Evaluating the Origin of the Brain Metastatic Tumors by Using DWI Parameters

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Abstract

Background: Brain metastases are the most common tumors in the human central nervous system (CNS), with an occurrence 10 times higher than primary brain tumors in adults. A radiologist usually diagnoses these tumors. Typically, magnetic resonance imaging (MRI) has been used to evaluate the status and number of metastases, the design of surgical treatment or radiotherapy, and the response to treatment. This study aimed to consider the origin of metastatic tumors of the brain using diffusion-weighted imaging sequence.

Methods: In this study, 95 lesions observed in 51 patients with different types of brain metastasis who analyzed with standard brain MRI protocols such as T2-weighted fast spin-echo in sagittal, coronal and axial planes and T1-weighted spin-echo sequences before and after injection of contrast enhancement and diffusion-weighted imaging. The diffusion-weighted imaging included an echo-planar spin-echo sequence with two b values (0,1000 s/mm) and calculated apparent diffusion coefficient (ADC) maps. We measured the ADC-value on normalized ADC maps and compared them with different methods. ANOVA was used to compare ADC among all groups as well as T-test for every two groups.

Results: The results showed that patients with lung cancer (squamous cell carcinoma, SCC) had the lowest mean ADC ($658.70*10^{-3}$ mm²/s) and breast cancer patients with the highest mean ADC($935.52*10^{-3}$ mm²/s). This study demonstrated that most Brain metastases had low and intermediate ADC values. The analysis showed no significant difference among all groups. However, ADC values in breast cancer and kidney and lung (adenocarcinoma) were statistically higher in comparison to other groups. There were no critical discrepancies between ADC values in brain metastases from Breast cancer and lung cancer (adenocarcinoma) and kidney.

Conclusion: It seems that evaluating the origin of the brain metastatic tumors by using diffusion imaging (DWI) parameters could be helpful to prevent invasive methods like biopsies in some situations. Although it needs more studies to achieve this purpose.

Keywords: Metastatic tumors; Brain; Magnetic resonance imaging; DWI; ADC.

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Introduction

Brain metastases (BMs) are the most common tumors in the human central nervous system (CNS), with an occurrence ten times higher than primary brain tumors in adults. A radiologist usually diagnoses these tumors. Typically, magnetic resonance imaging (MRI) has been used to evaluate the status and amount of metastases, the design of surgical treatment or radiotherapy, and the response to treatment. Newer techniques of MRI have also been used to help diagnose single BM due to high-grade gliomas or abscesses.[1]

BM is a recurrence of cancer associated with high mortality. Types of primary tumors are different in their tendency to produce BMs with kidney cancer, breast cancer, and lung cancer (squamous cell lung, SCC), which show most of such cases related to the CNS. The survival time prediction of BM patients is only a few months. Several scores presented to classify the risks of metastases such as recursion parameters, prognostic evaluation (GPA), and diagnostic grading prognostic evaluation (DS-GPA). These results are based on guidelines with diagnostic properties, containing performance status, age, primary tumor condition, previous extant metastases, and BM numbers. The average overall survival from BM

identification is only 3 months. The optimal group, up to a maximum of 25.3 months, is among the most popular groups, including long-term survivors. Imaging scalars have not considered for prognostic hazard classification with the exclusion of the numeral of BM. MRI using the T1 weighted, T2 and FLAIR weighted imaging for the routine brain protocol to the determination of tumors; and for better visualizing the area of tumor injecting the contrast media. Increasingly, advanced imaging techniques such as magnetic resonance spectroscopy, MRI perfusion, or diffusion imaging (DWI) are used to describe brain lesions in order to provide more clinical information.[2]

Early diagnosis of BMs is an achievement of the precise and innovative methods of CNS imaging which, like the advancement of oncology treatments, leads to prolonged survival of the patient, as well as an increase in the incidence of metastases in the brain. Standard MRI sensitivity is high, but its characteristics are limited in the diagnosis of brain tumors and modifications in its treatment.[3]

In the routine MRI, signal strengths of the brain tumors may change due to their histopathology. They also show a different signal intensity in MRI, according to their components (i.e., solid tumors, degeneration, hemorrhage, and cysts). The signal intensities for these tumors have informed in the diffusion-weighted imaging. These tumors can precipitate an abscess or early infarction in diffuse images. To understand the intensity of the signal in diffusion images, understanding its mechanism is essential. DWI can show early changes and minor areas of the brain that are not visible on routine imaging. DWI includes both quantitative and qualitative information that can be very important for tumor detection.[4]

