Differentiation between High Grade Glioma and Solitary Brain Metastasis Using Combined Diffusion-Weighted Imaging and Diffusion Tensor Imaging

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Abstract

Background: High-grade gliomas (HGGs) and brain metastases (BMs) can display similar imaging characteristics on conventional MRI. In HGGs, the peritumoral edema is infiltrated by the malignant cells, which was not observed in BMs. Our study aims to determine whether the fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values could differentiate HGGs from BMs.

Results: Twenty patients with provisional MRI diagnosis of high grade gliomas WHO grade III & IV versus metastatic brain tumors, examination was done on 1.5 tesla scanner, patients were divided into two groups based on pathology results, the fraction anisotropy (FA) was measured in the enhancing tumor parts and immediate peri-tumoral edema. The minimum and mean ADC in the enhancing tumor (ADC_{min}, ADC_{mean}) and the minimum ADC in the peritumoral region (ADC_{edema}) were measured from ADC maps. Values of FA and ADC measured in the peri-tumoral edema were significantly high in the metastatic than primary high malignant glial tumors, yet no significant differences in the values of FA and ADC measured in the enhancing tumor parts of the two groups. According to ROC curve analysis, a cutoff value of 0.119 for the FA measured in the peri-tumoral edema with sensitivity (100%) and specificity (75%) and a cutoff value of 1.7 x 10^{-3} for the ADC_{edema} with sensitivity (87.5%) and specificity (75%) generated the best combination of for distinguishing between HGGs and BMs.

Conclusion: FA and ADC values were found to distinguish between HGGs and solitary BMs. The peritumoral FA and ADC values are better than the intratumoral FA and ADC values in predicting the tumor type.

Key Words: High Grade Glioma (HGGs), Brain Metastases (BMs), Fractional Anisotropy (FA), Apparent Diffusion Coefficient (ADC).

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Background

High-grade gliomas (HGG) and brain metastases (BMs) are two of the most common malignant brain tumors in adults. In general, the differentiation between them is possible with clear clinical history or the presence of multiple metastatic lesions. However, it is hard to see the distinction in a patient presenting with solitary metastatic mass and unknown primary malignancy, as these two neoplasms often display similar signal intensity features and contrast enhancement patterns on conventional magnetic resonance imaging (MRI) (1).

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Multiple studies report on the use of Diffusion-weighted imaging (DWI) and Diffusion tensor imaging (DTI) for differentiating HGG from solitary brain metastasis (SBM) (2-15). HGG typically shows an infiltrative growth pattern with invasion of the surrounding brain tissues, whereas BMs shows an expansive growth pattern causing displacement of the surrounding brain tissue (16 and 17). Therefore, assessment of the enhancing tumor and peri-enhancing area with DWI and DTI parameters has been introduced (6, 8 and 11).

DWI findings and apparent diffusion coefficient (ADC) measurements provide additional information about the tissue microstructure. An inverse relationship was observed between ADC values and tumor cellularity (18). Therefore, measuring ADC values in contrast-enhancing tumors and peri-tumoral edema could differentiate HGGs from BMs (5).

Recently, diffusion tensor imaging (DTI) has been widely used in intracranial neoplasms. As an advanced MRI technique, it describes the movement of water molecules by using fractional anisotropy (FA), which represent the directionality of water diffusion (19), DTI has the advantage of giving more detailed information about the involvement and integrity of the matter tracts in the peri-tumoral regions (20).

This study aims to evaluate the diagnostic performance of DWI and DTI for differentiating HGG from SBM.

Patients and Methods

Patients

All patients were referred to MRI unit at Police authority hospital from neurosurgery department and private clinics in the duration between November 2018 and February 2022. The local ethics committee approved this prospective study and full written consents were obtained from all patients prior to the examination. Only patients with final histo-pathological diagnosis after surgery or biopsy were included. Patients with previous cranial operation or radiotherapy and patients without histo-pathological diagnosis were excluded.

The study included 20 patients provisionally diagnosed to have intra-axial neoplasm on conventional MRI (14 males; 70 % and 6 females; 30 %). Based on histo-pathological results patients were divided into two groups: group 1 with primary HGG including 12 patients (60%) [5 females and 7 males with the mean age 49.17 years] and group 2 with BMs including 8 patients (40%) [1 female and 7 males with the mean age 54 years].

