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## ORIGINAL ARTICLE

# Role of Diffusion Weighted Magnetic Resonance Imaging DW-MRI in Proper Surgical Planning for Pituitary Macroadenoma Resection.

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## ABSTRACT

**Background:** Assessment pituitary macroadenoma consistency before surgical resection is crucial for neurosurgeons for appropriate choice of the surgical procedure. So, we sought to evaluate the DW-MRI role as a noninvasive method in predicting pituitary macroadenoma consistency.

**Methods:** Conventional MRI sequences, DWI-MRI with ADC map were done on twenty-four patients. We determined the tumor consistency both macroscopically by neurosurgeons and microscopically by histopathologists.

**Results:** According to ADC values, we had three categories of macroadenoma consistency; the mean ADC value of the soft category was  $(0.49) \times 10^{-3} \text{ mm}^2/\text{s}$ , the intermediate category was  $(0.80) \times 10^{-3} \text{ mm}^2/\text{s}$  and the hard category was  $(0.98) \times 10^{-3} \text{ mm}^2/\text{s}$ . The soft tumors were well suctioned by endoscopic transsphenoidal procedure. While transsphenoidal approach failed in completely removing the intermediate and hard tumors and they needed further extensive transcranial approach with sensitivity 100% and specificity 83.8%.

**Conclusion:** As a part of the routine pre-operative assessment of macroadenoma consistency, we should include DWI and the corresponding ADC value to choose the suitable resection approach with recommendation of ADC cut off value of  $0.61 \times 10^{-3} \text{ mm}^2/\text{s}$ , for proper differentiation of soft macroadenomas from the intermediate/hard adenomas.

**Key words:** ADC, Diffusion weighted magnetic resonance imaging DW MRI, Pituitary macroadenoma.



## INTRODUCTION

Pituitary macroadenoma is one of the most common sellar space occupying lesions. It is considered as a benign tumor of the pituitary gland. Surgical resection is indicated for sellar decompression of masses causing visual field defects, central nervous system pressure effects and pituitary function disorders [1]. The pituitary macroadenomas were categorized into soft, intermediate and hard types according to histopathology and surgical viewpoint of tumor consistency [2]. Choosing the appropriate method relies partially on an inner characteristic of the tumors; its integrity. Neurosurgeons decided that the transsphenoidal endoscopic suctioning is more convenient for tumors with soft texture, while craniotomy is more ideal for the intermediate & harder ones. Therefore, pre-operative tumor integrity testing can help to determine the perfect operational approaches and therapies that will not only improve the chance of full tumor elimination but also decrease recurrence levels [3]. The consistency of the pituitary macroadenomas can be assessed by using the DW MR imaging and the

linkage between tumor cellularity and ADC levels [4]. There is inverse proportion between ADC values and the tumor cellularity; tumors with many cells have lower ADC values and vice versa [5]. We use tumor cellularity and ADC value correlation to assess the appropriate approach whether recent minimally invasive endoscopic transsphenoidal approach or transcranial approach.

## METHODS

A total number of 24 patients were scheduled for MRI at Radio-diagnosis department, Zagazig university hospitals. They were referred by neurosurgeons for suspicion of having pituitary macroadenoma. Inclusion criteria: Patients with pituitary macroadenomas that had been diagnosed by conventional MRI & DWI and proved later by histopathologists. Exclusion criteria: Patients with obstacles for MRI (implanted electric and electronic devices, heart pacemakers, insulin pumps, implanted hearing aids and intracranial metal clips). Patients with previously operated macroadenoma with residual lesions were excluded as well as patients with invasive macroadenoma. We explained our study to the

patients then we took an informed approval from them. The study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. Patients' preparations. Full history taking and clinical analysis was done then we asked all patients to get rid of any metallic subjects as well as they were asked about any contraindication to MRI examination (except that made of Titanium). Imaging and image analysis: (pre-operative MRI): Using a Philips 1.5 T MRI equipment of closed configuration, the patients placed on supine position; their heads were rested on a vacuum pillow and the head coils were used.

All patients were subjected to the following MRI protocols: Conventional MRI as follow; Pre-contrast axial, coronal and sagittal T1WIs using the following parameters TR 400–550 m/s, TE 15 m/s, FOV 250, matrix 256 x 256, section thickness 3 mm, interslice gap 1 mm and coronal T2-weighted turbo spin-echo (T2 TSE) using the following parameters TR 3500–4800 m/s, TE 110 m/s, FOV 250, matrix 256 x 256, slice thickness 3 mm, interslice gap 1 mm, then post contrast axial, coronal and sagittal T1WIs after IV injection of Gd-DTPA (gadopentetate dimeglumine) 0.1 mm/kg body weight (0.2 ml/kg) were done. Before administration of the contrast material, breath hold DWI was done in axial and coronal planes, with a single-shot spin-echo echo-planner sequence (TR/TE: 2000/33–55, matrix size 128 x 128, section thickness 5 mm, interslice gap 1 mm, FOV 38 cm, b values 0 and 1000 s/mm<sup>2</sup>).

