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Value of amide proton transfer magnetic resonance imaging and apparent diffusion coefficient in grading of meningioma

Jureerat Thammaroj, M.D.[1*], Sopiruch Yuthawong, M.D.[1], Arunnit Boonrod, M.D.[1], Amnat Kitkhuandee, M.D.[2], Mix Wannasarnmetha, M.D.[1], Warinthorn Phuttharak, M.D.[1], Saranya Jaruchainiwat[1]

[1]Department of Radiology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand 40002
[2]Department of Surgery, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand 40002

[*]jurtha@kku.ac.th

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ABSTRACT

Background: Meningioma is the most common intracranial extra-axial tumor in general populations with world health organization (WHO) grading ranging from grade 1 to grade 3 depending on subtypes which indicate the prognosis and management plan. Amide proton transfer (APT) is the new molecular MRI technique based on chemical exchange saturation transfer mechanism while apparent diffusion coefficient (ADC) is a conventional technique measuring of the magnitude of diffusion of water molecule within tissue.

Aim: To study whether the APT and ADC values correlate with meningioma WHO grading.

Materials and methods: A cross-sectional study was conducted at Department of Radiology, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand between July 2021 and December 2021. We performed MRI in patients with extra-axial tumors using conventional, APT and DWI sequences. Two experienced neuroradiologists placed the ROIs within the solid portion of the tumor those showed highest APT value and lowest ADC value in consensus manner and blinded to clinical data. The patients were later classified into groups based on pathological results. APT and ADC values were compared between groups.

Results: A total 23 patients with presumptive diagnosis of meningioma on pre-operative MRI were included with 20 patients who had pathological confirmed meningioma (17 patients with typical meningiomas WHO grade 1, two patients with atypical meningiomas WHO grade 2 and one anaplastic meningioma WHO grade 3). The mean and maximal APT values in an atypical meningioma group (WHO grade 2-3) were significantly higher than in a typical meningioma group with p-values of 0.023 and 0.024, respectively. There was no significant difference in mean and minimum ADC values and ADC ratios among the typical and atypical meningioma groups. The multivariate logistic regression analysis showed that higher APT values increased relative risk of high-grade tumors by a factor of 2.51 using mean APT (95%CI 0.81-7.74, p value 0.001, area under ROC curve 0.9097) and 2.48 using maximum APT (95%CI 0.75-8.1, p value 0.001, area under ROC curve 0.9064). A mean APT cut point of 3.52 provides good specificity in differentiating low and high grade meningiomas (sensitivity 67%, specificity 94% and area under ROC curve 0.8021)

Conclusion: The APT-weighted image offers an additional technique in differentiating low and high grades meningioma, while there is no difference of ADC values among the meningioma grades.

Keywords: Extra-axial tumor, meningioma, atypical meningioma, amide proton transfer, apparent diffusion coefficient.

Introduction

Meningiomas is the most common intracranial extra-axial tumor in general populations accounting for 10-30% of all brain neoplasms[1–3]The average prevalence of meningiomas in Thailand was 3.015 per 100,000 populations[4]. Based on world health organization (WHO) grading system on 2021, meningiomas are classified as 15 subtypes and grading ranging from grade 1 to grade 3, which indicates the prognosis and recurrence[5]. Atypical meningiomas and malignant meningiomas (WHO grades 2 and 3) show much higher recurrence rate, as 9% recurrence in typical meningioma to 28 and 75% recurrence in atypical and malignant meningioma.

According to the NCCN guidelines[6], management of meningiomas depend on the WHO grading, size of tumor and the patient's symptoms. Grade 1 meningioma that is smaller than 3 cm and causes no symptom can be managed by observation, thus, the adverse effect of the surgery can be avoided. Grade 2 and 3 meningiomas require surgical resection and radiation therapy to avoid recurrence.

