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Apparent diffusion coefficient value of brain metastasis from lung carcinoma as potential predictor of epidermal growth factor receptor mutation

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Abstract

Background Lung carcinoma metastases to the brain occurred in 40% of all lung carcinoma cases and it occupied the top ranking of mortality of cancers. MRI plays an important role in predicting mutations of lung carcinoma.

Objective This study aimed to compare apparent diffusion coefficient (ADC) values from brain MRI among lung carcinoma patients with and without epidermal growth factor receptor (EGFR) mutations which result in brain metastases.

Methods Data of fifty-two patients with brain metastasis from lung carcinoma during 2019 to 2022 were taken. The three regions of interest (ROI) were placed to the mutation, non-mutation, and non-lesion groups to predict ADC values.

Results The ADC values of the EGFR mutation group were not significantly different from either the non-EGFR mutation group or the non-lesion group. The average ADC value of the EGFR mutation group was the lowest, followed by the non-EGFR mutation group and the non-lesion group. The prediction of ADC values in the EGFR mutation group ranged 0,773–0,815 $\times 10^{-3}$ mm^2/s, followed by the non-EGFR mutation group 0,82 $\times 10^{-3}$ mm^2/s, and non-lesion group 0.841 $\times 10^{-3}$ mm^2/s.

Conclusions The ADC values in contrast-brain-MRI can be used as a predictor of EGFR mutations in lung carcinoma with lower prediction value than non-EGFR mutation patients. The ADC values in MRI can contribute in diagnosing and planning further management for lung carcinoma towards precision therapy era.

Keywords Magnetic resonance imaging, Brain metastasis, EGFR mutation, Lung carcinoma

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Background

Lung carcinoma occupies the top rank of mortality globally in which 85% of its types is non-small cell carcinoma (NSCC). In Indonesia, lung cancer occupied the highest incidence rate in males in 2019 by 19.4 per 100,000 population with an average mortality rate of 10.9 [1]. Half of the patients with lung cancer were diagnosed at the age of 65 years old with an average age at diagnosis was 70 years old and one-third of the patients was diagnosed at the age of 45 years old [2].

Lung carcinoma metastases to the brain occur in 40% of all patients of NSCC. As many as 10–15% of the patients were diagnosed earlier with brain metastases than the diagnosis of lung carcinoma. In its development, experts succeeded in detecting genetic mutations involved in the pathogenesis of lung carcinoma and then developed it as a targeted therapy with better therapeutic effectiveness [3]. In line with this, precision medicine is known. It refers to an approach to treating medical abnormalities by taking into account individual variability associated with genetic and environmental factors. Imaging plays an important role in the era of precision medicine for conducting early diagnosis, guiding the therapeutic process, evaluating response to therapy, and assessing disease recurrence [4].

Magnetic resonance imaging (MRI) has potential to determine targeted therapy decisions for lung cancer patients who need genetic mutation markers [5]. Compared to other radiological modalities, MRI is more sensitive in evaluating intracerebral lesions so that abnormalities in the brain can be detected earlier. In addition, MRI can also confirm the constituent components of a lesion so that it can distinguish primary tumour, secondary tumour, tumour due to infection, and post-radiation fibrous tissue. The apparent diffusion coefficient (ADC), a mathematical calculation derived from diffusion weighted imaging (DWI) sequence, has been used to differentiate glioma grades [6], describe a posterior fossa solid tumour in a paediatric patient [7], correlate with predictive histopathological features of brain metastatic masses [8], and predict the extent of tumour lesions in cases of lung carcinoma [9]. This study aimed to compare the ADC values of brain metastases in patients of lung cancer with or without epidermal growth factor receptor (EGFR) mutations. By this study, MRI will be developed to predict the occurrence of mutations in patients of lung carcinoma with brain metastases.