Automatically ADC maps were calculated, and ADC values were estimated by using circumferential ROI (8–50 mm<sup>2</sup>) in the solid central parts of macroadenomas.

**Surgery:** Using the transsphenoidal approach, all patients with macroadenoma underwent surgical excision. At surgery, the neurosurgeon, who didn't know the preoperative DWI data, assessed the tumor consistency according to three categories: soft (easily removable through suction); intermediate and hard (not removable through suction).

**Histopathological diagnosis:** Our diagnosis was assured pathologically after surgical resection.

### STATISTICAL ANALYSIS

Using the Roc curve, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), statistical analysis was done to detect authenticity of ADC in assessment of tumor consistency. Variances between quantitative paired groups were evaluated by paired t test for significance, P value was set at <0.05 for significant outcomes & <0.001 for high significant outcomes.

### RESULTS

In the current study, we include twenty four patients; formed of 10 males and 14 females, their ages ranging from 29 to 42 years old, with a mean age of 34.38 years

According to DWI signal intensity in correlation with the ADC value measured on ADC map, our cases were categorized into three groups of macroadenoma regarding their cellularity & texture (**Table 1**). Soft macroadenoma group (n = 10): they displayed hyperintense signal on DWI with diffusion restriction as a result of high cellular content and showed a mean ADC value of (0.49) x 10<sup>-3</sup> mm<sup>2</sup> /s; ranging from (0.38) x 10<sup>-3</sup> mm<sup>2</sup>/s to (0.60) x 10<sup>-3</sup> mm<sup>2</sup> /s. (**Fig. 1**).

Hard macroadenoma group (n = 9): they were hypointense signal on DWI with unrestricted diffusion because of few cellular content and revealed mean ADC value (0.98) x 10<sup>-3</sup> mm<sup>2</sup>/s; ranging from (0.87) x 10<sup>-3</sup> mm<sup>2</sup>/s to (1.11) x 10<sup>-3</sup> mm<sup>2</sup>/s. (**Fig. 2**). The intermediate group (n= 5): they appeared isointense on DWI and had mean ADC value of (0.80) x 10<sup>-3</sup> mm<sup>2</sup> /s; ranging from (0.64) x 10<sup>-3</sup> mm<sup>2</sup>/s to (0.90) x 10<sup>-3</sup> mm<sup>2</sup> /s. (**Fig. 3**). After the operation and histopathological assessment, there were two false positive findings in two cases of the intermediate adenomas as they assured to be soft macroadenoma by histpathology. Additionally, some interfere between ADC values of intermediate & hard groups were detected (**Table 2**). A significant association between the pituitary macroadenoma consistency and the ADC values was reflected by statistical analysis and this association can be used to predict tumoral consistency (p value < 0.001) at ADC values of 0.61 x 10<sup>-3</sup> mm<sup>2</sup> /s with sensitivity 100%, specificity 83.3% and accuracy 91.5% (**Table 3**).

**Table (1):** This table shows measured ADC values among different pituitary macroadenoma groups:

Variable	Soft (n=10)	Intermediate (n=5)	Hard (n=9)
▪ ADC mean ± SD (x 10 <sup>-3</sup> mm <sup>2</sup> /s)	0.49 ± 0.10	0.80 ± 0.09	0.98±0.09
▪ Range	0.38 - 0.60	0.64 - 0.90	0.87-1.11