Brain MRI Protocol

The MR imaging was performed using a 1.5 tesla scanner (Ingenia, Philips) using dStream HeadNeck 20 channel coil, firstly noncontrast study was done, the T1 (TR/TE:620/20 ms), T2 (TR/TE:5430/95 ms) and FLAIR (TR/TE/TI: 10500/120/2800 ms) sequences with matrix 80 x 80, FOV 230 x 177 mm^2 and slice thickness about 5 mm were obtained, then post-intravenous (IV)-contrast T1 image study was done using gadoterate meglumine, and 0.5 mL/kg (0.1 mmol/kg) body weight with maximum dose of 10 mL was administrated (using 20 to 22 G venous cannula) as an intravenous bolus injection at a flow rate of approximately 2 mL/s.

DTI data were obtained using a single-shot echo planar imaging sequence (TR/TE 3118/93 ms) with parallel imaging (SENSitivity Encoding [SENSE] reduction factor P2). Diffusion gradients were applied along 32 axes, using a b-value of 0 and 1000 s/mm^2. A field of view (FOV) of 224 x 224 mm^2 and a data matrix of 92 x 88 were used, leading to voxel dimensions (2.43 x 2.54 x 2.5 mm^3). Forty-eight slices were obtained, with a thickness of 2.5 mm, with no gap, and with the total scan duration of about 7–8 min.

All the images will be transferred to the workstation (Philips extended MR workspace) supplied by the manufacturer.

Using the region of interest (ROI) analysis. In the intra-tumoral region, ROIs were placed in the solid parts of the tumor. These ROIs were drawn to avoid hemorrhagic, cystic, and necrotic components. Their diameter were in the range of 10–120 mm according to the size and morphology of each tumor. The ROI with the lowest ADC values were chosen as the minimum ADC (ADC_{min}) and an average value from multiple ROIs were chosen as the mean ADC and FA (ADC_{mean} and FA). The peri-tumoral region defined as the area outside the margin of the solid part of the tumor. ROIs (~100 mm2) were placed as closely as possible to the tumoral margin using T1W post-contrast reference images. The ROI with the lowest ADC and mean FA values were chosen as the minimum ADC and FA (ADC_{edema} and FA_{edema}).

A receiver operating characteristic (ROC) analysis was used to determine the cutoff value of the minimum ADC that had the best combination of sensitivity and specificity for distinguishing between glioblastoma and metastasis. A p value of < 0.05 indicated a statistically significant difference.

Results

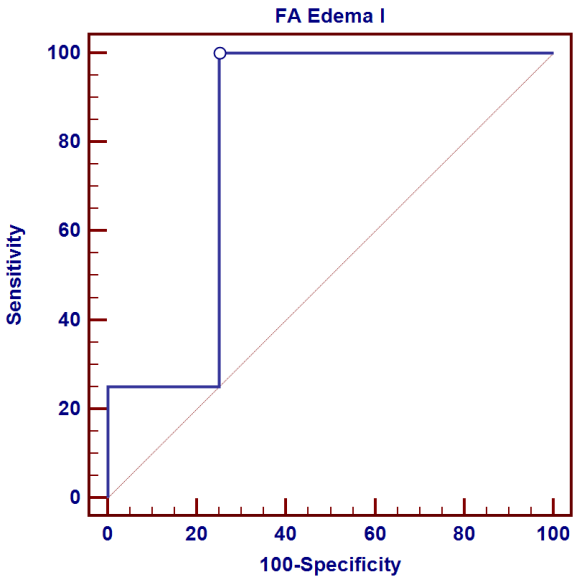
The study includes 20 patients (14 males, 6 females; age range, 30–87 years; mean age, 51.1 ± 14.5 years), divided into two groups: group I includes 12 patients of pathologically proved HGG (world health organization{WHO} grade III & IV) and group II includes 8 patients of SBM with known primary (4 patients with lung carcinoma, 1 patients with breast cancer, 1 patient with gastro-esophageal carcinoma, 1 patient with melanoma and 1 patient with thigh sarcoma), (Table 1).

Table 1. Characteristics of the patients included in the study.

		Pathology		Test value	P-value	Sig.
		HGG	SBM			
		No.= 12	No.= 8			
Age	Mean±SD	49.17 ± 17.70	54.00 ± 8.04	-0.719•	0.481	NS
	Range	30 – 87	44 – 65			
Sex	Female	5 (41.7%)	1 (12.5%)	1.944*	0.163	NS
	Male	7 (58.3%)	7 (87.5%)			

(Table 1) P-value > 0.05: Non significant (NS); P-value < 0.05: Significant (S); P-value < 0.01: Highly significant (HS)
*: Chi-square test; • Independent t-test

There was no significant difference between both groups in the measurement of FA value in the enhancing tumor parts. There was significant difference between both groups in the measurement of FA in the peritumoral edema with P values (0.02) (Table 2), the FA is greater in immediate peri-tumoral edema of the metastases with AUC = (0.812), the cutoff value was (0.119), at or above which metastases should be considered with sensitivity 100% and specificity = 75% (Fig 1).



Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
>0.119	0.812	100.00	75.00	72.7	100.0

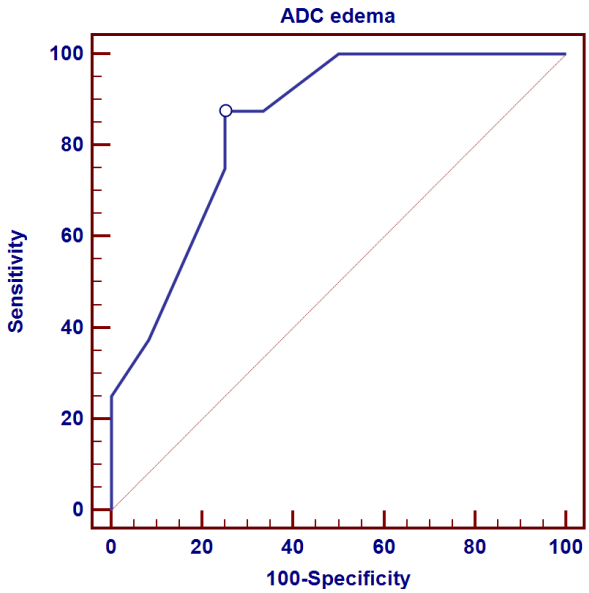
Figure 1. ROC curve for FA Edema to differentiate between HGG and SBM group

Table 2. The measured FA in the enhanced tumor parts and peri-tumoral edema in both groups

		Pathology		Test value≠	P- value	Sig.
		HGG	SBM			
		No.= 12	No.= 8			
FA Intratumoral	Median (IQR)	0.1835 (0.0811 – 0.236)	0.115 (0.0832 – 0.116)	-1.083	0.279	NS
	Range	0.0747 – 0.384	0.0804 – 0.179			
FA Edema	Median (IQR)	0.1135 (0.0954 – 0.1455)	0.1575 (0.1355 – 0.304)	-2.321	0.020	S
	Range	0.0825 – 0.2	0.121 – 0.439			

(Table 2) P-value > 0.05: Non significant (NS); P-value < 0.05: Significant (S); P-value < 0.01: Highly significant (HS)
≠: Mann-Whitney test

There was no significant differences between both groups in the measurement of mean or minimal ADC value in the enhancing tumor parts. There was significant difference between both groups in the measurement of ADC value in the peritumoral edema with P values (0.005) (Table 3), the ADC shows high values in peritumoral edema of metastases with AUC = (0.849) with cutoff value equal to or greater than (1.7 x 10-3) for metastases with sensitivity = 87.5% and specificity = 75% (Fig 2).



Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
>0.0017	0.849	87.50	75.00	70.0	90.0

Figure 2. ROC curve for ADC Edema to differentiate between HGG and SBM group

Table 3. The measured ADC in the enhanced tumor parts and peri-tumoral edema in both groups

		Pathology		Test value≠	P- value	Sig.
		HGG	SBM			
		No.= 12	No.= 8			
ADC $_{mean}$	Median (IQR)	0.0014 (0.0011 – 0.156)	0.0011 (0.0008 – 0.0013)	-1.702	0.089	NS
	Range	0.0005 – 0.345	0.0007 – 0.0014			
ADC $_{min}$	Median (IQR)	0.001 (0.0009 – 0.14)	0.0009 (0.0008 – 0.059)	-1.547	0.122	NS
	Range	0.0004 – 0.298	0.0007 – 0.117			
ADC $_{edema}$	Median (IQR)	0.0014 (0.0013 – 0.0018)	0.002 (0.002 – 0.2485)	-2.823	0.005	HS
	Range	0.0009 – 0.1640	0.0014 – 0.333			

(Table 3) P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
≠: Mann-Whitney test.

Discussion

Multiple studies report on the use of DWI and DTI for differentiating high-grade glioma from solitary brain metastasis based on the measurements of FA and ADC in the intra-tumoral enhancing components and peri-tumoral edema.

