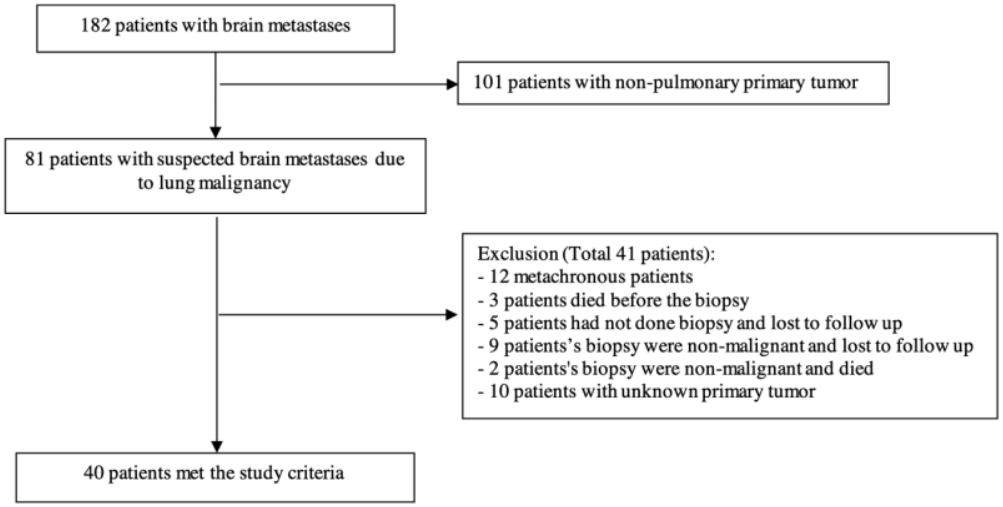


Figure 1. Research Subject Acquisition Flow

Descriptive analysis was conducted to determine the duration needed until the diagnosis of brain metastases due to lung cancer was established and also the proportion of patients with brain tumors due to lung cancer who were established within 2 weeks. Data processing and analysis were performed using IBM SPSS Statistics 21 (IBM Corporation, Armonk, NY, USA). The proportions of categorical variables were compared using Chi-square or Fisher's exact. Multivariate logistic regression analysis was conducted to determine the relationship between demographic characteristics, clinical characteristics, characteristics of brain metastases, and characteristics of lung cancer with the duration of diagnosis.

This research had obtained written permission from the Ethics Commission of the Faculty of Medicine, Universitas Indonesia with letter number KET-370/UN2.F1/ETIK/PPM.00.02/2022 and protocol number 22–04–0423 on April 18th, 2022. Data collection was carried out after obtaining research permission from Dr. RSUPN. Cipto Mangunkusumo with official memorandum numbers LB.02.03/2.6.1/0568/2022 and LB.02.03/2.6.1/0708/2022.

RESULTS

Baseline Characteristics

Our study shows that (Table 1) the majority of the subjects were male (80%) in the age group of 50 years and over (77.5%). The median age was 55 (33-69) years. The clinical characteristics of the research subjects mostly had a good performance status (62.5%). Headache appeared to be the most frequent symptom (70%) with a median NRS of 5 (IQR 4-8), followed by decreased consciousness (47.5%) with a mean GCS score of 12, and seizure (40%). Among 40 subjects, 32 subjects (80%) had comorbidities. Pneumonia, hyponatremia, and hypertension were the three main comorbidities, with the proportions of 45%, 30%, and 25%, respectively.

Table 1. Baseline Characteristics of The Subjects (Total n=40).

Characteristics	n (%)
Age	
< 50 years	9 (22,5%)
≥ 50 years	31 (77,5%)
Median age (range)	55 (33-69)
Gender	
Male	32 (80%)
Female	8 (20%)

KPS score	
≥60	25 (62,5%)
< 60	15 (37,5%)
Clinical Manifestations	
Headache	28 (70%)
Decrease of consciousness	19 (47,5%)
Seizure	16 (40%)
Cancer pain	1 (2,5%)
Degree of Consciousness (GCS), n=19	7 (17,5%)
Mild	12 (30%)
Moderate – Severe	12
Mean GCS score	
Headache Intensity, n=28	
Mild	11 (27,5%)
Moderate – Severe	17 (42,5%)
Mean NRS score	5 (IQR 4-8)
Comorbidity	
Yes	32 (80%)
No	8 (20%)
Comorbidity Description	
Pneumonia	18 (45%)
Hyponatremia	12 (30%)
Hypertension	10 (25%)
Anemia	6 (15%)
Heart disease	5 (12,5%)
Diabetes Mellitus	4 (10%)
Sepsis	3 (8%)
Others	11 (27,5%)