Methods

The population of this study were all patients who had an advance brain MRI examination confirmed as brain metastases with multiple brain lesions. The brain metastases lesions of each patient was identified from basic MRI sequences such as T1, T1 with contrast, T2 and T2 with fluid-attenuated-inversion-recovery (FLAIR), gradient-echo (GRE), and DWI. The inclusion criteria were the patients diagnosed with lung carcinoma through histopathological examination and had undergone the EGFR mutation examination. The patients with uncomplete data and other primary site-organ malignancy were excluded. The patients' age was determined based on the date of brain contrast-enhanced MRI examination. Brain MRI data were taken retrospectively from January 1, 2019 to February 28, 2023. The results of the mutation examination were divided into EGFR mutation and non-EGFR mutation groups. The apparent diffusion coefficient (ADC) values were obtained by placing the region of interest (ROI) and calculating the ADC values at the MRI 3 Tesla (3 T) workstation with b-value of 0–1000. The setting of MRI pieces was made with thickness of 6 mm and the space between the pieces was 3 mm.

Values of ADC were obtained by placing the ROI that was made in the form of a circle with a diameter of 1.5×1.5 mm to 3×3 mm [10] in the largest lesion, intralesional peripheral aspects, and taken three times in the same lesion (ROI 1, 2, 3). ROI placing avoided the edema, necrotic, cystic components and bleeding areas which were identified through T1, T1 with contrast, T2, T2-FLAIR, and GRE. ROI placement was also performed on the contralateral side of the lesion in which the falx cerebri performed as the mirror to obtain the ADC values in the non-lesion area. ADC value was assessed under blinded and randomized method.

Statistical analysis

The analysis of the ADC values in the EGFR mutation group, the non-EGFR mutation group and the non-lesion group was carried out by statistical tests. Since the data were not normally distributed, the non-parametric Kruskal–Wallis test was applied. Determination of the predictive value in each group was based on the average ADC value displayed in the form of value ± standard deviation (SD). Furthermore, the group with EGFR mutation was analyzed using the receiver operating characteristic (ROC) curve to determine the range ADC predictive value from which sensitivity and specificity were established.

Results

A total of 788 patients from January 1, 2019 to February 28, 2023 met the population criteria. The study subjects were determined based on inclusion criteria, consisting of brain metastatic status which is decided based on the results of contrast-enhanced brain MRI examination. The required sequences included T1, T1 with contrast, T2, T2 FLAIR, GRE, and DWI. Based on the inclusion

criteria, a total of 52 patients were obtained, consisting of 25 patients with EGFR mutations and 27 patients with non-EGFR mutations. The age, sex, and type of pulmonary carcinoma based on histopathological results varied between patients as shown in Table 1. The mutational status of EGFR was obtained through tissue examination by immunohistochemical methods.

The average age of patients was 56.1 years which were mostly between 55–56 years with the oldest age 72.8 years and the youngest age 32.7 years. Based on the results of statistical examination (independent t-test), it was known that the age of patients between the EGFR mutation group and the EGFR non-mutation group was not significantly different with p-value = 0.3. The results of histopathological examination which was taken through core biopsy found that as many as 50 study patients (96%) had lung adenocarcinoma, while as many as 2 study patients (4%) had small cell carcinoma (Fig. 1).

The EGFR mutation group was dominated by females with a total of 18 patients (72%), whereas the non-mutation group had higher number of males with a total of 15 patients (55%). The ADC values of ROI 1,2,3 in the EGFR mutation group were compared to the non-EGFR mutation group, followed by comparison of each group with the non-lesion sections as listed in Table 2. The inter-observer reliability of measuring ADC values was confirmed by Kappa value with the level of agreement 0,83 which indicated almost perfect agreement [11].

The mean ADC value in the EGFR mutation group of $0.81 \pm 0.25 \times 10^{-3}$ mm^2/s was lower than both the ADC value in the non-EGFR mutation group of $0.82 \pm 0.23 \times 10^{-3}$ mm^2/s with $p = 0.956$ and the ADC

Table 1 The distribution of age, sex, type of carcinoma and EGFR mutation status

Characteristics		The number of patients ($n = 52$)	Percentage (%)
Age (years)	32–45	7	13.5
	46–60	31	59.6
	61–73	14	26.9
Sex	Male	22	42.3
	Female	30	57.7
Type of carcinoma	Adenocarcinoma	50	96
	Small cell carcinoma	2	4
EGFR mutation status	EGFR Mutation	25	48.1
	Non-EGFR mutation	27	51.9