Most brain tumors are surrounded by a T2 high-signal abnormality that traditionally has been termed "vasogenic edema." Vasogenic edema is the most frequent form of brain edema associated with brain tumors. Local disruption of the blood–brain barrier increases capillary permeability and induces a pressure gradient from the vascular to extracellular compartment that results in the retention of plasma fluid and protein in the extracellular spaces (21). In general, the nonenhancing area of an abnormality that surrounds the enhancing tumor core is referred to as "peritumoral edema." In metastatic brain tumors peritumoral edema is synonymous with vasogenic edema, in which increased extracellular water from leakage of plasma fluid due to altered tumor capillaries is present but no tumor cells are present (9). In glioma, however, peritumoral edema is better referred to as "infiltrative edema" because it represents vasogenic edema and infiltrating tumor cells that are behind the blood–brain barrier and that usually invade along the white matter tracts (9). Differentiation of vasogenic edema from

infiltrative edema has been attempted using DWI on the basis of the premise that water diffusivity is facilitated to a greater degree in vasogenic edema than in infiltrative edema because of a lack of intervening tumor cells in the former (21 and 22).

Our results showed that there was significant difference between both high grade glioma and metastasis as regard the measurement of FA in the peritumoral edema yet with no significant difference as regard the intratumoral measurements (fig 3-6). Our results are consistent with a study done by El-Serougy et al. They reported no significant differences as regards enhancing parts indicating limited sensitivity and specificity of this parameter in tumor differentiation; however, significant difference was noted in the peri-tumoral edema with higher FA in peri-tumoral edema of the metastases rather than the high grade glioma (23). They reported FA cutoff value of 0.295 at or above which metastases should be considered which is slightly different from our study's cutoff value.

One likely reason for these contradictory results is the lack of standardized methods, both for acquisition as well as post-processing and selection of region of interest (ROI) as the peri-tumoral edema of the metastasis shows different regions of variable compressed displaced and edematous tracts, in each region the values differs (23).

Our results was different from the study done by Mao et al. (24), found that HGGs showed a higher tumoral FA value than SBMs but no significant differences were found between the peritumoral edema of HGGs and SBMs. That can be due to heterogeneity of the brain masses with areas of hemorrhage and necrosis affecting the FA reading as well as the lack of standardized method for region of interest placement.

In our study we measured the minimum and mean ADC in the enhancing tumor (ADC_{min}, ADC_{mean}) and the minimum ADC in the peritumoral region (ADC_{edema}) to determine whether there was a statistical difference between groups.

As regard the peritumoral edema we included only the minimum ADC value measurements as the regions with minimum ADCs have been suggested to reflect the highest tumor cell density which represent the infiltrative component in the peritumoral edema (25, 26 and 27) while in the tumor measurements we used both the mean and minimum ADC values secondary to the expected heterogeneous nature of brain gliomas and metastasis.

Our results showed that there was no significant difference between high grade glioma and brain metastasis mean and minimum ADC yet there was significant difference in their peritumoral edema.

Our results are consistent with studies done by Lee et al (1) and Caravan et al (5) which have found lower ADC values associated with the peritumoral edema of the HGGs than those for the peritumoral edema of BMs. They reported a cutoff value of 1.302×10^{-3} mm^2/s and 1.332×10^{-3} mm^2/s for distinguishing between GBMs and BMs which is lower than the cutoff value of our study that was 1.7×10^{-3} mm^2/s.

The difference in the cut off value can be attributed to the lack of standardized method in ROI placement, the heterogeneity of the tumor and the relatively low sample size.

The difference in the cut off value can be attributed to the lack of standardized method in ROI placement and the relatively low sample size.

Our results was also similar to the studies done by Oh J et al (21), Rollin N et al (27), Yamasaki F et al (28), Bulakabasi N et al (29) and Stadnick TW et al (30) showing that tumoral ADC is not useful for distinguishing between glioblastomas and metastatic tumors yet it was different from the studies done by Chiang et al (25) and Krabbe et al (26) that found that tumoral ADC of cerebral metastasis is significantly higher than that of high-grade astrocytoma. That can be secondary to the fact that BMs represent a heterogeneous group of tumors and their microscopic characteristics may depend on their origin.

Our results support the hypothesis that minimum ADC values can detect neoplastic cell infiltration in peritumoral edema in patients with glioblastoma. Therefore, analysis of these peritumoral regions may prove to be more robust than analysis of the lesion itself. (31 and 32).