Brain Metastases and Lung Mass Characteristics

Table 2 shows the characteristics of brain metastases and lung mass. More than half of the brain lesions were multiple (77.5%) and supratentorial (75%). According to the location of the lung mass, the proportions were similar for the central, peripheral, and combined central and peripheral, with the proportions being 45%, 20%, and 35%,

respectively. The most frequent histopathological types (85%) were non-small cell lung cancer (NSCLC).

Table 2. Characteristics of Brain Metastases and Lung Mass (Total n=40).

Subject Characteristics	n (%)
Location of Brain Metastases	
Supratentorial	30 (75,0)
Infratentorial	1 (2,5)
Leptomeningeal	1 (2,5)
Supratentorial and Infratentorial	8 (20,0)
Number of Brain Metastases	
Solitary	9 (22,5)
Multiple	31 (77,5)
Lung Mass Location	
Central	18 (45,0)
Peripheral	8 (20,0)
Central and Peripheral	14 (35,0)
Histopathological Type of Lung Mass	
Small cell lung cancer (SCLC)	4 (10,0)
Non-small cell lung cancer	34 (85,0)
*(*NSCLC)	2 (5,0)
Neuroendocrine Tumor	

Duration of Time to Diagnose Brain Metastases due to Lung Cancer

The majority of subjects (70%) were diagnosed with brain metastases due to lung cancer in more than two weeks or more than 14 days, and only twelve subjects (30%) were diagnosed within two weeks or 14 days. The median duration to establish the diagnosis was 18.5 days (IQR 12-34 days). The median duration to discover a lung mass from suspected brain tumor patients was seven days. The median length of time needed to perform a biopsy after being diagnosed with a lung mass was eight days. Moreover, it took a median of six days to obtain the results of anatomical pathology after a biopsy (Table 3).

Table 3. Length of Time Required to Diagnose Brain Metastases due to Lung Cancer

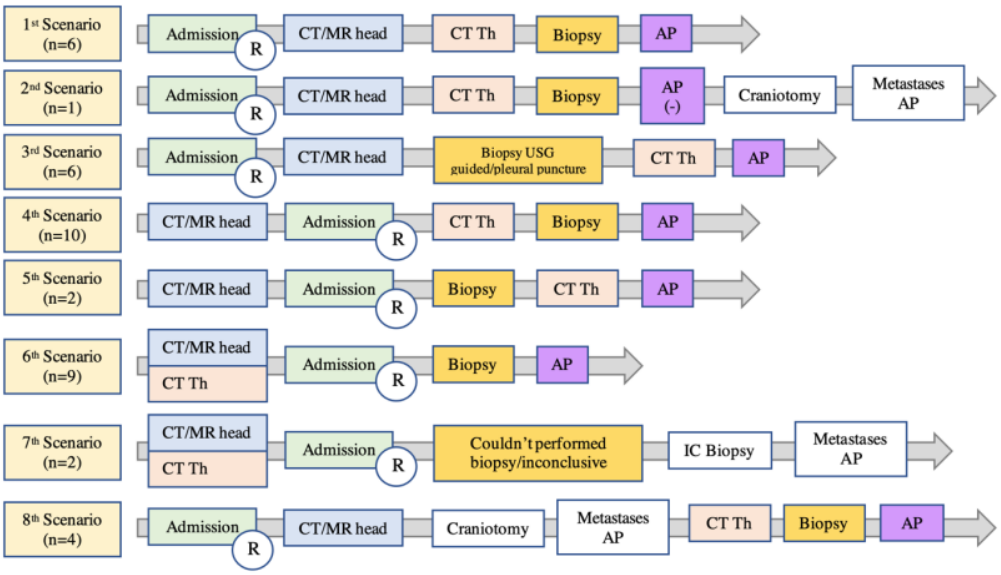
Variable	Median (IQR)
Duration of time required for patients with suspected brain metastases to be diagnosed as metastases from lung cancer	18,5 days (12-34 days)
• Number of patients diagnosed with brain metastases due to lung cancer ≤2 weeks	12 (30%)
• Number of patients diagnosed with brain metastases due to lung cancer >2 weeks	28 (70%)
Duration of time required to discover a lung mass of a suspected metastatic brain tumor patient	7 days (4-11 days)
Duration of time required to perform a biopsy after a patient was diagnosed with a lung mass	8 days (4.5-13 days)
Duration of time required to obtain the anatomical pathology results following a biopsy	6 days (3.5-7 days)