MRI of the brain is commonly used for the investigation of patients and follow them up, and DWI sequences are commonly used to distinguish tumors from abscesses. Recently, however, it has been used to help differentiate metastasis from the glioma, to design surgical treatment and even to predict the treatment process. In BM, it is noticeable that the apparent diffusion coefficient (ADC) increases with decreasing cellulite, and the tissue buildup within the tumor increases.[5]

An embodiment of the motion of water molecules in the extracellular space is the principle of imaging based on diffusivity. The constrained movability of water molecules caused low exudation ability reduces the diffusion in extracellular space; this function of water molecules make a hyperintense signal in the DWI and low ADC values. In return, the excessive emission rate due to increased mobility of water molecules produces a hypo or iso signal on DWI and high ADC values.

DWI indications examined to show a correlation with different histopathologic distinguishing; such as tumor category, tumor grade, tumor cell concentration, cellulite, or intracerebral hemorrhage, and prognosis of survival in several cases in the types of tumors inside and outside the cranium. However, the correlation of prediction with DWI and histomorphologic evidence in patients with BM have not been methodically deliberated yet.[2]

Metastatic tumors of the brain are usually diagnosed accidentally due to neurological symptoms in the patient or following a CT scan or MRI of the brain region. Less than 10% of the BMs diagnosed before primary cancer, and this is when the patient undergoes a CT scan or MRI for other medical reasons, and the tumor detected randomly. The patient may not have any neurological symptoms and a history of cancer at the time of referral. Doctors currently perform biopsies to insistent the origin of metastatic tumors or use MRI and CT scans for other parts of the body to identify the origin of the tumor. For patients with brain, metastases are surgery, and whole-brain radiotherapy (WBRT) is the most common medication. If corticosteroids prescribed along with some systemic treatments, it can also influence cranial metastases. Repeated WBRT is available for part of the brain, but the effectiveness of this method is relatively low. There is a need for new therapies, and among innovative clinical trials, radiotherapy and stereotactic biopsy have considered as innovative therapies.[6]

Stereotactic biopsy is a surgical procedure in which a thin needle is inserted into the brain by a surgeon to extract a small piece of tissue for examination under a microscope. Stereotactic biopsy using 3D imaging technology, as well as CT scan and MRI data, are utilized for testing a tumor or a part of the brain. Stereotactic biopsy is a minimally invasive method. The highest risk is the bleeding that can cause anything from mild headaches to stroke, coma, or even death. The risk of post-biopsy bleeding is about 5%, and the risk of death is about 1%. Other post-biopsy side effects include headache at the site of biopsy, infection, and seizure. Moreover, the dangers that can be caused by anesthesia are inevitable.[7]

The purpose of this study was to implement a new non-invasive approach to recognize the origin of brain tumors by using MR imaging before surgery.

Materials and Methods
Patients
The study community included patients who had cancers and referred to the MRI department with a neurosurgeon's definitive diagnosis for the treatment, recurrence, or recovery of the disease. Among 10 000 chronological patients who underwent MR imaging in Shohadaie Tajrish hospital among 2015 and 2017, 1285 people were imaged to find out BM. After the imaging, 125 patients were noticed, between who mistrustful to BM.

Therefore 60 of 125 patients had conventional MR imaging and DWI in their history of MRI. We excluded 9 of 60 patients from our study because of different diagnoses such as hemorrhage, primary brain tumors like glioblastoma or astrocytoma, and any other lesions.

MRI Examination

MRI performed with a 1.5T system (Avento; Siemens, Erlangen, German) with an 8-channel head coil. We obtained T1-weighted images with imaging parameters of 675/15(TR/TE), a slice thickness of 5 mm, an interslice group of 1.5 mm, a field of view of 20 to 24, and a matrix of 320*256; T2-weighted spin-echo images with imaging parameters of 4000/85 (TR/TE)), a slice thickness of 5 mm, an interslice group of 1.5 mm, a field of view of 20 to 24, and a matrix of 320*256; fat-suppressed short tau inversion recovery (FLAIR) imaging parameters of 9000/125(TR/TE), a slice thickness of 5mm, an interslice group of 1.5 mm, a field of view of 20 to 24, and a matrix of 256*192; and DWI was performed in the transverse plane using a spin-echo, echo-planar imaging sequence with the following parameters of 6000/102 (TR/TE), a slice thickness of 5mm, an interslice group of 1.5 mm, a field of view of 20 to 24, and a matrix of 128*128, diffusion gradient encoding in 3 orthogonal directions; $b = 1000s/mm^2$. DWI scans performed before contrast-enhanced T1-weighted imaging. T1-weighted spin-echo images after intravenous administration of contrast medium with a dose of 0.1 mg/kg obtained.

