Can Average Value of Apparent Diffusion Coefficient (ADC) from Magnetic Resonance Images Predict Consistency of Intracranial Meningioma?

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Background: *Surgery for intracranial meningioma is either relatively simple or extremely difficult based heavily on tumor consistency.*
Objective: *To examine the average diffusion constant from apparent diffusion coefficient (ADC), acquired from routine magnetic resonance imaging (MRI), whether it can reliably predict consistency of intracranial meningioma. The secondary objective is to find out if tumor consistency correlate with its histopathology.*
Material and Method: *Prospectively collected data between July 2009 and July 2011, including demographic, radiographic, intra-operative findings, and histopathology, was evaluated. Eligible patients must have had pre-operative conventional MRI obtained at Faculty of Medicine Ramathibodi Hospital, with calculated average diffusion constant from ADC. All of the included patients' meningioma resection as well as histopathology were performed at our institute. During each surgical resection, unaware of the MRI interpretation, the operating neurosurgeon classified each meningioma as having soft, firm, or hard consistency. Pathology of 2007 WHO grade I vs. II, tumors was independently reported by neuropathologist without knowledge of pre-operative radiographic and intra-operative tumor consistency.*
Results: *Fifty-eight patients with intracranial meningioma met the inclusion criteria. The average ADC values amongst soft, firm, and hard consistency tumors were not statistically different ($p = 0.82$). As for WHO grades, neither the T2 weighted images (T2W) intensity nor the average ADC value showed differences between grade I and grade II meningioma ($p = 0.84$ and $p = 0.31$ respectively). The only significant correlation was observed between hyperintensity signal on T2W and high proportion of soft consistency tumors ($p = 0.001$). In addition, meningiomas with soft consistency were more commonly associated with WHO grade II histopathology ($p = 0.01$).*
Conclusion: *Although theoretically sound, average ADC did not reliably predict consistency of intracranial meningioma. Nevertheless, tumors with soft consistency often exhibited hyperintensity signal on T2W and were frequently associated with WHO grade II. This adds to prior studies reiterating similar findings. Neurosurgeons should utilize such information to prepare well before performing intracranial meningioma surgery.*

Keywords: *Meningioma, MRI, Consistency, DWI, Apparent diffusion coefficient, ADC, T2W*

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Meningioma is the most common benign intracranial tumor. Magnetic resonance image (MRI), with and without contrast, is an important tool for diagnosis as well as for therapeutic planning. It provides information regarding location, vascularity, size, tumor extension, or invasion, and more. These details of meningioma enable the surgeon to plan effectively in dealing with it. Tumor consistency is one of the crucial factors influencing not only the difficulty of its resection but also increase operative time and consequently affects surgical outcome[1,2]. Many studies reported predictability of tumor consistency, from radiographic features, with varying reliability[2,3]. Fractional anisotropy (FA) image could effectively forecast consistency of meningioma. However, due to its high cost, this technique has not been routinely used[4]. Some publications demonstrated relationship between tumor consistency and T2-weighted (T2W)

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image MRI[2,3,5-9]. However, the mixed results from these publications have made prediction of meningioma consistency, before surgery, rather difficult with MRI.

Based on MRI concepts, diffusion-weighted image (DWI) and apparent diffusion coefficient (ADC) value, automatically calculated by software, should ideally reflect the best measurement of water diffusion's rate at that location of interest[10,11]. Hence, our hypothesis was that, in firm to hard consistency tumors, MRI ought to exhibit restricted diffusion resulting in lower ADC value. The present study was designed to pursue correlation between the average ADC value and the consistency of meningioma. Moreover, by utilizing this value from routine cranial MRI, there was no extra cost added. Therefore, if our research demonstrates reliability in association with intracranial meningioma consistency, this discovery could be important. In addition to the ADC, we evaluated the relationship between T2W signal intensity and tumor consistency. Our secondary objective was to find out if histopathology of WHO grade I and II meningioma correlated with T2W, ADC value, and its consistency.

Material and Method

Patient selection

After approval by our institutional ethic review board, data of eligible patients between July 2009 and July 2011 was prospectively recorded. Informed consent was obtained prior to enrollment to our study. Our inclusion and exclusion criteria are shown below.

Inclusion criteria

Patients with intracranial meningioma, who underwent both pre-operative MRI and craniotomy for tumor resection at our institute, were included. In addition, these patients must have had definitive histopathology confirmation of meningioma.