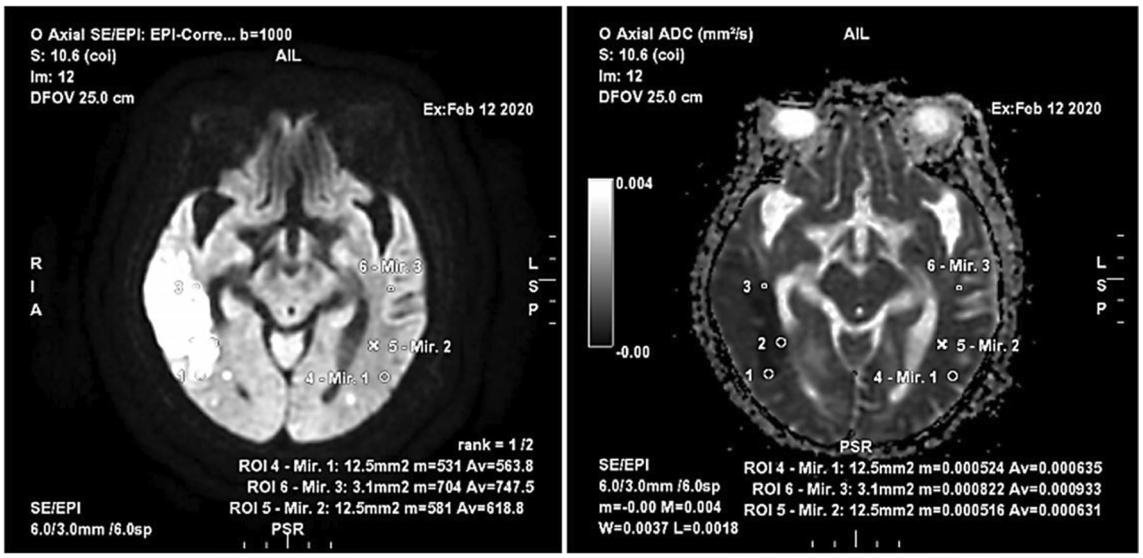

Fig. 1 ROI 1, 2, 3 were carried out by a mirroring process to obtain ADC values from non-lesion tissues on the contralateral side of the tumour named Mir-1, Mir-2, Mir-3 (Author's courtesy)

Table 2 Comparison of ADC values between groups

Patients' Group	ROI 1 (10^{-3} mm^2/s)	ROI 2 (10^{-3} mm^2/s)	ROI 3 (10^{-3} mm^2/s)	ADC_{lesion} Mean (10^{-3} mm^2/s)	ADC_{min} Mean (10^{-3} mm^2/s)	ADC NL Mean	ADC_{lesion}/ ADC NL Ratio (%)
EGFR Mutation	0.79 ± 0.24	0.82 ± 0.26	0.82 ± 0.26	***0.81 ± 0.25**	**0.76 ± 0.24**	**0.87**	**94**
Non-EGFR mutation	0.8 ± 0.21	0.83 ± 0.23	0.83 ± 0.26	**0.82 ± 0.23**	**0.76 ± 0.21**	**0.92**	**94**
				***p* = 0.956**	***p* = 0.985**		
The mean of ADC value of non-lesion sites				***0.89 ± 0.21**			
				******p* = 0.636**			

ROI Region of interest, *ADC* Apparent diffusion coefficient, *EGFR* Epidermal growth factor receptor, *NL* Non lesion

* *p* The *p* value that comparing mean of ADC in EGFR mutation group and in non-lesion

value in the non-lesion group of $0.89 \pm 0.21 \times 10^{-3}$ mm^2/s with $p = 0.636$. The same trend was also found in the ADC_{min} value of the EGFR mutation group which was lower than the ADC_{min} in the non-EGFR mutation group. Figure 2 shows a boxplot diagram comparing the EGFR mutation, non-EGFR mutation, and non-lesion groups to determine the predictive value of ADC. Furthermore, the group with EGFR mutation was analyzed using the ROC curve with the predicted ADC value of lung carcinoma patients of $0.773–0.815 \times 10^{-3}$ mm^2/s with 65.3% sensitivity and 46.9% specificity.

Discussion

Low ADC value is associated with malignant tumors [8]. Brain metastatic tumors have malignant character as well as the nature of its primary tumor (lung carcinoma). EGFR mutation in pulmonary carcinoma indicates high malignancy and need to be identified to determine the appropriate and efficient therapy regimen. Therefore, ADC values of brain metastatic tumors in EGFR mutation group which are lower than non-mutation group become an important consideration for determining targeted therapy in pulmonary carcinoma patients [4].