The ADC values calculated as follows: $ADC = -[In(S/S_0)]/b$, where S is the SI of the region of interest (ROI) obtained 3 orthogonally oriented DWIs or diffusion trace images, S_0 is the SI of ROI acquired through reference T2-weighted images and b is the gradient b factor with a value of 1000 s/mm². The ADC maps were calculated on a pixel-by-pixel basis.[1]

In the following step, measurement of the signal intensity of the lesion in DWI images was done in two ways: by the radiologist and by using software calculations, a quantitative measure of the intensity of the signal was done placing the ROI onto the lesion (center of each lesion).

All patients also provided with a pathologist's report, which determined the origin of metastatic brain tumors. It is necessary to know pathological information to compare and connect the ADC parameter and signal intensity with the origin of tumors.

Image Analysis

All MR images were read by a radiologist experienced in the brain MRI interpretation who did not have any previous knowledge regarding the histopathological type of the brain.

Conventional MR images assessed for the evaluating features of each BM. We selected the tumor with short-axis larger than 1 mm.

The final number of BM that selected in the analysis was equal to 95. In the case of a patient with multiple BM, everyone evaluated separately. The assessment of ADC value includes drawing 3 ROIs with the same diameter for covering the pathologic area in all sections in which it was present and averaging the results. Figure 1 shows

the area of ROIs for accounting these different ADC values; 3 uniforms ROIs composed of more than 10 pixels were manually drawn to calculate the SI on T2-weighted images and the ADC values on the map. In this study, we excluded the edematous areas from analysis to avoid presenting a false high ADC. All the ADC values were averaged from three-time measurement and expressed as the mean ± standard deviation. Three ADC values (min ADC, max ADC, mean ADC) calculated for all selected brain tumors.

Apparent Diffusion Coefficient

The axial slice with the largest size of the tumor has chosen, and three elliptical ROIs of 10 mm² were drawn within the borders of the tumor on ADC maps, avoiding areas of cyst, necrosis or hemorrhage. The Radiant software then delivers the maximum and minimum ranges for the given ROIs. Placing the ROIs were displayed in Figure 2.

In this study, ANOVA and *t* test were used to calculate the data and connect the factors. For ease, analyses of the data related to the signal intensity and ADC done separately. Finally, ADC values correlated with the pathology reports of the brain dissection samples.

Results

In this study, 95 lesions observed in 51 patients. The mean age of patients was 51.6±11.9 years. The youngest was 24, and the oldest age was 78. The total number of patients participating in this study was 28 women (54.9%) and 23 men (45.1%).
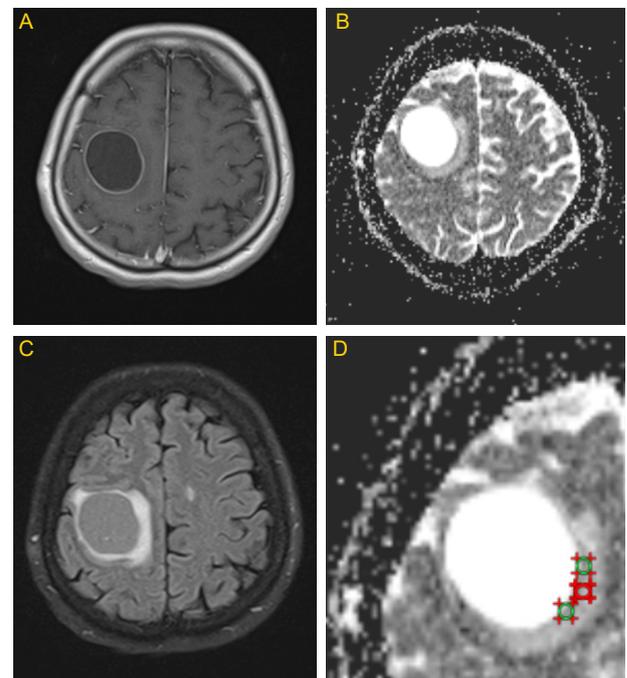
Figure 1. Placing ROIs on the ADC map. 45-year-old female breast cancer presents with nausea. (A) Postcontrast T1-weighted sequence demonstrate a lesion. (B) An ADC map generated from B=1000 images. (C) Flair sequence to investigate the area of edema. (D) Three ROIs are drawn interior the tumor border.
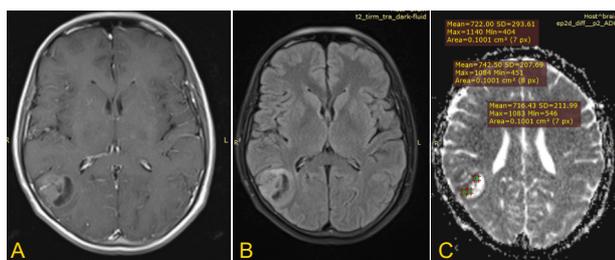
Figure 2. Imaging Findings of Brain Metastasis in Lung Adenocarcinoma. (A) T1-weighted image after intravenous administration of contrast medium showing lesion with inhomogeneous enhancement. (B) The lesion had edema in flair sequence. (C) ADC map. The calculated ADC values range shown and how the ROIs placed. .