Based on the results of our study, we may recommend the analysis of multiple ROIs of the peritumoral region for an accurate differentiation between HGGs and BMs. Thus, at least two or three ROIs should be placed within the peritumoral edema, as closely as possible to the tumoral margin, but without risking any contamination with tumoral tissue (5)

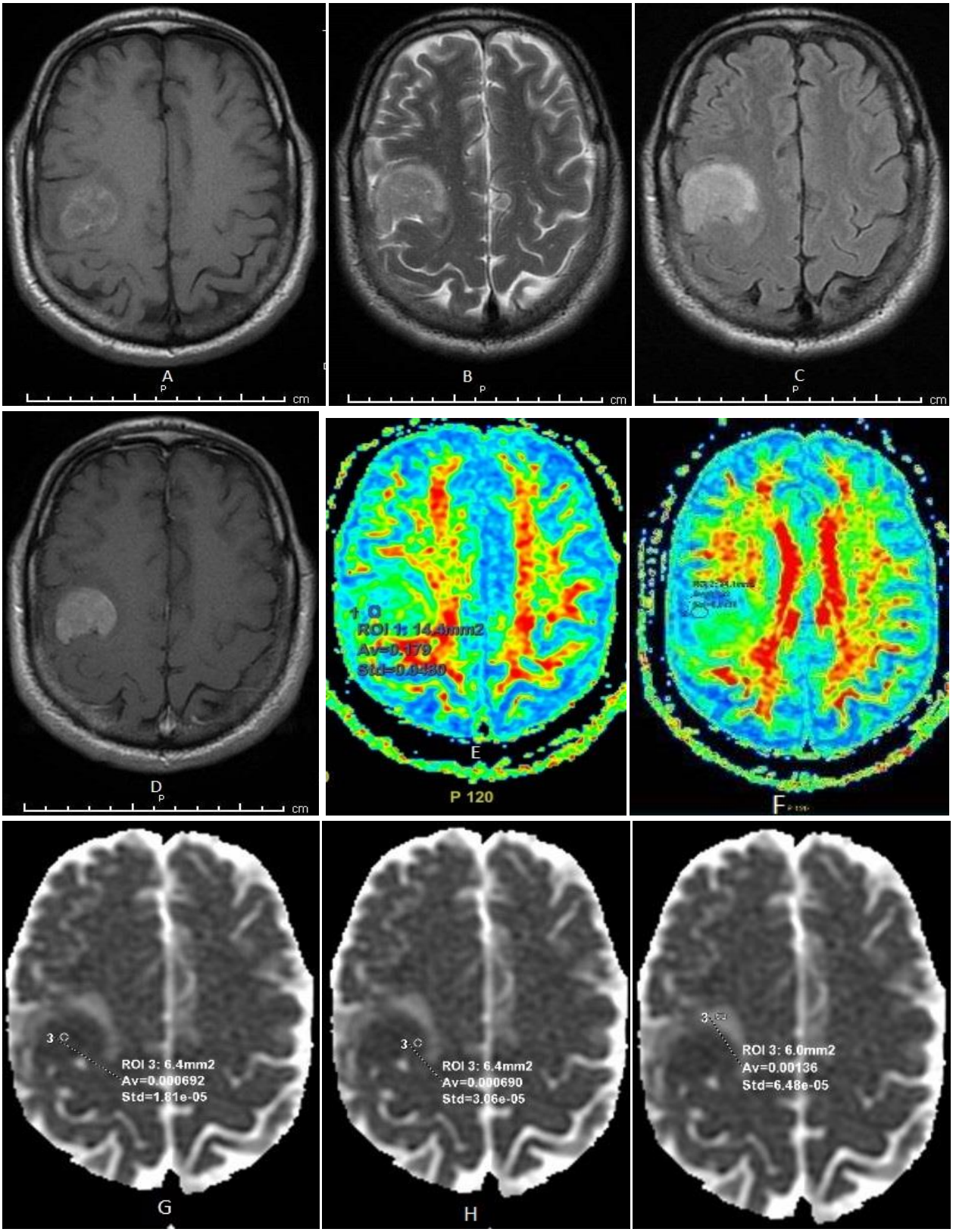


Figure 3. Male patient 51 years old with pathologically proved metastatic melanoma (A), (B) and (C) images Axial T1, T2 and FLAIR images respectively, showing right parietal intra axial lesion with surrounding vasogenic edema and heterogeneous post contrast enhancement (D). (E) and (F) FA map with two regions of interest measured within the enhancing part of the tumor and within the immediate peri-tumoral edema demonstrate slightly elevated FA value in the immediate peri-tumoral edema, (G) and (H) ADC map with two regions of interest measured within the enhancing part of the tumor and (I) within the immediate peri-tumoral edema