Typical imaging appearances of meningiomas on conventional MRI include uniform contrast enhancement, are often calcified, have a clear interface with the brain, and are well-defined masses. In contrast, atypical meningiomas are more likely to have heterogeneous enhancement, may lack calcification, bony changes in form of destruction, indistinct interface with brain parenchyma, heterogeneous postcontrast enhancement, and edematous changes >6 mm thick in adjacent brain parenchyma and show features like necrosis or more aggressive edema[7].

However, meningiomas without these atypical features can become atypical or malignant on pathological result. The prediction of atypical/malignant meniogiomas on pre-operative imaging can aid in surgical planning and additional treatment options.

Apart from conventional MRI technique, amide proton transfer (APT) is the novel molecular MRI technique based on chemical exchange saturation transfer mechanism demonstrating the molecular specificity of the tissue of interest, which can be obtained without contrast media administration[8]. High cellularity of malignant tumors causes high protein concentration, thus increased the amine concentration and increased APT-weighted signals. Prior studies have showed significant higher APT weighted signals in malignant tumors like gliomas[9–11]. In terms of meningiomas, previous studies also showed the utility of an APT-weighted image in differentiating benign and atypical meningiomas and also correlation of the APT signals with the Ki-67 proliferation status of the tumor[12,13]. However, the number of studies of the utility of APT in differentiating of meningiomas is limited.

The diffusion weighted imaging (DWI) is a well-known advanced imaging technique that demonstrates the diffusivity of free water molecules in a voxel corresponding with the tumor cellularity. The previous studies found controversial correlations between ADC value and meningioma type, some showed significantly low ADC values in atypical meningioma[14–17] as compared with typical meningioma and some showed no statistically significant differences between the two groups[18–21].

Our study aims to evaluate the correlation of APT-weighted values and grading of meningioma using 3 tesla MRI scanner.

Materials and Methods

A cross-sectional study was conducted at Department of Radiology, Srinagarind Hospital, Faculty of Medicine of Khon Kaen University, Thailand between July 2021 and December 2021. This study was approved by institutional review board (IRB) with a waiver of informed consent.

POPULATIONS

We included all patients with extra-axial tumors who had MRI performed between July 2021 and December 2021 with presumptive diagnosis of meningioma on pre-operative MRI and had final pathological result. The exclusion criteria were patients with too small tumor size for ROI placement, poor MRI imaging quality for analysis such as intratumoral hemorrhage or near skull-based tumor location, inadequate tissue for pathological diagnosis, and inconclusive pathological result.

All included patients, either pathological proven meningioma or other tumors were classified into two groups based on WHO grading as WHO grade 1 group and WHO grade 2-4 group. Patients with meningioma were also classified as typical and atypical meningioma groups.

IMAGING PROTOCOL

All patients with any intracranial extra-axial space-occupying lesions were scanned with the 3T MR

(Phillips Achieva dStream; Philips, Best, the Netherlands) scanners. Using a routine brain protocol (Sagittal 3D TFE T1W imaging, Ax TSE T2W and 3D FLAIR imaging, Coronal T2W gradient/Ax SWI and post contrast axial, coronal and sagittal imaging); 3D TFE T1W images (8.6/4.1; number of signals acquired, 1 mm; section thickness, 5 mm; intersection gap, 1 mm; matrix, 256x256; field of view [FOV], 23 x 23 cm), TSE T2W images (4,500/96; number of signal acquired,1; section thickness, 5 mm; intersection gap, 1 mm; matrix, 400x270; FOV, 23 x 20 cm). T1-weighted fat-suppressed gradient echo sequences after administration of gadolinium contrast 0.1 mmol/kg (Gadobutrol, Gadovist; Bayer Healthcare Pharmaceuticals) was also performed as part of the routine protocol. A single shot echo-planar diffusion-weighted imaging sequence was performed. Imaging parameters of DWI were as followings: 3,000-45,00/89-95 (TR/TE) with diffusion sensitivities b=0 and b=1,000 s/mm^2. The diffusion gradients were applied sequentially in three orthogonal directions to generate 2 sets of axial DW images. The ADC maps were automatically generated from the datasets of DWI images using the operating console and ADC value were calculated. Post-Processing DWI data was transferred to a Synapse 3D workstation (Fujifilm Medical Systems, USA, Inc.) and the ADC map was generated.