The maximum number of BMs resulted from breast cancer, followed by lung (adenocarcinoma) and gastrointestinal cancer.

The mean ADC values were $935.52*10^{-3}$ mm²/s for breast cancer, $903.06*10^{-3}$ mm²/s for lung (adenocarcinoma), $847.89*10^{-3}$ mm²/s for kidney, $755.27*10^{-3}$ mm²/s for ovarian, $723.51*10^{-3}$ mm²/s for GI, $720.02*10^{-3}$ mm²/s for melanoma, $682.17*10^{-3}$ mm²/s for cervix and $658.70*10^{-3}$ mm²/s for lung (Table 1).

The results showed that patients with lung cancer had the lowest mean ADC ($658.70*10^{-3}$ mm²/s) and breast cancer patients with the highest mean ADC ($935.52*10^{-3}$ mm²/s). This study demonstrated that most BMs had low and intermediate ADC values. The analysis showed no significant difference among all groups. However, ADC values in Breast cancer and kidney and lung (adenocarcinoma) were statistically higher in comparison to other groups. There were no critical discrepancies between ADC values in BMs from breast cancer and lung cancer (adenocarcinoma) and kidney.

Discussion

DWI has been used to depict water movability in white matter and gray matter of the brain.[8] The most typical indication of DWI is differentiating cerebral infarction, multiple sclerosis, gliomas, and brain abscesses, arachnoid, and epidermoid cysts and other diseases.[9,10]

Nowadays, medical science in the field of surgery is making strides towards finding ways to do surgery without the need for an incision in the patient's body, and in order to reduce the number of complications of the operation. In this regard, the relevant tools and software can be handy.

Therefore, research in this area is at the center of the attention of doctors, especially surgeons. Accordingly, in this study, with the help of software, introspection of brain intra-axial tumors was investigated, and significant results obtained. The results of the study showed that using MRI and some sequences optimized and sensitized to registering a diffusion and with the assistance of advanced software analysis, useful information about the origin of a metastatic tumor can be found. This is a path to finding the answers to some questions about the origins of a metastatic tumor for which the current procedure includes biopsies in order to accede an answer. It should note that similar qualitative and visual studies in other countries have not yet achieved reliable results.

Metastatic tumors of the brain are usually diagnosed accidentally due to neurological symptoms in the patient or following a request for CT scan or MRI from the brain region. Less than 10% of the brain metastases detected before the early cancers, and this is when the brain subjected to a CT scan or MRI test for other medical reasons, and the tumor diagnosed accidentally, and the patient may be at the time of referral, there is no neurological symptoms and no history of cancer.[4]

Considering the fact that metastatic tumors have various origins, finding the area of the body causing metastasis in the brain region is one of the critical points for the diagnosis and treatment of patients, as well as the choice of therapies such as radiotherapy, chemotherapy, and surgery related to the technical information of value that imaging has achieved. Due to the complexity of this technique of imaging and the absence of effective education of expert physicians and imaging centers, the comprehensive applications of this method, like study of the origin of metastatic tumors, as well as the evaluation of the response to treatment before and after therapeutic procedures, require further studies in this field.[6,9,10]

In this research, bringing the facility of the RADIANT

Table 1. Descriptive Indicators for the Mean ADC of Lesion Area by the Type of Cancer