IQR: Interquartile Range

Diagnosis Flow of Patients with Brain Metastases due to Lung Cancer

Figure 2 presents eight flow scenarios to establish a diagnosis of brain metastases due to lung cancer. The most common scenarios were the 4th scenario and the 6th scenario. In scenario four, the subjects had a head CT scan or MRI before admission, then underwent a chest CT scan followed by an inpatient biopsy, and finally obtained their pathology results. As for scenario six, in addition to having a head CT scan or MRI, the subjects also had a chest CT scan before admission, then underwent a biopsy and obtained the pathology result at the time of hospitalization.

Figure 2. Diagnosis Flow of Patients with Brain Metastases due to Lung Cancer at Cipto Mangunkusumo General Hospital.



R: Rontgen; CT/MR Head: Head Computerized Tomography/Magnetic resonance; CT Th: Thorax Computerized Tomography; AP: Anatomical Pathology Results

The duration of time of each scenario varies. From the shortest to the longest time taken to establish the diagnosis, the fifth scenario had the shortest time (mean 10±2.82 days), followed by the third scenario with a median duration of 13 days (IQR 11-15 days). The sixth scenario had a median duration of 17 days (IQR 11-23 days), while the fourth scenario had a median duration of 22 days (IQR 16-33 days). Next, the first scenario with a mean duration of 24.33±12.77 days. The seventh scenario had an average of 32 days±7.07 days. Moreover, scenario eight had a mean of 33 days±20.60 days. Last, the second scenario took the longest time of 45 days.

Relationship between Subject, Brain Metastases, and Lung Mass Characteristics with Duration of Time for Diagnosis

Table 4 shows the relationship between several aspects of the subject's characteristics and the length of time needed to establish the diagnosis. There was no significant relationship between the baseline characteristics, clinical characteristics, and duration of time required to establish the diagnosis of brain metastases due to lung cancer (p>0,05). Besides, Table 5 displays the relationship between brain metastases and lung mass characteristics with the duration of time required to establish the diagnosis. It revealed no statistically significant relationship between the two (p>0,05).

Table 4. The Relationship Between Baseline and Clinical Characteristics with the Duration of Time Required for Diagnosis

Variable	Diagnosis established ≤2 weeks	Diagnosis established >2 weeks	OR (CI 95%)		p
Baseline Characteristics [31]					
Age					
<50 years	4 (44,4)	5 (55,6)	2,30	(0,49-	0,41[b]
≥50 years	8 (25,8)	23 (74,2)	10,74)		
Gender					
Male	8 (25,0)	24 (75,0)	0,33	(0,06-	0,21[b]
Female	4 (50,0)	4 (50,0)	1,65)		
KPS score					
≥60	9 (28,1)	23 (71,9)	0,65	(0,13-	0,67[b]
<60	3 (37,5)	5 (62,5)	3,31)		
Clinical Characteristics					
Decrease of consciousness (DOC)					
Yes	5 (26,3)	14 (73,7)	0,71	(0,18-	0,63[a]
No	7 (33,3)	14 (66,7)	2,80)		
Headache					
Yes	9 (32,1)	19 (67,9)	1,42	(0,31-	0,73[b]
No	3 (25,0)	9 (75,0)	6,55)		
Seizure					
Yes	6 (37,5)	10 (62,5)	1,80	(0,46-	0,49[b]
No	6 (25,0)	18 (75,0)	7,08)		
Comorbidity					
Yes	9 (28,1)	23 (71,9)	0,65	(0,13-	0,67[b]
No	3 (37,5)	5 (62,5)	3,31)		

Severity of DOC (n=19)					
Mild	1 (14,3)	6 (85,7)	0,33	(0,03-	0,60 [b]
Moderate-Severe	4 (33,3)	8 (66,7)	3,80)		
Headache Intensity (N=28)					
Mild	3 (27,3)	8 (72,7)	0,68	(0,31-	1,00 [b]
Moderate-Severe	6 (35,3)	11 (64,7)	3,61)		