Exclusion criteria

Patients without pre-operative MRI or no pathology confirmation of meningioma performed at our institute were excluded. Furthermore, patients with extracranial meningioma or those with prior cranial irradiation were not included.

MRI protocol

Prior to surgical resection, all patients underwent either 1.5- or 3.0-Testla magnetic resonance imager using standard head coil with 240x240 millimeter (mm) field-of-view (FOV). Our conventional brain MRI consisted of the following sequences, sagittal T1-weighted (T1W), coronal gradient-echo (GRE), axial T1W, fast spin echo T2W, and axial fluid-attenuated inversion recovery (FLAIR). After administration of 0.1 millimole per kilogram, gadopentetate dimerglumine, contrast-enhanced axial, and coronal T1W images were acquired. In all sequences, the section thickness was 5 mm with interslice gap of 1.5 mm. DWI was obtained by using an axial echo-planar SE sequence with 5-mm slice thickness in 20 seconds. In addition, DWI and ADC maps, from the native diffusion images, were subsequently illustrated by utilizing standard software on General Electric (GE Medical systems, Chicago, Illinois, United States) computer workstation. Applying the inversed b-value from DWI, of 1,000 seconds per square mm (s/mm^2), the ADC values ($x10^{-3}mm^2/s$) were calculated.

Methods

Pre-operative MRI findings (Fig. 1)

Each patient's MRI was prospectively reviewed by the second author, a neuroradiologist. The T2W, DW images, and ADC maps were classified as hypo-, iso-, or hyperintense in comparison with normal gray and white matter, respectively. Each tumor's ADC values were calculated using a subprogram of the Functool image analysis software (GE Medical systems, Chicago, Illinois, United States). To minimize variability of our measurements, the region of interest (ROIs), varying from 30 to 150 mm^2, were placed manually in the solid part of the tumor so as to avoid cystic or paramagnetic substance areas. The ROIs were placed far, approximately 5 mm, from meningioma's border. Subsequently, ADC values were averaged. For control, the ADC value from normal white matter on the contralateral normal brain, without influence from the tumor, was also recorded and compared.

Intra-operative findings

All of the operating neurosurgeons were unaware of the aforementioned ADC values. For the purpose of the present study, the lowest level of amplitude from Cavitron Ultrasonic Surgical Aspirator (Integra® CUSA® Excel+[Plainsboro, New Jersey, USA]) required to remove the tumor was used for reference. During each surgery, the operating neurosurgeon categorized meningioma's consistency as described below.

1) Soft consistency was for tumors that required only suction or low CUSA amplitude of less than 40% for removal.

2) Firm consistency was for meningiomas that

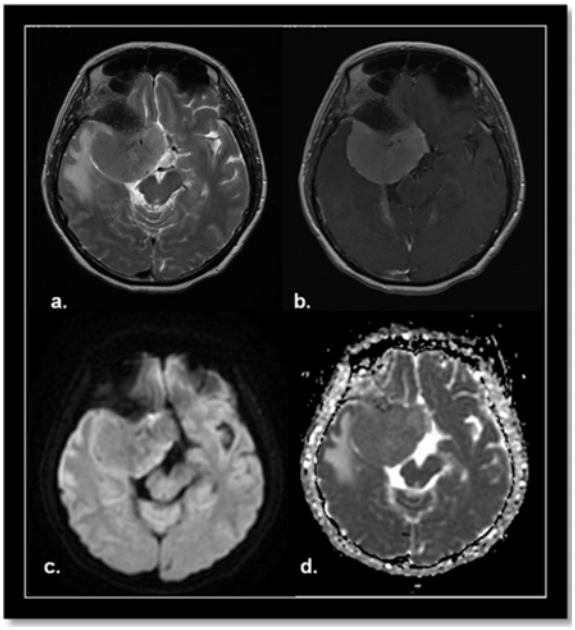

Fig. 1 Magnetic resonance imaging scans, with different series, of a 41-year-old woman who had a right sphenoid wing meningioma. Its average apparent diffusion coefficient (ADC) value was $1.39x10^{-3}$ square millimeter per second. a) T2-weighted image demonstrated hypointensity signal of the tumor. b) Contrast-enhanced T1-weighted image showed, typical for meningioma, vivid enhancement and dural tail sign. c) Restricted diffusion on the diffusion weighted image, d) ADC maps. Operating neurosurgeon categorized this tumor as having hard consistency.

could not be removed by suction only. CUSA amplitude between 40 to 90% was typically necessary.