Type of Cancer	Average	Middle	Standard Deviation	Min	Max
Breast	935.52	983.13	207.53	501.00	1294.75
Cervix	682.17	639.00	115.03	525.0	976.14
GI	723.81	689.71	140.73	475.40	993.00
Kidney	926.26	937.71	245.00	670.00	1236.00
Lung (adenocarcinoma)	903.06	832.83	289.43	432.43	1464.71
Melanoma	720.02	682.00	105.88	520.00	939.00
Ovarian	755.2	773.63	59.73	617.00	844.67
Lung (SCC)	658.70	628.14	166.78	443.38	1093.00

software, and using a sensitive sequence for displaying changes in water content of structures, factors were considered, ADCs. The analysis of the DWI sequence achieved. There is no significant distinction between the ADCs of the surrounding area of the tumor in the different groups, while there is a critical difference between the ADCs of the tumor center and the area around the tumor, as well as between ADC values of the tumor center in different groups. For example, Kono et al,[10] in 2001, carried out-DWI in patients with brain tumors, found that ADC could be useful in detecting the malignancy of astrocytoma and glioblastoma They also exhibit low-grade astrocytoma, ADC-value more than the rest of the tumors, and ADC is associated with the origin of tumors in both astrocytoma and meningioma.

Studies have indicated that a lower-grade tumor has an ADC-value higher than that of high-grade tumors, and this part of the findings from this study is similar to the results from our fact-finding, so that metastatic tumors the origin of metastatic lung (SCC) tumors with lower ADC produces more severe damage to the brain and lung cancer (SCC) is the most occasion of metastasis in the brain from all dominant tumors that occurrence metastases in brain. The lung cancer has a short cycle of time from the moment that primary cancers were determined, and also has the short cycle of time to death (3 months).[10]

Also, Berghoff and colleagues concluded in 2013 that they performed diagnostic tests in patients with metastatic tumors and their relation to survival time. The metastatic tumors have a signal intensity greater than or equal to the brain tissue, and in tumors with higher signal strengths in DW images, they have shorter survival time than other tumors. In this study, they did not mention the numerical values of the ADC parameter, nor did they mention the paternity of the tumor and the type of tumor,[5] but in our results we found the relationship between the tumor cluster and the type of tumor in which the statistical results obtained show this in data analysis of ADC parameter using RADIANT software and paired t-test, the significant correlation found between numerical values of the ADC of the metastatic tumor site with the origin of kidney, breast, and lung (adenocarcinoma) with other groups of BM. As we can see, there is a critical discrepancy between the ADC values of the tumor center with the origin of kidney, breast, and lung (adenocarcinoma) with different groups, in summary, it can be stated that the tumor is more malignant, the lower the ADC number.

This explanation suggests the ADC map independently afford extra, bizarre, scientifically useful information in comparison with the post-contrast T1-weighted sequences.[11]

On the other hand, in the analysis of signal strength data using RADIANT software and paired t test and ANOVA, a significant correlation found between the intensity of the signal of the metastatic tumor center with different origins. As can be seen, there is no critical discrepancies in the signal intensity around the tumor in disparate groups, and there is a critical discrepancy among the two groups. However, there is a significant difference between the intensity of the signal of the tumor center in different groups — for example, a study by Hayashida et al in 2006 concluded that the intensity of the signal obtained in DW images reflects the histological characteristics of metastasis. In DW images, we can increase the irritability of the sequence to the lesions by varying the b-values and obtain different signal strength,[3] so in our studies, RADIANT software has been used to measure the intensity of the signal. In this paper, the intensity of the signal in the DWI sequence is compared with that of the eye, while the use of parameters can change the intensity of the signal, and on the other hand, in the DWI sequence, the intensity of the signal is influenced by the phenomenon of random motion of water molecules, but in the intensity sequence T2 the signal is also contrived by the diffusion appearance and the comforting moment of T2, so it is slightly more accurate. Studies in this regard advocate that brain metastatic tumors with lung origin cause more damage to the blood-brain barrier and, on the other hand, create more cellular discharges which would lower the ADC number in this group of patients. Also, this category of Tumors causes massive and unconscious effects in the tumor site, which is one of the reasons for lower ADCs.[2]

Suggestions for Future Studies
This study is capable of performing in areas other than the brain, such as pituitary lesions, liver, limb mass, and similar software programs used in this study to identify the origin of the tumor. Also, more advanced software can be used to obtain more accurate results. A further limitation was the low number of patients included in the sample. Further studies can report better and more accurate results regarding DW-MRI by choosing more samples.

Conclusion
The histology of brain metastases may forecast the signal intensity on DWI. Metastatic brain tumors with the vary of histologic category indicated different signal intensity on DWI. The results of this paper state that most brain metastases had low and intermediate ADC values. Our explanation found an extensive irregularity of BM-ADC values. It seems that evaluating the origin of the brain metastatic tumors by using DWI parameters is a useful technique to eliminate invasive methods like biopsies.

Conflict of Interest Disclosures
The authors declare that they have no conflict of interests.

Ethical Statement
This study approved by ethical committee of shahid beheshti university of medical science.

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