[a]Chi-Square Test; [b] Uji Fisher's Exact Test

Table 2. Relationship between the Characteristics of Brain Metastases and Lung Mass with Duration of Time Required for Diagnosis

Variable	Diagnosis established ≤2 weeks	Diagnosis established >2 weeks	OR (CI 95%)	p
Location of Brain Metastases				
Supratentorial				
Yes	11 (28,9)	27 (71,1)	0,41	0,52
No	1 (50,0)	1 (50,0)	(0,2-7,11)	[b]
Infratentorial				
Yes	2 (22,2)	7 (77,8)	0,60	0,69
No	10 (32,3)	21 (67,7)	(0,11-3,43)	[b]
Supratentorial and Infratentorial				
Yes	1 (12,5)	7 (87,5)	0,27	0,39
No	11 (34,4)	21 (65,6)	(0,03-2,50)	[b]
Number of Brain Metastases				

Solitary	3 (33,3)	6 (66,7)	1,22	1,00
Multiple	9 (29,0)	22 (71,0)	(0,25-5,98)	[b]
Location of Lung Mass				
Central				
Yes	10 (31,3)	22 (68,8)	1,36	1,00
No	2 (25,0)	6 (75,0)	(0,23-7,97)	[b]
Peripheral				
Yes	5 (22,7)	17 (77,3)	0,46	0,27
No	7 (38,9)	11 (61,1)	(0,12-1,83)	[a]
Central and Peripheral				
Yes	3 (21,4)	11 (78,6)	0,52	0,48
No	9 (34,6)	17 (65,4)	(0,11-2,33)	[b]

[a]Chi-Square Test; [b]Fisher's Exact Test

Last follow-up on 40 study subjects, revealed that 60% of subjects (n=24) died, 2.5% of subjects (n=1) still alive, and 37.5% of subjects (n=15) lost to follow up. In 60% of the subjects who died, the duration from admission to death was a median of 48 days (IQR 34-95 days).

DISCUSSION

Our study revealed a median duration of 18.5 days (IQR 12-34 days) for establishing the diagnosis of brain metastases from lung cancer at "Dr. Cipto Mangunkusumo" General Hospital. The duration of the diagnosis process in this study included the time for diagnosing a lung mass (7 days, IQR 4-11 days), the time needed to perform a biopsy (8 days, IQR 4.5-13 days), and also the time required to obtain the anatomical pathology results (6 days, IQR 3.5-7 days). The median time needed to identify a lung mass and to perform a biopsy afterward had already taken two weeks. The Clinical Practice Guidelines of "Dr. Cipto Mangunkusumo" General Hospital recommended getting an established diagnosis within two weeks. In addition, the British Thoracic Society also recommended obtaining the histological or cytological results within two weeks after the biopsy.[6] Our data did not correspond with these recommendations, only 30% of our

subjects had an established diagnosis according to the clinical practice guidelines of "Dr. Cipto Mangunkusumo" General Hospital.

Verma, et al. in their study in Singapore regarding lung cancer patients undergoing diagnostic procedures, revealed the mean interval from abnormal chest CT to biopsy procedure was 16±26 days, the time interval from biopsy procedure to diagnosis 11±19 days, and the interval from abnormal chest CT to diagnosis 27±33 days.[7] Meanwhile, the American College of Pathologists recommended that the duration from the time a pathology investigation is requested/ordered to the time the results are published is no more than two working days.[8]

From the study of Onal et al., the mean life expectancy in patients with squamous cell carcinoma was 11.50±1.40 months, 12.60±1.59 months in adenocarcinoma patients, and 8.70 ±1.87 months in other types of NSCLC patients. In addition, that study found that patients who did not receive radiotherapy (HR, 3.25; P<0.001) or chemotherapy (HR, 1.85; P=0.001) had a statistically significant reduction in overall survival.[9] Study by Fureder et al. demonstrated that the survival of patients receiving targeted therapy after molecular examination showed a significant improvement in survival (20 months vs 7 months).[10]

A faster diagnosis can support earlier initiation of treatment which affects better outcomes in cancer patients. Knowing the duration of the diagnosis of each diagnostic step including the duration of identifying lung mass as the primary tumor, the time needed to perform the biopsy, and obtaining the histopathological results, could help and encourage time efficiency in diagnosing. However, in this retrospective study using electronic health records and manually written medical records, only one subject recorded a clear reason for a delayed biopsy procedure, which was a COVID infection. As for the other 39 subjects, there were no records regarding the reasons for the delay in the diagnostic procedures or delay in establishing the diagnosis.