3) Hard consistency tumors were those barely removable by CUSA at its full (100% amplitude) power. Most commonly, either piecemeal removal or cutting loop was needed.

Histopathology findings

Specimens of intracranial meningioma were examined for histopathology confirmation along with 2007 subtype classification as well as the WHO grades[12]. Our neuropathologist, the third author, was not aware of radiographic or intra-operative findings.

Statistical analysis

All of the analyses were performed using SPSS version 11.5 for windows (IBM Corp, New York, USA). Descriptive statistics were presented as mean $\pm$ standard deviation (SD). Comparison of average ADC values, ADC ratio, and mean normal ADC values between WHO grades of meningioma were analyzed using paired t-test with normal distribution. Logistic regression analysis was applied to determine the effect of multiple variables on meningioma consistency. Differences in signal intensity on T2W images, ADC maps and tumor consistency were assessed using the Chi-square test. A *p*-value of 0.05 or less was considered statistically significant.

Results

Between July 2009 and July 2011, one hundred twenty-seven patients underwent craniotomy for intracranial meningioma. Fifty-eight patients fulfilled our inclusion criteria whilst 69 patients were excluded. There were 53 females and five males with mean age of 50.4 (range 23 to 72) years. Of the 58 tumors categorized, from intra-operative observation, by operating neurosurgeons, 20 (34.5%) tumors were soft, 24 (41.4%) were firm, and 14 (24.1%) were hard consistency. The average ADC values $\pm$ SD ($x10^{-3}mm^2/s$) amongst soft (0.71 ± 0.35), firm (0.7 ± 0.33) and hard (0.76 ± 0.41) consistency tumors did not reach statistical differences ($p = 0.82$) (Table 1 and Fig. 2). However, significant association between hyperintensity signal on T2W image and soft consistency was observed ($p = 0.001$). (Table 1 and Fig. 3).

There were 46 (79.3%) WHO grade I and 12 (20.6%) WHO grade II meningiomas, but no WHO grade III in this cohort. Quantitative comparison of the average ADC value and T2W intensity signal between meningioma grades did not reach statistical significance ($p = 0.31$ and $p = 0.84$ respectively) (Table 2). However, there was correlation between tumor consistency and WHO I vs. II grade. Soft tumors were more likely to be WHO grade II than firm or hard consistency ($p = 0.01$) (Table 1 and Fig. 4).

Discussion

Meningioma consistency is a key factor influencing surgical outcome for tumors, in particular, at skull base[7]. Furthermore, the consistency will greatly influence operative time[1,2]. Diffusion tensor imaging (DTI) with FA was developed to evaluate the magnitude and direction of water diffusion. Kashimura et al reported significant correlation between FA value, calculated from DTI, and meningioma consistency[4]. However, due to its high cost, this technique has not been popular. With DWI routinely performed as part of our conventional MRI protocol, the average ADC value, calculated from DWI, could be vastly helpful to predict

meningioma consistency without additional cost or time to patients. In theory, the ADC value should determine water diffusion of tissue. Therefore, this study explored into the relationships of tumor consistency, histologic WHO grade of meningioma with conventional MR imaging, and ADC value. Unfortunately, the findings did not turn out as the theory. It failed to establish significant association between the average ADC value