The purpose of this study was to evaluate the ADC values of brain metastases in lung cancer patients who had EGFR mutations or not. In this study, the mean of ADC value in the EGFR mutation group was lower than in the non-EGFR mutation group that might be useful in the prediction of EGFR mutation of lung carcinoma. The ADC values in both groups were lower than the ADC values in non-lesion areas with index < 1. Based on the boxplot diagram, the EGFR mutation group has the lowest value and is in the 3rd quartile below the non-EGFR mutation group. Thus, in general, malignant lesions have lower ADC values than normal tissues where lesions with EGFR mutation status have the lowest ADC values compared to the other two groups (non-EGFR mutation and non-lesion) (Figs. 3 and 4).

Tumour cellularity and tumour grade were related to ADC values from ADC maps (ADC values are inversely proportional to tumour cellularity). When compared to normal brain tissues, primary brain tumours with higher cellularity or grade often have lower ADC values [12]. A study conducted by Jung et al. [8] revealed that the ADC values of the secondary brain tumor from the lung cancer in the gene mutation group were lower than the non-mutation group even though the ADC values could not differentiate tumour histology types. However, the use of the ADC values in determining the type of tumour is still promising as the results of Mohamed et al. [7] study in differentiating common tumours in children, including juvenile pilocytic astrocytoma and medulloblastoma. Cutoff values of more than 1.3×10^3/s for juvenile pilocytic astrocytoma and less than 0.9×10^3/s for medulloblastoma appear to provide the diagnosis which may guide subsequent diagnostic testing, treatment planning, and outcome. Different results were obtained in Al Agha et al. [6] study which confirmed that ADC values were inversely connected with glioma grades. However, at a high b-value (3000) there is still a stronger correlation between the ADC values and the malignancy grading of glioma. Therefore, the ADC values can still be used to predict the grading of a glioma.

The hypointensity in ADC revealed a true restricted diffusion of hyperintensity in DWI sequence as conducted in this study before determining ADC value. Human body is composed of 60–70% water molecules. The water molecules are located both intracellularly and extracellularly. Water molecules in the human body undergo a process of diffusion. However, related to the complexity of the human body which consists of intracellular and extracellular compartments, water molecules have different diffusion characteristics. In the extracellular environment, water molecules undergo relatively free diffusion, whereas intracellular molecules tend to exhibit restricted diffusion. The relative proportions of the