For APT-weighted image, two main parameters are considered including APT-weighted percentage (APTw%) and magnetization transfer ratio asymmetry in percent (MTR_{asym}). The APT-weighted image (Amide proton transfer) was scanned before the contrast media was injected in a multishot TSE technique. The imaging parameters were as the followings; FOV 230x180x60 mm, acquisition voxel 1.8x1.8x0.6 mm, reconstruction voxel 0.9x0.9x6 mm, reconstruction matrix 256, slice number 10, TSE factor 174 radial, Fat suppression SPIR, Saturation $B1_{rms}$ 2 μT, Saturation duration 2s, continuous saturation, number of acquisitions=1.

To generate reliable APT-weighted imaging contrast, the magnetization transfer ratio asymmetry in percent (MTR_{asym}) was assessed by acquisition of a Z-spectrum, where a series of water signal levels was measured as a function of different frequency offsets, Δω. The water frequency (at 4.75 ppm in the proton MR spectrum) is placed at 0 ppm in the Z-spectrum. The Z-spectrum was aligned per voxel using information of local magnetic field variation (B0 field map). Then the asymmetry was evaluated by subtracting the positive frequency side S[+Δω] from the negative side S[-Δω] and normalized to an unsaturated image (S_0 APT image).

$$MTR_{asym}(\%) = (S[-\Delta\omega] - S[+\Delta\omega])/S_0$$

The MTR_{asym} was displayed as percent level (relative to S0) and referred to as APTw%

APTw% = MTRasym [Δω=+3.5ppm](%)

MTR_{asym} [Δω=+3.5ppm](%) = magnetization transfer ratio asymmetry at +3.5 ppm offset frequency

Post-Processing APT data was transferred to a Synapse 3D workstation (Fujifilm Medical Systems, USA, Inc.) and APT maps were generated.

Three regions of interest (ROIs) were placed at the strongest signal intensity within the lesion by visual assessment and reported as maximal and mean APT values. The ROI area was not less than 10 mm^2.

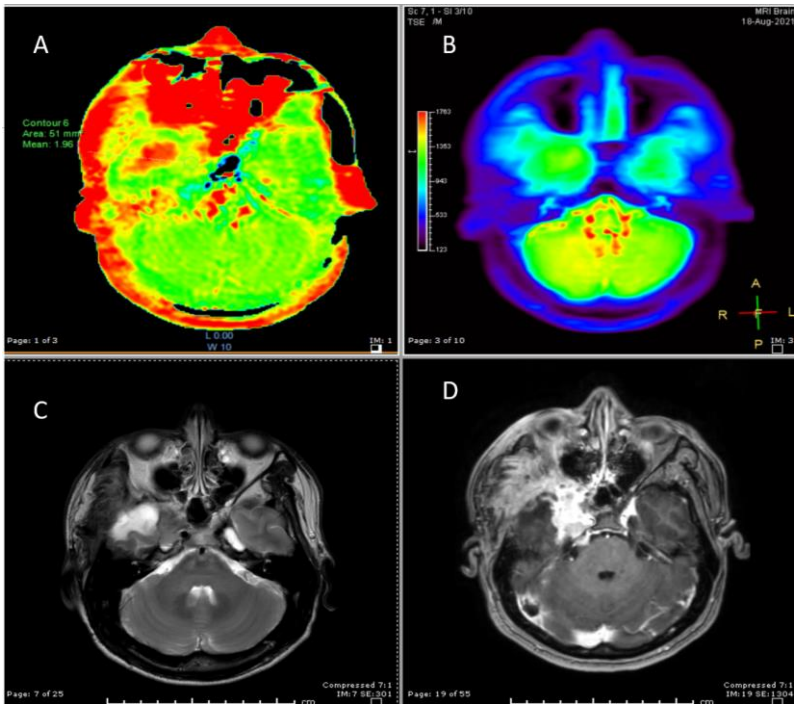
IMAGING ANALYSIS

Two neuroradiologist who were blinded to the patient's clinical information and pathological diagnosis reviewed the conventional MRI findings, APT-weighted images and DWI-weighted images. The ROI placement was performed in a consensus manner (M.W. 4 years of experience and J.T. 20 years of experience).