**Table (2):** This table shows analysis of pituitary macroadenoma consistency by DWI & ADC against histopathology:

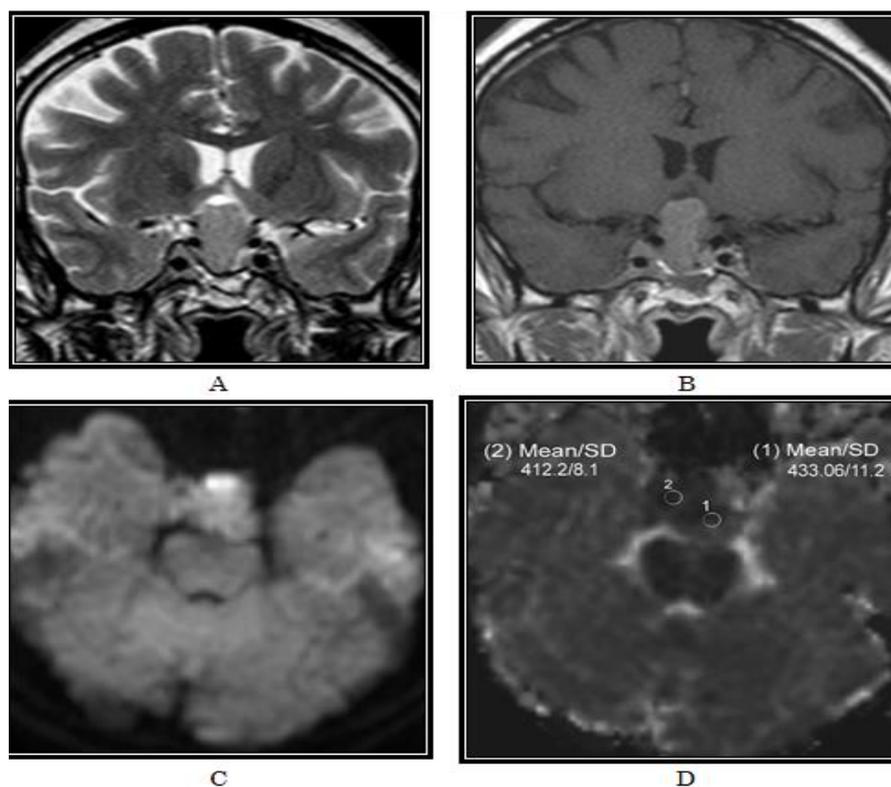
Variable	Soft		Intermediate		Hard		Total	X <sup>2</sup>	P
	N	%	N	%	N	%			
▪ DWI & ADC results	10	41.6%	5	20.8%	9	37.5%	24	24	<0.001**
▪ Histo-pathology	12	50%	3	12.5%	9	37.5%	24		

χ<sup>2</sup>: Chi square test \*\* : Highly significant (p < 0.01)

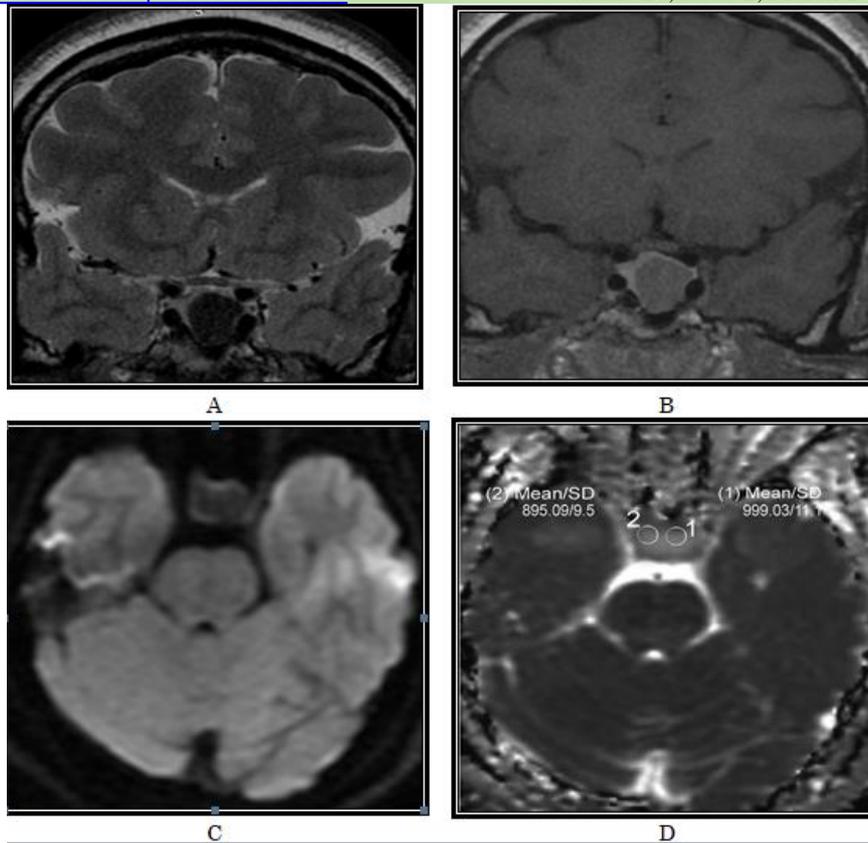
**Table (3):** This table shows validity of ADC in diagnosis of hard and intermediate (irresectable) pituitary macroadenoma from Soft ones (resectable):

ADC	AUC (CI)	P	TP	FP	TN	FN	Sens.	Spec.	PPV	NPV	Accuracy
>0.61	0.99 0.97-1	<0.001 **	12	2	10	0	100	83.3	85.7	100	91.7