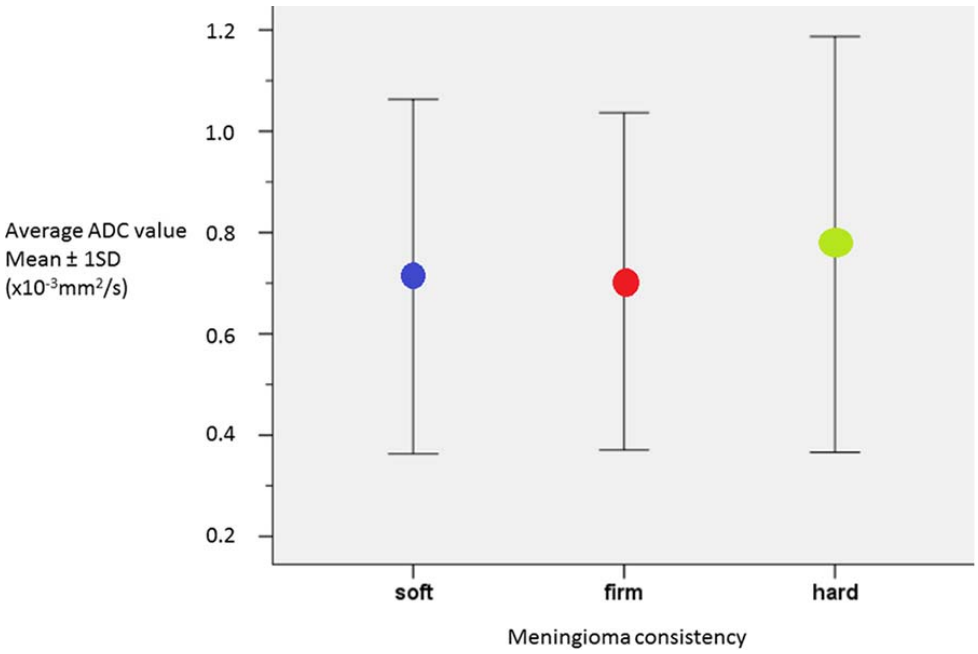

Fig. 2 Bar graph of meningioma consistency and the average value of apparent diffusion coefficient (ADC) ($x10^{-3}$ square millimeter per second [mm^2/s]) demonstrates no significant relationship.

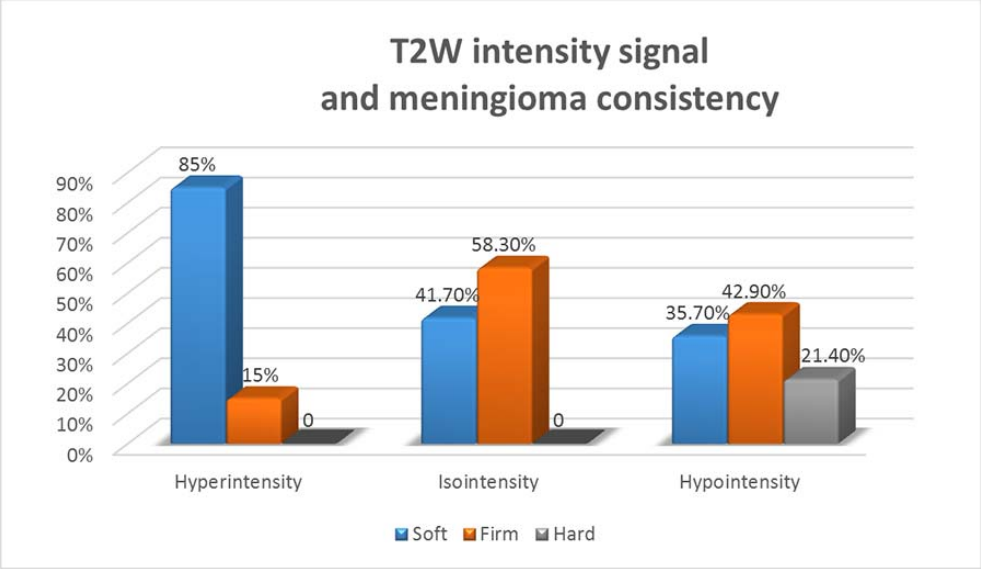

Fig. 3 Distribution of meningioma consistency on different T2-weighted (T2W) appearance. Note the significant association between hyperintensity signal and high proportion of soft consistency tumor.

Table 1. Analysis of meningioma consistency with average apparent diffusion coefficient (ADC) value (x10^{-3} square millimeter per second [mm^2/s]) shows no association. Note the significant link between soft tumor consistency with hyperintensity T2-weighted (T2W) signal and with histopathology of WHO grade II

	Meningioma consistency			*p*-value
	Soft n = 20	Firm n = 24	Hard n = 14	
Magnetic resonance images (MRI)				
Average ADC value (x10^{-3} mm^2/s)	0.71	0.70	0.76	0.82
T2W signal (%)				
Hyperintense	17 (85%)	10 (41.7%)	5 (35.7%)	0.001
Isointense	3 (15 %)	14 (58.3%)	6 (42.9%)	
Hypointense	0 (0%)	0 (0%)	3 (21.4%)	
Histopathology				
Meningioma WHO grade (%)				
Grade I (n = 46)	11 (24%)	22 (48%)	13 (28%)	
Grade II (n = 12)	9 (73%)	2 (16%)	1 (11%)	0.01

Table 2. The average value of apparent diffusion coefficient (ADC) (x10^{-3} square millimeter per second [mm^2/s]) or T2-weighted (T2W) signal could not significantly distinguish meningioma WHO grades

MRI	Meningioma WHO grade		*p*-value
	I n = 46	II n = 12	
Average ADC value (x$10^{-3}$$mm^2/s$)	0.752	0.618	0.31
T2W image (%)			0.84
Hyperintense	24 (52.2%)	8 (66.7%)	
Isointense	19 (41.3%)	4 (33.3%)	
Hypointense	3 (6.5%)	0 (0%)	

and tumor consistency.