For DWI-weighted images, three ROIs were placed on ADC maps at the solid enhancing area that showed the lowest ADC value, avoiding the necrotic, cystic and hemorrhagic area. In case of non-enhancing tumor component, the ROIs were placed at the solid part of the tumor identified on T2-weighted images. The ratio between the mean lowest ADC value within the solid tumor to normal cerebral or cerebellar white matter (in posterior fossa tumor) was calculated.

For APT-weighted images, three ROIs were placed in the enhancing area that showed the highest APT signal intensity, avoiding the necrotic, cystic and hemorrhagic area. In case of non-enhancing tumor component, the ROIs were placed at the solid part of the tumor identified on T2-weighted images. To avoid artifact at the skull base, the ROIs were placed by correlation with the precise anatomy on T2-weighted images and correlation with the S_0 APT image (the image without saturation). (Figure 1)

Figure 1: Meningioma, meningothelial variant (WHO grade I)



(A): APT image shows increased APT signal of the right cavernous sinus in red color
(B): S_0 APT image shows corresponding slightly increased APT signal area at the right cavernous mass. Area of red color coonsistent with artifact at skull base.
(C): T2-weighted image and (D): contrast-enhanced T1-weighted image shows meningioma of right cavernous sinus

Statistical analysis

All data were analyzed using SPSS statistics Version 19.0.2. Descriptive statistics were used to describe the demographic data. Categorical data (Sex, previous RT, Preserved operation) were demonstrated as percent by using Pearson chi-square. Continuous data (Age, APT mean, ADC max, ADC mean, ADC min, and ADC ratio) was demonstrated as mean, standard deviation and range in case of normal distribution by using an independent t-test. In non-normal distribution data, the data were demonstrated as median and interquartile ranges using the Mann-Whitney U test. To determine the tumor grade by using APTw% and ADC value, multiple logistic regression was used. Comparing the diagnostic performance of APTw% and ADC value was done by using Chi-square test. The optimal cut point level was obtained by using Youden index. The significant level was defined as 0.05 p-value.

Results

During the 6 months period, there were a total of 99 MRIs performed with APT-weighted imaging. All these patients had been diagnosed with intracranial space-occupying lesions. There are 76 cases excluded from this study due to intra-axial lesion, lack of adequate pathological result, inadequate image quality, inadequate residual tumor size, no recurrence and severe artifact either from intratumoral hemorrhage or near skull-based location. Thus, the sample size of this study was 23 extra-axial lesions. Categorized according to WHO grading, there are eighteen cases with WHO grade 1 (one case with schwannoma and the rest 17 cases with meningioma), two cases with WHO grade 2 (atypical meningioma), one case with WHO grade 3 (anaplastic meningioma) and two cases with WHO grade 4 (one MALT lymphoma of the dura and one metastatic thyroid carcinoma). In a total of 20 cases of meningioma, there are two atypical meningiomas (WHO grade 2) and one anaplastic meningioma (WHO grade 3). The demographic data (sex, age, prior history of radiation therapy, and prior history of surgery) showed no significant difference among groups as shown in Table 1 (for meningioma cases) and Table 2 (for extra-axial tumor cases).

Table 1 Demographic data in patients with meningiomas (regarding typical vs atypical meningioma groups), N=20.