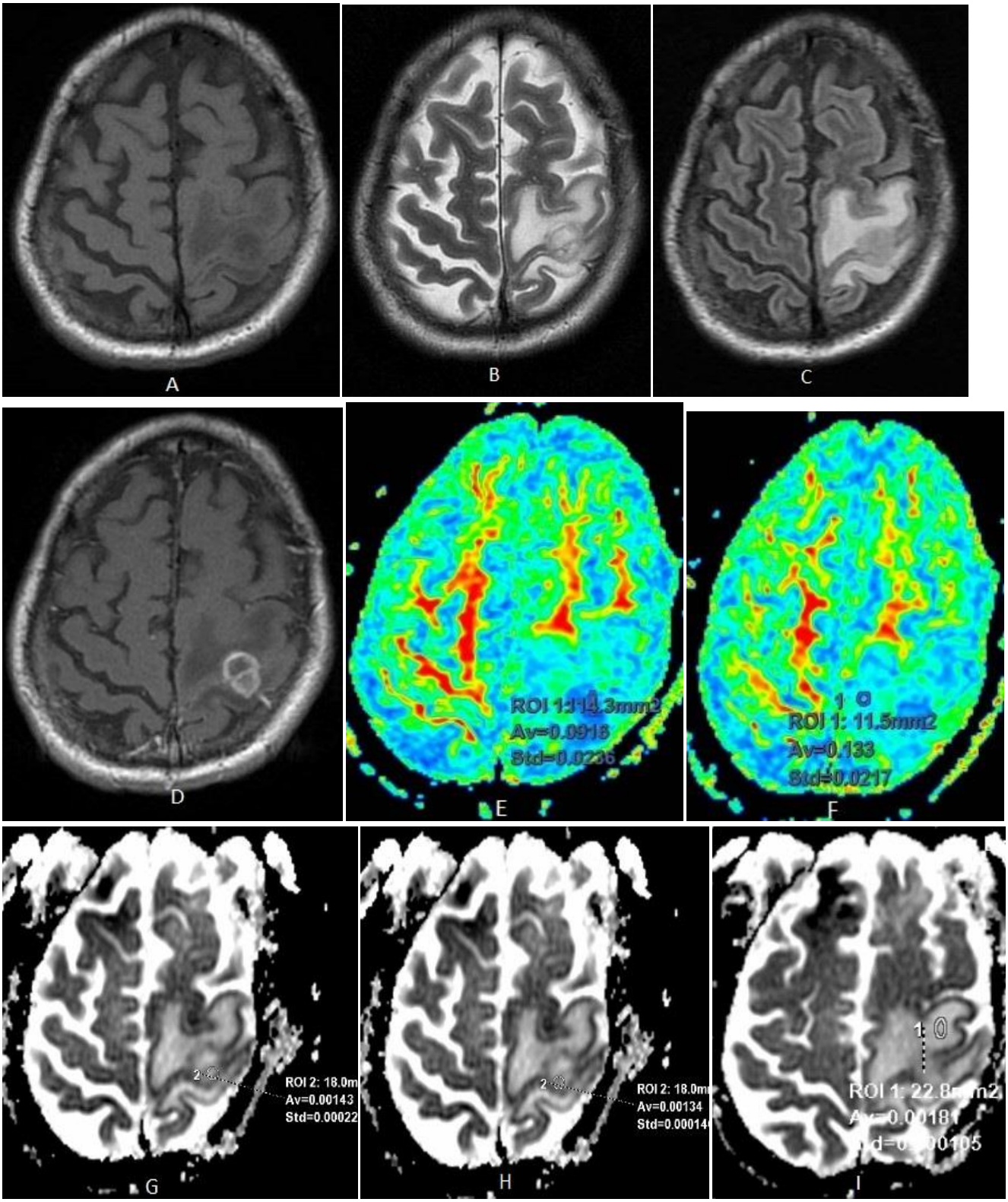


Figure 4. Male patient 54 years old, pathologically proved metastatic pulmonary squamous cell carcinoma (A), (B) and (C) images Axial T1, T2 and FLAIR images respectively, showing left parietal lesion with surrounding vasogenic edema and heterogeneous post contrast enhancement (D). (E) and (F) FA map with two regions of interest measured within the enhancing part of the tumor and within the immediate peri-tumoral edema demonstrate elevated FA value in the immediate peri-tumoral edema, (G) and (H) ADC map with two regions of interest measured within the enhancing part of the tumor and (I) within the immediate peri-tumoral edema