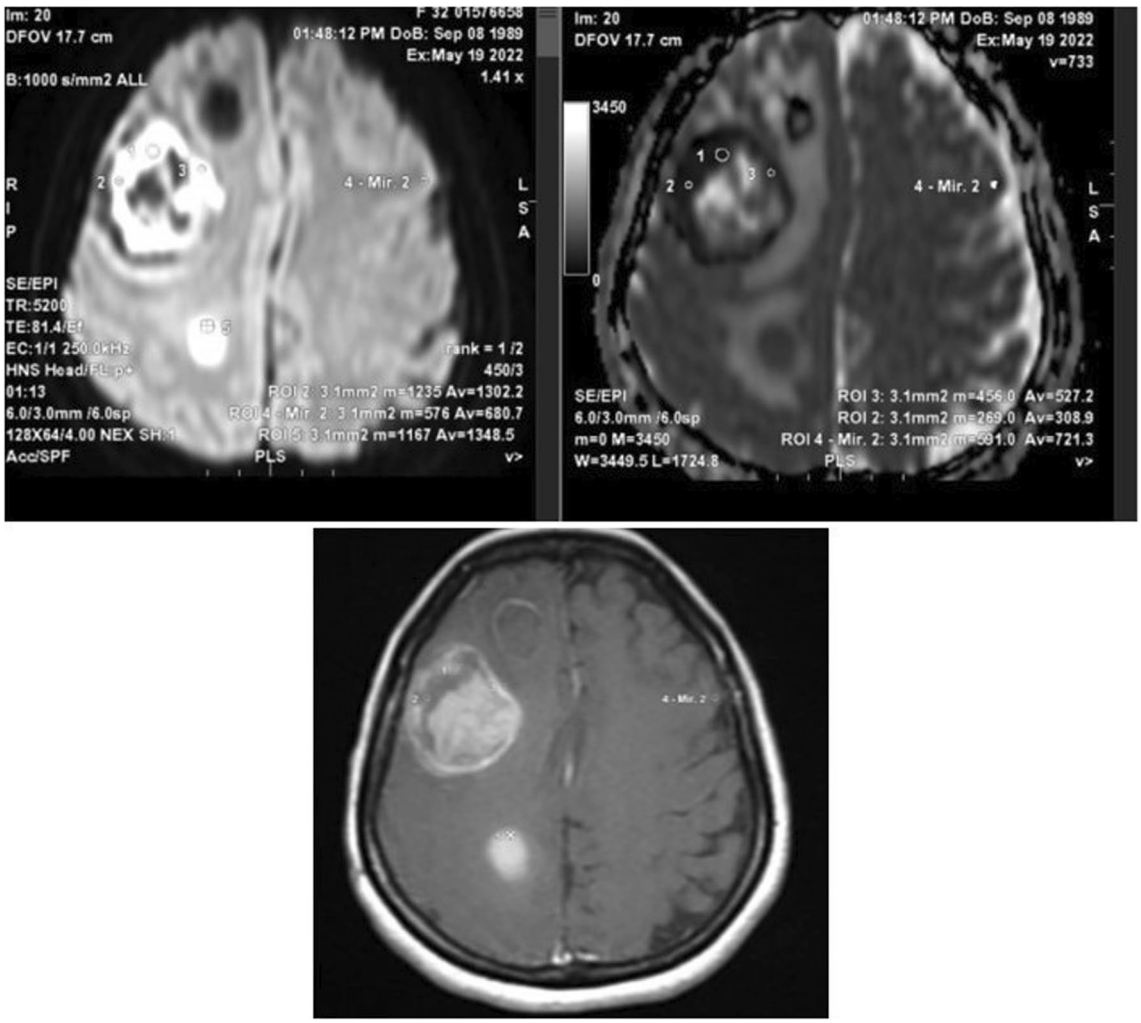

Fig. 2 The biggest lesion from multiple brain metastasis lesions was chosen for placing ROI and measuring the ADC value. Hyperintensity in DWI sequence was confirmed by ADC hypo intensity; T1 with contrast confirmed that the lesions had absorbed contrast media heterogeneously to ease the identification of lesion edge (Author's courtesy)

distribution of water molecules between these compartments are altered by a pathological process. For example, in cases of high-grade malignancy, metastatic lesions, or in tissues undergoing acute infarction, the intracellular proportion may be higher [13].

The imaging of MRI with DWI sequences provides qualitative and quantitative information regarding diffusion activity. This makes MRI is not only used to assess anatomical structures in detail through conventional MRI sequences (T1, T1 with contrast, T2, T2 FLAIR, and GRE) but also to assess tissues/organs functionally. Through conventional MRI, both EGFR mutated and non-mutated patients cannot be differentiated. From T1 and T1 with contrast we can determine the types of lesions, whether it is a mass or not. From T2 and T2 FLAIR we conclude the elements of lesion and the oedema around the lesion. In GRE, we can determine the blood indicating a lesion with haemorrhagic transformation. The b-value parameter determines the amount of diffusion expressed in s/mm^2. Diffusion is measured qualitatively by evaluating imaging features and quantitatively by a parameter called ADC. Quantitative assessment on the ADC map is carried out by placing ROI in an area with true restriction.

Restricted diffusion areas in DWI sequences supplemented with ADC values can indicate several disease entities, including hyperacute infarction, high cellularity tumours associated with a high degree of malignancy, and metastatic tumours. ADC values are described in mm^2/s units. Several studies have attempted to determine the predictive ADC values in normal tissue and abnormal lesions in cases of infection or malignancy. The ADC value in the cortical grey matter ranges from $0.56–0.78\times10^{-3}$ mm^2/s. In the white matter, it ranges