	Typical meningioma (n=17)	Atypical meningioma (n=3)	P-value
Age; Mean (SD)	50.41 (6.86)	41.33 (19.43)	0.504
Sex			0.284
Male	1 (5.88)	1 (33.33)	
Female	16 (94.12)	2 (66.67)	
Prior RT			>0.999
No	11 (64.71)	2 (66.67)	
Yes	6 (35.29)	1 (33.33)	
Prior surgery			0.509
No	3 (17.65)	1 (33.33)	
Yes	14 (82.35)	2 (66.67)	
APT mean; Mean (SD)	2.63 (0.60)	3.61 (0.86)	0.023
APT max; Mean (SD)	2.65 (0.58)	3.61 (0.86)	0.024
ADC mean; Mean (SD)	0.97 (0.21)	0.76 (0.09)	0.105
ADC min; Median (IQR))	0.93 (0.78-1.06)	0.77 (0.66-0.83)	0.153
ADC ratio to normal white matter; Median (IQR)	1.21 (1.06-1.45)	1.09 (0.99-1.20)	0.315

Note: typical meningioma WHO grade 1, atypical meningioma WHO grade 2&3

Table 2 Demographic data in all extra-axial tumor cases

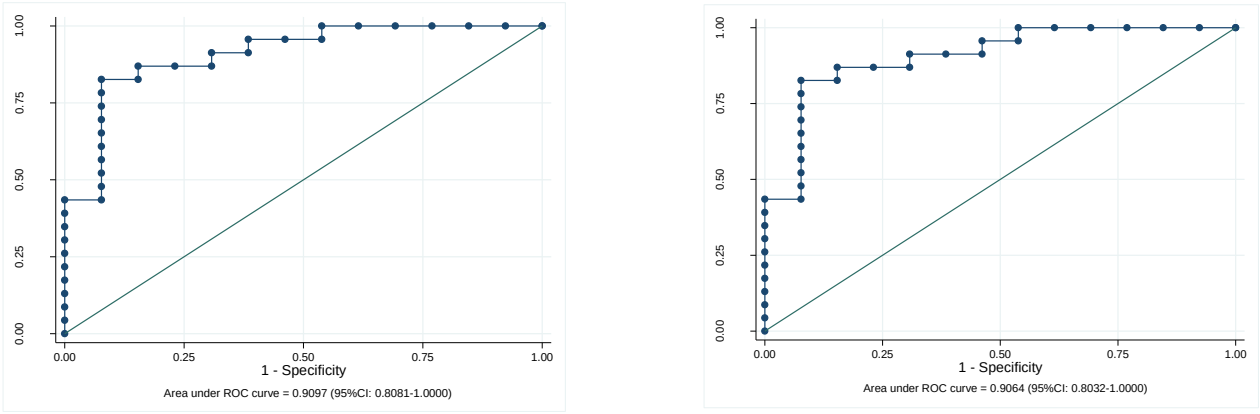
	WHO		
	Grade 1 (n=18)	Grades 2-4 (n=5)	p-value
Age			0.970
Median (IQR)	48.5 (44 - 56)	48 (46 - 58)	
Mean (SD)	48.44 (10.67)	46.2 (15.75)	
Sex			0.539
Male	2 (11.11)	1 (20.00)	
Female	16 (88.89)	4 (80.00)	
Previous RT			>0.999
Yes	6 (33.33)	1 (25.00)	
No	12 (66.67)	3 (75.00)	
Operative			0.291
Yes	15 (83.33)	3 (60.00)	
No	3 (16.67)	2 (40.00)	
APT mean			0.036
Mean (SD)	2.60 (0.59)	3.34 (0.86)	
Median (IQR)	2.68 (2.21 - 3)	3.59 (2.68 - 3.78)	
APT max			0.039
Mean (SD)	2.63 (0.58)	3.34 (0.86)	
Median (IQR)	2.71 (2.21 - 3)	3.59 (2.68 - 3.78)	
ADC mean			0.118
Mean (SD)	0.96 (0.20)	0.80 (0.15)	
Median (IQR)	0.96 (0.86 - 1.07)	0.78 (0.70 - 0.83)	
ADC min			0.179
Median (IQR)	0.93 (0.78 - 1.06)	0.77 (0.66 - 0.83)	
Mean (SD)	0.88 (0.29)	0.77 (0.15)	
ADC ratio			0.233
Median (IQR)	1.22 (1.06 - 1.45)	1.09 (1.09 - 1.17)	
Mean (SD)	1.21 (0.39)	1.11 (0.08)	

Note: WHO grading 2021

In patients with meningiomas, the mean and maximal APT values in the atypical meningioma group (WHO grades 2-3) were significantly higher than in typical meningioma group with 0.023 and 0.024 p-values, respectively. There were no significant differences in mean and minimal ADC values and ADC ratios among the typical and atypical meningioma groups. Due to small sample size, the multivariate logistic regression was not performed.