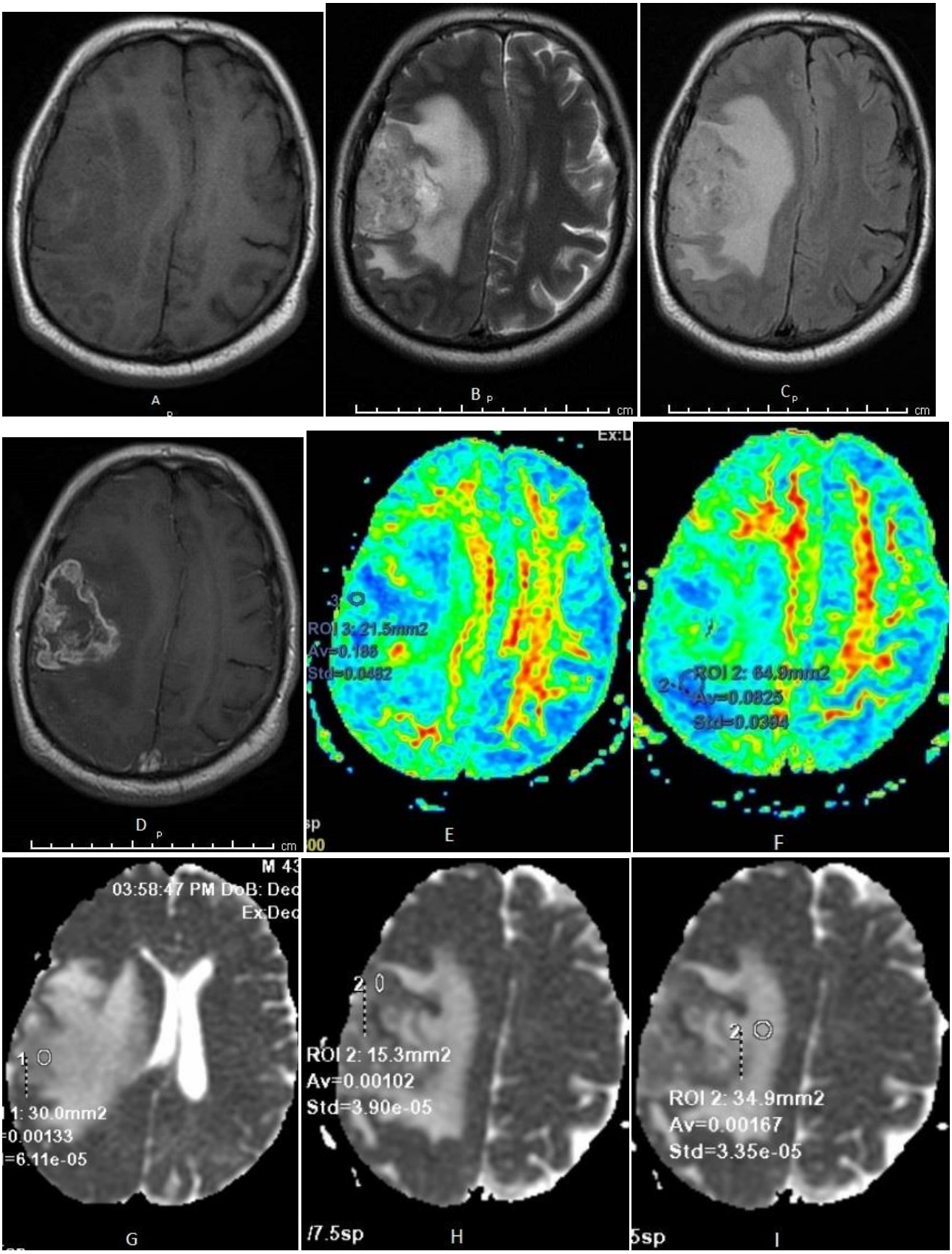


Figure 5. Male patient 43 years old, pathologically proved high grade glioma (A), (B) and (C) images Axial T1, T2 and FLAIR images respectively, showing right fronto-parietal intra axial lesion with surrounding vasogenic edema and heterogeneous post contrast enhancement (D). (E) and (F) FA map with two regions of interest measured within the enhancing part of the tumor and within the immediate peri-tumoral edema demonstrate decreased FA with displacement of fibres, (G) and (H) ADC map with two regions of interest measured within the enhancing part of the tumor and (I) within the immediate peri-tumoral edema demonstrates slightly decreased ADC within the immediate peri-tumoral edema