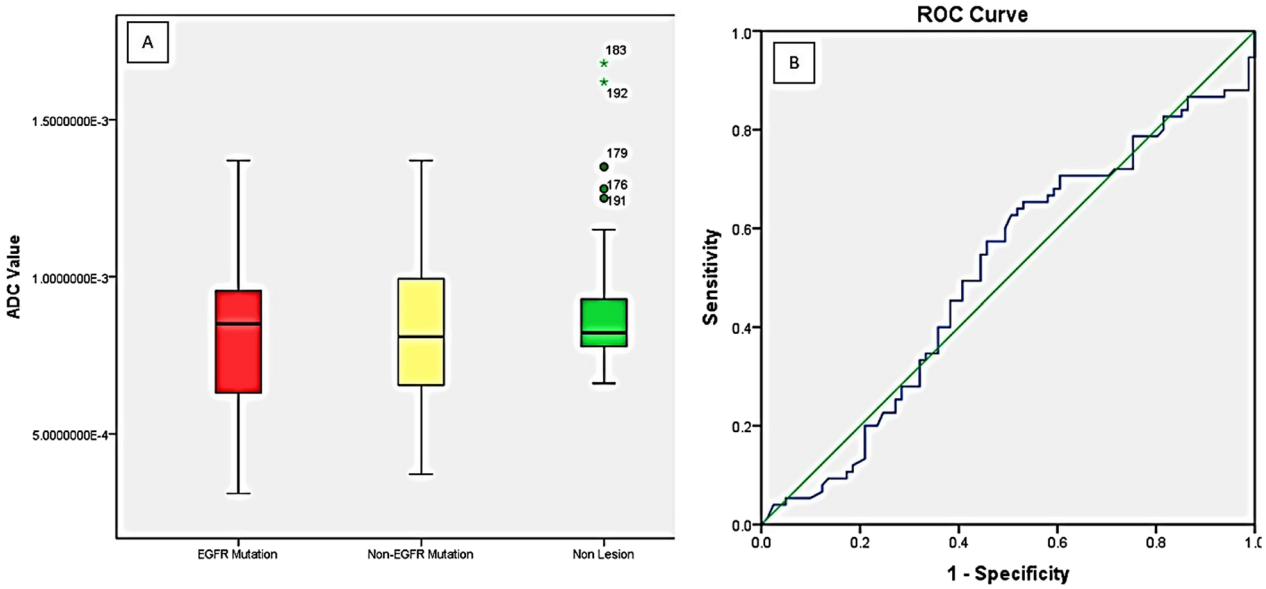

Fig. 3 Boxplot diagram of EGFR mutation, non-EGFR mutation, and non-lesion (**A**), and ROC curve in the EGFR mutation group (**B**)

from 0.319–0.686 × 10^{-3} mm^2/s. Whereas in liquor cerebrospinal, it ranges from 1.59–2.43 × 10^{-3} mm^2/s. In general, ADC value which is less than 1.0–1.1 × 10^{-3} mm^2/s gives a hypointense in ADC map and restricted diffusion area (hyperintense) in DWI sequences. It also has a linear relationship with malignancy. In cases of brain metastases from lung carcinoma, the ADC values have been studied and used as a determinant with a value of 0.68 ± 0.12 mm^2/s in small cell lung carcinoma and 1.47 ± 0.31 mm^2/s in non-small cell carcinoma [14]. In addition, it is necessary to pay attention to the determination of the b-value which contributes to the assessed diffusion values. In brain imaging, the use of b-values can vary. Generally, it used b-value of 0–1000 mm^2/s.

Measurement of ADC values in cases of central nervous system tumours has high precision and accuracy. This has been proven in research using two different types of MRI modalities, namely Elekta Unity MR® 1.5 T and Philips Ingenia® 1.5 T at the primary tumour sites, which include the white/grey matter areas and liquor cerebrospinal [15]. Based on this research, it produced a low bias value, namely − 0.05 ± 0.03 μm^2/ms in white matter, -0.08 ± 0.05 μm^2/ms in grey matter, − 0.1 ± 0.1, and − 0.08 ± 0.07 μm^2/ms in primary tumours with the coefficient of variation of 1.4%/1.8% on all examinations.

Mutation of EGFR in lung carcinoma can be in the form of an E746-A750 deletion on exon chromosome 19 and an amino acid substitution at L858R on exon chromosome 21. These two mutations are also referred to as classic mutations which contribute to 85% of EGFR mutations in non-small cell lung carcinoma [16]. There are several other EGFR mutations in lung carcinoma that are rare, for example the mutation of G719X (G719C, G719S, and G719A) on exon chromosome 18, the mutation of S768I and T790M on exon chromosome 20, insertion on exon chromosome 20, and the mutation of L861Q on exon chromosome 21 [17].