In all included patients, the mean and maximal APT values in higher grade group (WHO grade 2-4) were significantly higher than in WHO grade 1 group with 0.036 and 0.039 p-values, respectively. There were no significant differences in mean and minimal ADC values and ADC ratios among the typical and atypical meningioma groups. The multivariate logistic regression showed that a higher APT value increased relative risk of high grade tumor by a factor of 2.51 (95%CI 0.81-7.74) and 2.48(95%CI 0.75-8.1) with p value = 0.001, area under ROC curve = 0.9097 and p value = 0.001, area under ROC curve = 0.9064 for mean and maximal APT values (Figure 2).

Figure 2: Multivariate logistic regression of the extra-axial tumor group



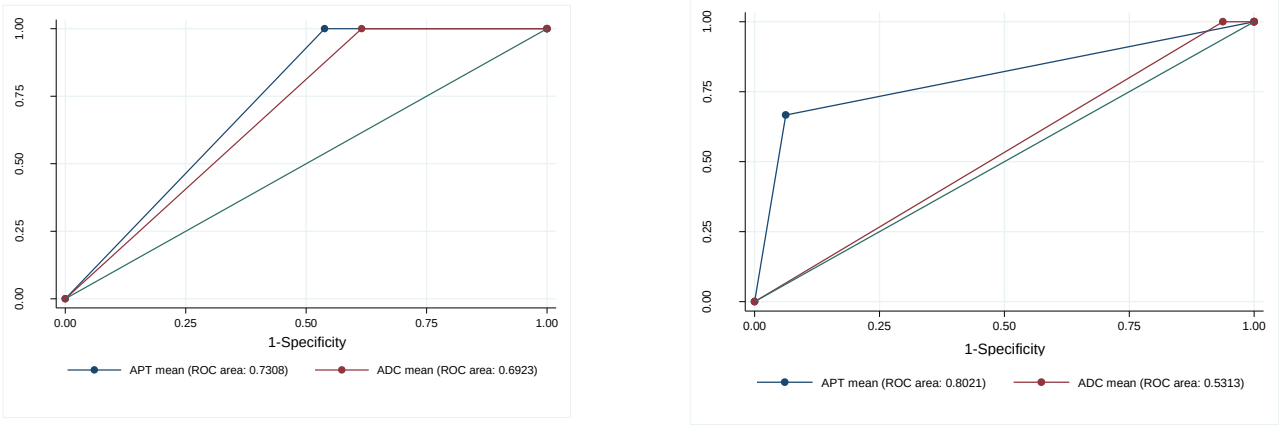
A B

(A) High APT mean increased relative risk of high grade tumor (WHO grade 2-4) by a factor of 2.51 (95%CI 0.81-7.74) with p value = 0.001 and area under ROC curve = 0.9097

(B) High APT max increased relative risk of high grade tumor (WHO grade 2-4) by a factor of 2.48 (95%CI 0.75-8.1) with p value = 0.001 and area under ROC curve = 0.9064

There were good sensitivity, specificity and high ROC area of the mean APT when using 1.69 and 3.52 cut points for differentiating tumor grading in all patients and in meningioma group (with 100% sensitivity 46% specificity 0.7308 ROC area and 67% sensitivity 94% specificity and 0.8021 ROC area, respectively). The optimal cut points of the mean ADC values were 0.50 and 0.60 x 10^{-3} for differentiating tumor grading in all patients and the meningioma group, showing relatively low specificity and low area under ROC curve (with 100% sensitivity 38% specificity 0.6923 ROC area and 100% sensitivity 6% specificity and 0.5313 ROC area) (Figure 3).