For the relationship between DWI and histological grade, various theories have been proposed to explain the decreased DWI in high-grade neoplasms. Such tumors usually exhibit increased cellularity, matrices, and high nucleus-to-cytoplasm ratio[13]. The fact that, typically, there is higher nucleus to cytoplasm ratio. Restricted diffusion is more common in high-grade meningiomas. Additionally, because of the decreased free diffusion of water or lower ADC when compared with low- grade tumor, few publications supported this association[14-16]. Nagar et al demonstrated significantly lower ADC value in atypical and malignant meningioma. From forty-eight meningiomas, twenty-five atypical tumors had lower ADC value (0.66 ± 0.13x$10^{-3}$$mm^2/s$) compared with 23 benign tumors (ADC = 0.88 ± 0.08x$10^{-3}$$mm^2/s$) ($p<0.0001$)[15]. In a recent study by Santelli et al, with larger cohort (n = 102), they did not find such relationship between the ADC value and WHO grade I versus grade II meningioma[17]. Similarly to this mentioned report, although the WHO grade II meningiomas had lower ADC value than WHO grade I in our study, the difference did not reach statistical significance. This finding may prove that DWI is not reliable as a bioimaging marker for meningioma grading.

More commonly than the ADC value, many suggested a strong correlation between hyperintensity signal on T2W and soft consistency of meningioma[2,5-9,18]. However, the meaning of consistency was rather variable among individual surgeon, which had not been uniformly categorized.

Fig. 4 Pie graph of 2007 WHO grade I and II meningiomas and tumor consistency. Note the large proportion of soft consistency in grade II tumors.

We attempted to minimize this discrepancy by using the requirement of CUSA amplitude for our definition of soft, firm, and hard tumor consistency. Nevertheless, our result is in agreement with most publications that meningiomas with hyperintensity signal on T2W image were likely to have soft consistency ($p = 0.001$) (Fig. 3). In contrast, Carpeggiani et al found no correlation between T2W signal intensity and tumor consistency[3].

From the present study, we found that WHO grade II meningiomas were mostly soft tumors (Fig. 4). Jaaskelainen et al revealed that soft meningioma consistency had influenced their tumor's recurrence rate. However, there was no mention of WHO grades in their study[19]. It could be presumable that soft consistency meningiomas might have high recurrence due to the frequency of WHO grade II histopathology. More study is needed to verify this correlation.

Despite the prospective and surgeon/pathologist-blinded nature of our study, notable limitations are as followed. First, there was no WHO grade III (anaplastic) tumor. As a result, unlike previous reports, we cannot conclude, with certainty, regarding

the correlation between ADC value and higher grades meningioma. Secondly, although we tried to minimize variation between surgeons in categorizing tumor consistency by using CUSA amplitude, the meaning of "lowest-power-requirement-to-remove-tumor" might be vastly different interpretation among individual neurosurgeon. Larger cohort and more detailed categorization of intra-operative tumor consistency with similar prospectively designed study could be important.

Conclusion

DWI and average ADC values could not reliably predict consistency nor WHO grade of intracranial meningioma. In contrast, significant correlation between hyperintensity signal on T2W image and soft consistency was observed. Additionally, WHO grade II meningiomas have much higher proportion of soft tumors than WHO grade I.

What is already known in this topic?

T2W images from MRI correlated with meningioma consistency. Much less known, though theoretically sound, is the ADC value from DWI and its relationship with tumor consistency.

What this study adds?

Despite prospectively collected data and interpretation from physicians who were not aware of radiology readings, the average value of ADC did not correlate well with neither meningioma consistency nor WHO grade.

Potential conflicts of interest

None.