Detecting EGFR mutation in lung carcinoma is important to identify disease progression and prognosis. Basically, a malignancy has several mechanisms that determine its development. These mechanisms include maintaining proliferation signals, inhibiting cell growth suppressors, activating invasion and metastasis, activating immortal replication, inducing angiogenesis, and causing resistance to cell death [18]. Gene mutations are also dynamic. Several mutations in certain genes have been identified as resistant to tyrosine kinase inhibitors (TKI), for example mutations in the T790M exon of chromosome 20 with an incidence of up to 50% of all patients with EGFR mutation. Tyrosine kinase (TK) activity in EGFR is disrupted due to several oncogenic mechanisms, such as mutations and increased expression of the EGFR gene. The disturbance results in excessive activation of EGFR-TK [18]. Furthermore, this activation also increases the movement and invasion of tumour cells which contribute to regional metastases and distant metastases.

Utilization of the ADC values as a predictor of EGFR mutation can provide information to clinicians to consider genetic examinations and specific therapy in the form of sensitive combination chemotherapy in lung carcinomas with EGFR mutation. The predicted value of

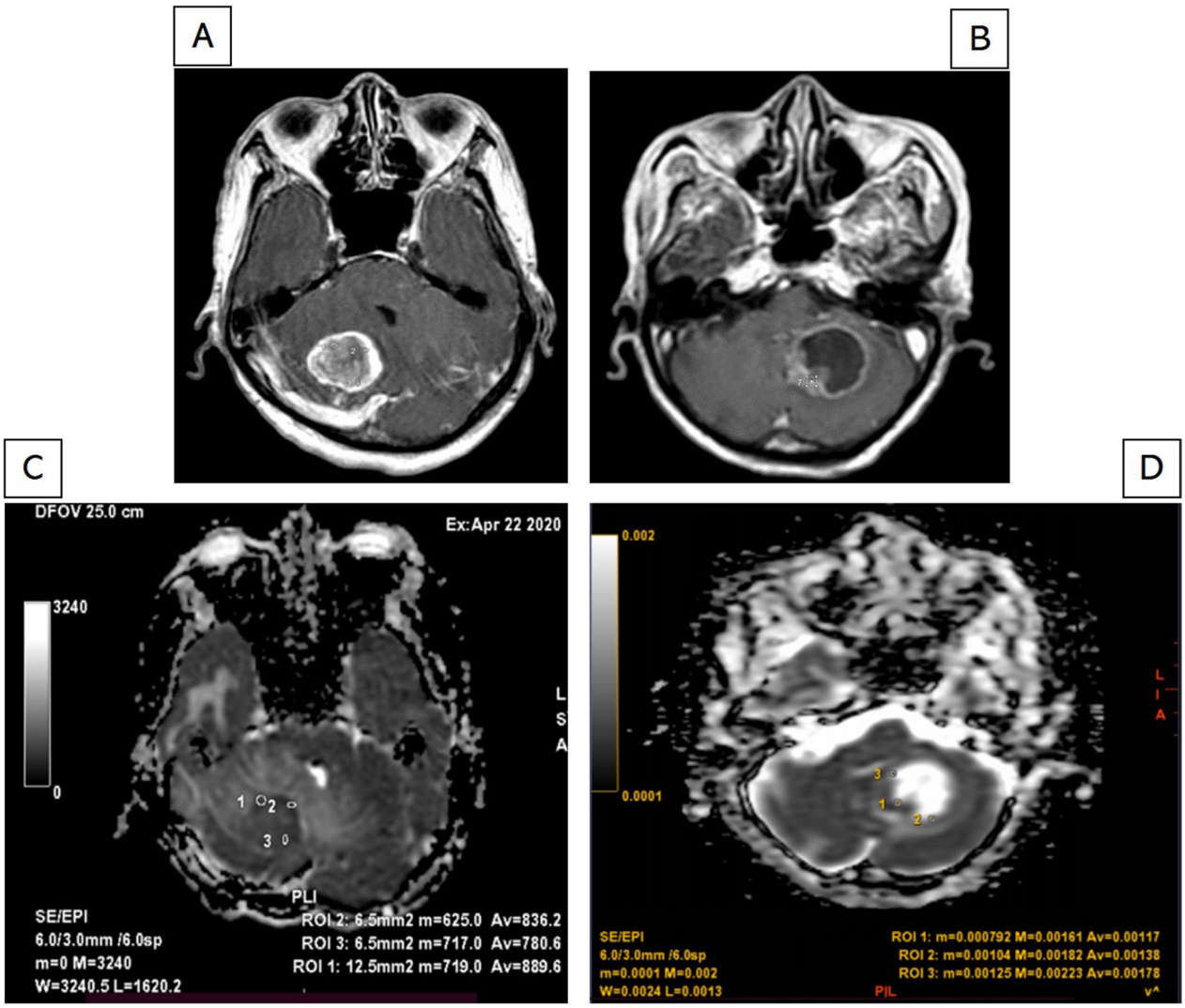

Fig. 4 The comparison between EGFR mutation group (**A** and **C**) and non-mutation group (B and **D**) by looking at T1 contrast and ADC value. Mutation group had lower average ADC value with heterogenous contrast enhancement (Author courtesy)

ADC in the EGFR mutation group is a reference for radiologists to predict EGFR mutation status in lung carcinoma. The discussion of the results of this study does not necessarily replace examination of EGFR mutation status with tissue examination using the immunohistochemical method. ADC itself provides a predictive value that will become information for radiologists and clinicians to determine EGFR mutation status. ADC will be more complete, and more accurate if it is followed by other MRI sequences, both conventional and advanced MRI.

Limitations

The author realized that this study still needed improvement due to a limitation. The limitation was the involvement of only one health centre/hospital so the chances of obtaining eligible patients were more limited. Nevertheless, one health centre had actually covered several cities within a wide radius of more than 500 km. However, multicentre involvement remains more recommended with more eligible patients. Finally, the results will better represent wider population.

Conclusions