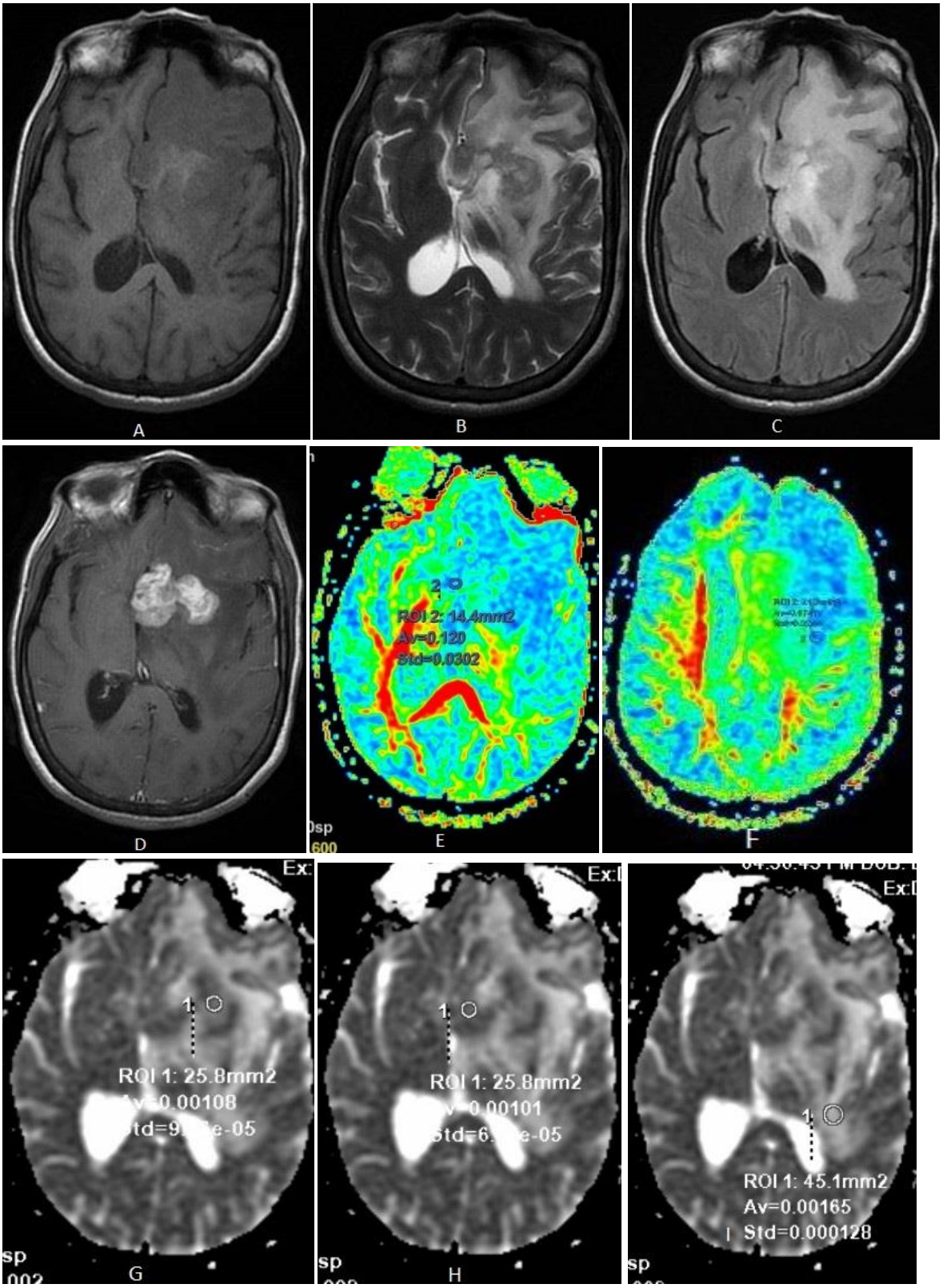


Figure 6. Female patient 30 years old, pathologically proved high grade glioma (A), (B) and (C) images Axial T1, T2 and FLAIR images respectively, showing left temporal intra axial lesion with surrounding vasogenic edema and heterogeneous post contrast enhancement (D). (E) and (F) FA map with two regions of interest measured within the enhancing part of the tumor and within the immediate peri-tumoral edema demonstrate reduced FA value in the immediate peri-tumoral edema, (G) and (H) ADC map with two regions of interest measured within the enhancing part of the tumor and (I) within the immediate peri-tumoral edema demonstrates slightly decreased ADC within the immediate peri-tumoral edema.

Conclusion

Our study showed that DTI is valuable tool in differentiation between brain metastasis and high-grade gliomas using FA and ADC maps measured in the peri-tumoral edema.

List of Abbreviations

ADC: apparent diffusion coefficient, AUC: area under the curve, BMs: brain metastases, DTI: diffusion tensor imaging, DWI: diffusion weighted imaging, FA: fractional anisotropy, HGG: high grade glioma, HS: highly significant, IV: intravenous, MRI: magnetic resonance imaging, NS: non-significant, ROC: receiver operating characteristic, ROI: region of interest, S: significant, SBM: solitary brain metastases, WHO: world health organization.

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