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การใช้ค่าเฉลี่ยของ apparent diffusion coefficient จากเครื่องเอ็มอาร์ไอในการคาดคะเนความเหนียวของเนื้องอกเยื่อหุ้มสมอง

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ภูมิหลัง: *การผ่าตัดเนื้องอกเยื่อหุ้มสมองจะง่ายหรือยากมากขึ้นอยู่กับความเหนียวของเนื้องอกเป็นสำคัญ*

วัตถุประสงค์: *เพื่อวิเคราะห์ค่าเฉลี่ยของ apparent diffusion coefficient (ADC) จากเครื่องเอ็มอาร์ไอในการคาดคะเนความเหนียวของเนื้องอกเยื่อหุ้มสมอง และเพื่อดูความสัมพันธ์ระหว่างความเหนียวกับลักษณะทางพยาธิสภาพของเนื้องอกเยื่อหุ้มสมอง*

วัสดุและวิธีการ: *รวบรวมข้อมูลผู้ป่วยที่ได้รับการผ่าตัดเนื้องอกเยื่อหุ้มสมองที่ตรวจเอ็มอาร์ไอก่อนผ่าตัดและทำการผ่าตัดสมองที่โรงพยาบาลรามาธิบดี ตั้งแต่เดือนกรกฎาคม พ.ศ. 2552 ถึง เดือนกรกฎาคม พ.ศ. 2554 โดยที่ผลการตรวจพยาธิสภาพเป็นเนื้องอกเยื่อหุ้มสมอง ขณะที่ทำการผ่าตัดสมองนั้น ประสาทศัลยแพทย์ที่ไม่ทราบผลของค่าเฉลี่ยของ ADC จะทำการจำแนกความเหนียวของเนื้องอกเป็น 3 ประเภท และพยาธิแพทย์รายงานการตรวจชิ้นเนื้องอกเยื่อหุ้มสมองตาม WHO grading โดยที่ไม่ทราบข้อมูลจากผลอ่านทางรังสีและผลการจำแนกความเหนียวของเนื้องอกจากห้องผ่าตัด*

ผลการศึกษา: *ในช่วงเวลาที่ทำการศึกษา มีผู้ป่วยจำนวน 58 รายที่มีข้อมูลเอ็มอาร์ไอ ข้อมูลการผ่าตัด และข้อมูลพยาธิสภาพที่ครบถ้วนตามวิธีการที่กำหนด จากการวิเคราะห์ข้อมูลพบว่า ค่าเฉลี่ยของ ADC ไม่มีความสัมพันธ์กับความเหนียวของเนื้องอกเยื่อหุ้มสมอง (p = 0.82) และไม่มีความสัมพันธ์กับชนิด WHO grade (p = 0.31) หากแต่การวิเคราะห์ตัวแปรอื่นพบว่า hyperintensity signal ของ T2W จากเอ็มอาร์ไอนั้นมีความเกี่ยวข้องกับความนุ่มของเนื้องอกอย่างมีนัยสำคัญ (p = 0.001) นอกเหนือไปจากนั้นยังพบอีกว่าเนื้องอกเยื่อหุ้มสมองที่มีความนุ่มมักจะเป็นเนื้องอกเยื่อหุ้มสมองชนิด WHO grade II (p = 0.01)*

สรุป: *แม้ว่าในทางทฤษฎีนั้นค่าเฉลี่ยของ ADC จากเครื่องเอ็มอาร์ไอ ควรจะเป็นเครื่องมือในการคาดคะเนความเหนียวของเนื้องอกเยื่อหุ้มสมองได้ดี หากแต่ผลการวิเคราะห์ข้อมูลกลับไม่พบความสัมพันธ์ที่มีนัยสำคัญ ดังนั้นการศึกษานี้แสดงให้เห็นว่ายังไม่สามารถนำค่าเฉลี่ยของ ADC มาใช้งานได้อย่างมีความน่าเชื่อถือ อย่างไรก็ตามการศึกษานี้ได้แสดงให้เห็นว่า hyperintensity signal ของ T2W จากเอ็มอาร์ไอนั้นมีความสัมพันธ์กับความนุ่มของเนื้องอกเช่นเดียวกับที่มีรายงานที่ตีพิมพ์ก่อนหน้านี้ และพบความเกี่ยวข้องระหว่างเนื้องอกเยื่อหุ้มสมองที่มีความนุ่มนั้น มักจะเป็นเนื้องอกเยื่อหุ้มสมองชนิด WHO grade II คณะผู้นิพนธ์หวังว่าข้อมูลที่นำเสนอนี้จะเป็นประโยชน์กับประสาทศัลยแพทย์ ในการวางแผนผ่าตัดเนื้องอกสมองได้อย่างมีประสิทธิภาพ*