Figure 3: Optimal cut point of mean APT and ADC value



A B

(A) Optimal cut point for differentiation tumor group in extra-axial tumor

(B) Optimal cut point for differentiation meningioma group

Discussion

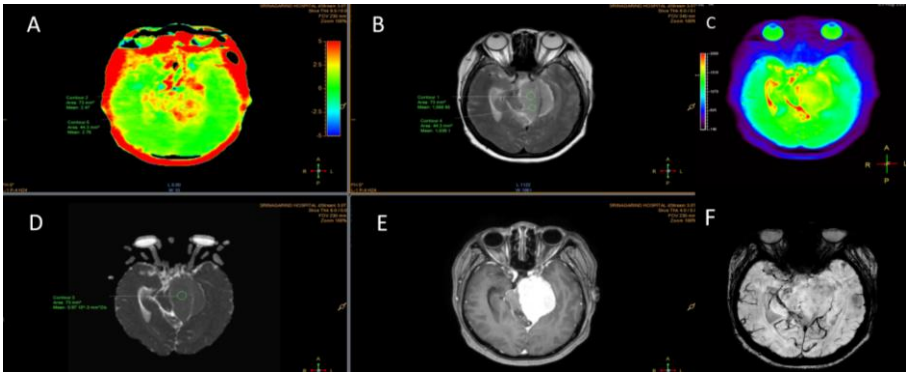
Our study emphasizes the superior advantage of APT in grading of meningioma than in ADC consistent with the study of Bio Joo et al(2018)[12], which showed that the APT value of atypical meningiomas was significantly higher than that of benign meningiomas (2.46% vs. 1.67%; P < 0.001) and between WHO grade 1 and WHO grades 2-4 extra-axial tumor(Figure 4 and Figure 5). Furthermore higher APT values was an independent predictor of atypical meningioma (adjusted OR, 11.227; P = 0.014) on multivariable logistic regression analysis.

A review paper on Amide proton transfer MR imaging in the characterization of brain tumors demonstrates promising results that APT MRI can differentiate between meningiomas and glioblastomas based on their distinct molecular profiles. The differences in amide proton transfer rates observed in APT MRI images correspond to variations in the histological and genetic features of the tumors. Moreover, APT MRI has shown potential in predicting tumor grade, assessing tumor aggressiveness, and monitoring treatment response[22].

APT images do not require any contrast media administration, thus this technique can be performed in patients with renal impairment or with any conditions that are contraindicated for contrast media injection.

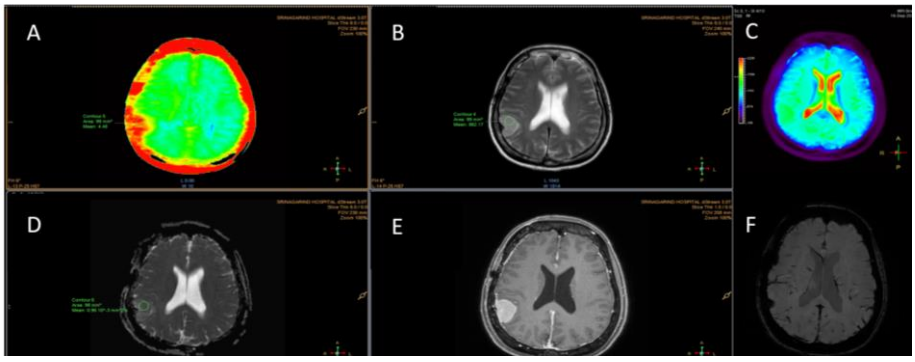
In contrast to the study of Hao Yu et al.(2018)[13], which showed that there was no statistically significant difference of the APT value between WHO grade 1 and WHO grade 2 meningioma, but APT value was positively correlated with Ki-67 labeling index (r = 0.817, p < 0.001). This could be from lack of WHO grade 3 meningioma included in the study of Hao Yu et al. which can result in different APT values. Furthermore, to date there was no such study comprising all subtypes of the meningioma including this study which cannot be avoided. Different types of meningioma may cause heterogeneity of the APT value among the same WHO group from different histopathologic appearances.