The modality of choice in determining the case of brain metastases from lung carcinoma is MRI. Low ADC values which are less than $1.0–1.1\times10^{-3}$ mm^2/s give a linear relationship with malignancy. The mean of ADC value in the EGFR mutation group with a predicted value of $0.773–0.815\times10^{-3}$ mm^2/s was lower than both the ADC value in the non-EGFR mutation group and

the non-lesion group. Therefore, in this case the ADC value on brain contrast MRI can be recommended as a predictor of EGFR mutation. Thus, the ADC value complements the advantages of MRI as a holistic modality in diagnosing and determining treatment towards the era of precision therapy.

Abbreviations

ADC	Apparent diffusion coefficient
DWI	Diffusion weighted imaging
EGFR	Epidermal growth factor receptor
FLAIR	Fluid attenuated inversion recovery
GRE	Gradient echo
MRI	Magnetic resonance imaging
NSCC	Non-small cell carcinoma
ROC	Receiver operating characteristic
ROI	Region of interest
3 T/1,5T	3 Tesla/1,5 Tesla
TK	Tyrosine kinase
TKI	Tyrosine kinase inhibitor

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Disclaimer
The views expressed in the submitted article are the authors' not part of an official position of the institution.

Author contributions
M.H. was responsible for conception, literature review, design of the work, data collection, designing figures and images, drafting and critical revision of the article. R.F.R. and T.D.A. supervised the project, contributed to the design and implementation of the research, criticize the manuscript, approving the final article version, and supporting data collection. All authors have read and approved the manuscript.

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Availability of data and materials
Raw data were collected from Radiology Department, Pathology Anatomy Department, and Pulmonology Department Dr. Moewardi General Hospital. Derived data supporting findings of this study are available from the corresponding author, M.H. by formal request.

Declarations

Ethics approval and consent to participate
Approval for this study was obtained from the Dr. Moewardi General Teaching Hospital Ethics Committee with protocol reference number 09/I/HREC/2023. All patient identifiers were hidden to ensure patient anonymity. Consent from the Dr. Moewardi General Teaching Hospital Director had been gained by issuing letter of permission.

Consent for publication
Consent to publish the data contained in this study had been gained from Dr. Moewardi General Teaching Hospital Director.

Competing interests
The authors declare that they have no financial, business, or personal relationships that may have inappropriately influenced in writing this article.

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