The discrepancy in duration for establishing the diagnosis was also related to the various scenario of diagnostic flows in our hospital as we described previously. Each scenario had a different average duration of time. The shortest interval was the fifth scenario with an average of 10±2.82 days, while the longest interval was the second scenario with 45 days. It was challenging to homogenize the flow because the patients' conditions varied when they presented to our hospital, and our diagnostic approach was adjusted accordingly. However, it is possible to conduct further studies through the data that we had presented. Therefore, future improvements can be performed regarding the flow of diagnosing brain metastases due to lung cancer in hospitals.

This study also assessed the association between the age groups and the length of time needed for diagnosis. Comorbidities were found more in the more advanced age

group. More than half of cancer patients aged 65 years had at least one comorbid condition.[11] The discovery of comorbidities in research subjects could hinder the diagnostic actions, such as CT scans and biopsies because they had to wait for the patient's condition to become stable before going for diagnostic examination. The majority of subjects in this study had comorbidities (80%) with pneumonia (45%) as the most common comorbidity. The incidence of infection increased the length of stay with an average of 12 days of hospitalization, with a comparison between patients with infection of 25.3 days and 5.69 days in patients without infection.[12] However, in this study, there was no statistically significant relationship between age, gender, KPS score, clinical manifestations, or comorbidities with the duration required for establishing the diagnosis within 2 weeks (14 days).

Brain metastases located in the infratentorial area generally have more severe neurological symptoms and general conditions than subjects with supratentorial lesions. Dou, et al. found that infratentorial brain metastases lesions were significantly associated with younger age, male gender, neuroendocrine lung and squamous cell carcinoma, more active tumor cell proliferation, and poorer outcome. Patients with metastatic lesions in the infratentorial area generally need improvement and stabilization before proceeding with the required diagnostic procedures.The location of the lung mass can influence the selection of modality and duration of diagnosis. The bronchoscopy modality has greater sensitivity (88%) in diagnosing malignancy of central lesions than peripheral lesions (34% sensitivity for peripheral lesions <2 cm and 63% for lesions >2 cm). The EMN and R-EBUS bronchoscopy techniques have higher sensitivity for peripheral lesions than ordinary bronchoscopy (MNS 71% and R-EBUS 73%). For peripherally located lung masses, transthoracic needle aspiration (TTNA) biopsy is more commonly used, which has a high sensitivity in diagnosing lung cancer (90%). Therefore, the location of a peripheral lung mass with transthoracic needle aspiration biopsy modality can facilitate the process of making the diagnosis of brain metastases due to lung cancer. Nevertheless, we found no statistically significant relationship between the location of brain metastases, the number of brain metastases, and the location of lung masses with the duration needed for diagnosing brain metastases due to lung cancer within 2 weeks (14 days).

Cipto Mangunkusumo General Hospital is a national referral hospital. Patient conditions varied with different complexities causing various flows to diagnose brain metastases due to lung cancer. In addition, this was an initial study to seek standardization of the duration for diagnosing brain metastases at Cipto Mangunkusumo General Hospital. Therefore, it had not included administrative factors such as payment scheme (all subjects

in this study were using national health insurance), the operative treatment schedule, and their effect on the duration of diagnosis.

CONCLUSION

The clinical practice guidelines at "Dr. Cipto Mangunkusumo" General Hospital for diagnosing brain metastases due to lung cancer within two weeks could only be applied to 30% of subjects in this study. There was no statistically significant relationship between age, gender, KPS score, decreased consciousness, headache, cancer pain, seizures, comorbidities, degree of loss of consciousness, headache intensity, location of brain metastases, number of brain metastases, and location of brain metastases and lung mass with the duration to establish diagnosis within two weeks (14 days). Collaboration between departments is needed to confirm the diagnosis faster.

Conflict of interest: There are no conflicts of interest.

Author's contributions: Data acquisition was done by AR. All authors analyzed and interpreted the data. The writing of the manuscript is mostly done by TA and AR. All authors read and approved the final manuscript.

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