Figure 4: Meningioma, meningothelial variant (WHO grade I): APT mean and APT max = 2.76, ADC value = 0.95 and ADC ratio = 1.22



(A) APT-weighted image shows increased APT signal at the left tentorial mass, ROIs were placed at the highest APT signal area corresponding to the S_0 image (C)
(B) T2-weighted image and (E) contrast-enhanced T1-weighted image show enhanced mass at the left tentorium in keeping with meningioma
(D) ADC maps with ROIs placed at the meningioma
(F) SWI shows no internal calcification or hemorrhage

Figure 5: Meningioma, Chordoid variant (WHO grade II): APT mean and APT max = 4.38, ADC value = 0.77 and ADC ratio = 1.09



(A) APT-weighted image shows increased APT signal at the right parietal convexity mass, note ROIs were placed at the highest APT signal area corresponding to the S_0 image (C)
(B) T2-weighted image and (E) contrast-enhanced T1-weighted image show enhancing mass at the right pareital convexity in keeping with meningioma
(D) ADC maps with ROIs placed at the meningioma
(F) SWI shows no internal calcification or hemorrhage

Another technique used in this study is diffusion weighted imaging, which can be assessed quantitatively by using the ADC value. Diffusion-weighted imaging is the sequence evaluating the diffusivity of the water molecule within the lesion which can imply the cellularity of tumor. The present study finds that there is no significant difference of the mean, minimal ADC value and ADC ratio to normal white matter between typical and atypical meningiomas and between WHO grade 1 extra-axial tumor and WHO grade 2-4 extra-axial tumor. This is consistent with the previous studies which show no additional value of the ADC value in differentiating tumor type[18–21,23]. Goran Pavlisa et al.[18]had given the hypothesis that the similarity of the ADC value in typical and atypical meningioma may be the result of a moderately pronounced difference in cellularity and the microscopic necrosis mixed with tumor cells in an atypical meningioma that would allow higher water diffusion more than the effect of tumor cellularity. Another hypothesis had been raised by Warinthorn Phuttharak et al.[24], whose previous study showed the correlation between ADC value and intra-operative meningioma consistency which was thought to be from an internal fibrotic component rather than cellularity. The hypothesis of these authors is that the ADC values are diverse within the same WHO graded-meningioma from histopathological heterogeneity among subgroups not only in cellularity nature but also in the internal fibrotic component or micronecrosis.

Strengths and limitations

Present study reveals the utility of the new advanced imaging technique which is the APT-weighted image in evaluation of the meningioma grading. The APT-weighted image can be used as an add on technique for evaluation the equivocal cases those are small extra-axial meningioma-liked tumors which can be treated by observation rather than surgical resection. Furthermore, this study compares the APT image and diffusion-weighted image which is the well-known technique in grading intraparenchymal glioma, but for meningioma there is still some controversy in tumor grading by using the ADC value.

The main limitation of this study is small number of the sample sizes and small number of atypical meningioma, which cannot be avoided. Since the authors institution has only a 6-month period using the APT-weighted image in the protocol, and the prevalence of atypical meningioma is low (roughly 10% of all meningioma prevalence). Moreover, the sample size does not include all subtypes of meningioma, which can cause heterogeneity in APT and ADC values within the same WHO grade. Further study with a larger sample size is required to confirm the accuracy of the study. Finally, most of the studied population had a previous surgical history at the tumor site, but placing ROI in the area of necrosis, cystic, and blood-stained part was avoided. Further study with a large number of pre-operative patients is required to overcome this limitation.

Conclusion

The APT-weighted image is the new advanced MRI technique based on chemical exchange saturation transfer mechanism demonstrating the mobile protein concentration in the tumor that is thought to be from the high cellularity of the tumor. The APT-weighted image can be used as an add on technique for extra-axial tumor grading especially meningiomas. The higher APT value increased the relative risk of being high grade tumor. Whereas there is no difference of ADC values among the meningioma grades.

Conflict of Interest Statement:

The authors have no conflicts of interest to declare.

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