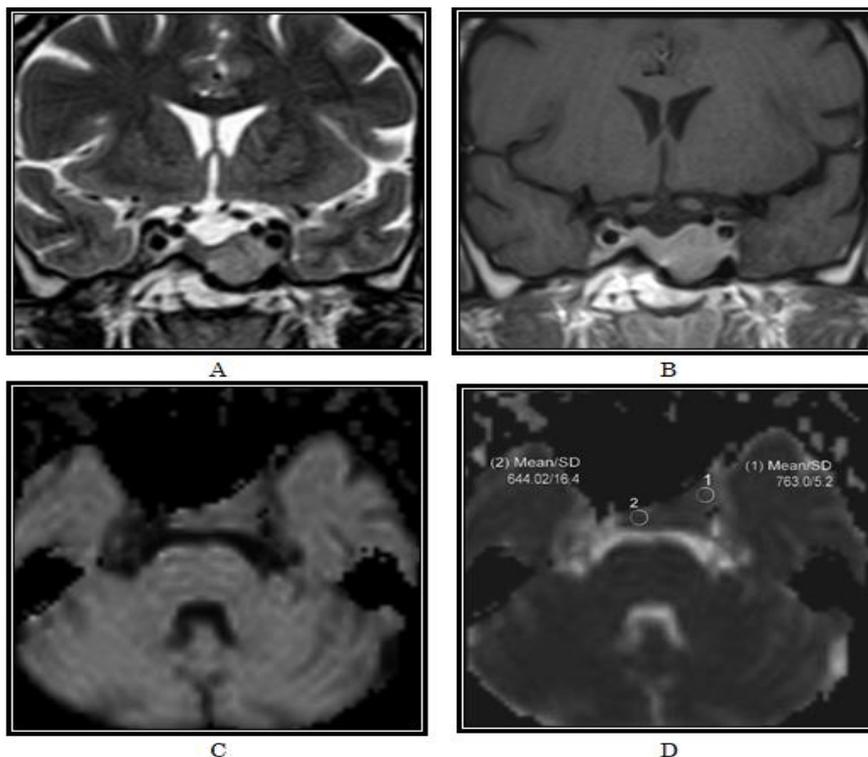
\*\* Highly significant (p<0.01) TP: True positive FP: False positive  
TN: True negative FN: False negative



**Figure (1):** A- Coronal T2WI revealed hyperintense sellar, supra sellar, infra sellar & right para sellar lesion. B- Coronal T1WI Post Gd DTPA revealed homogeneous enhancement of the lesion. C- Axial DWI displayed hyperintensity of the lesion which is consistent with restricted diffusion. D- ADC map revealed hypointensity of the lesion with ADC value  $0.42 \times 10^{-3} \text{ mm}^2/\text{s}$ .



**Figure (2):** A- Coronal T2WI revealed hypointense sellar & supra sellar lesion. B- Coronal T1WI Post Gd DTPA revealed homogeneous enhancement of the lesion. C- Axial DWI displayed hypointensity of the lesion which is consistent with unrestricted diffusion. D- ADC map revealed hyperintensity of the lesion with ADC value  $0.94 \times 10^{-3} \text{ mm}^2 / \text{s}$ .



**Figure (3):** A- Coronal T2WI revealed hyperintense sellar & left para-sellar lesion. B- Coronal T1WI Post Gd DTPA revealed homogeneous enhancement of the lesion. C- Axial DWI displayed isointensity to the brain parenchyma. D- ADC map revealed isointensity of the lesion with ADC value  $0.7 \times 10^{-3} \text{ mm}^2 / \text{s}$ .

## DISCUSSION

Pituitary adenomas are the most prevalent sellar pathology and they are generally considered as benign replication of the anterior lobe cells of the pituitary gland. Regarding the size, adenomas more than 10 mm in diameter are referred to macroadenomas, while lesions less than 10 mm are classified as microadenomas [1,6].

There are two surgical approaches to resect those pituitary adenomas, named trans-sphenoidal endoscopic surgery and trans-craniotomy, but the choice of the surgery partly relay on the consistency of the macroadenomas. Macroadenomas with soft consistency are easy to be curetted by means of suctioning through the trans-sphenoidal endoscopic approach, while the harder ones need the trans-cranial approach [3]. The transsphenoidal endoscopic procedure is less invasive; afford direct accessibility to the tumor with preservation of the residual normal pituitary tissue, providing earlier visual recovery and less visual field errors owing to the limited manipulation of the optic nerves and chiasma. However, macroadenoma consistency is a limitation; where soft one can be aspirated, while a more extensive procedure (transcraniotomy approach) is needed for the fibrous pituitary macroadenomas with hard consistency [7].

The percentage of collagen is the main determinant of the texture of the tumor, as soft macroadenomas are rich in cells with few collagen content while the hard one show few cells, excessive fibrous stroma and high content of collagen [8]. So, assessment of macroadenoma texture preoperatively is critical for neurosurgeons to determine which surgical procedure to use; whether transsphenoidal or transcranial method, which will not only increase the likelihood of full tumor removal, but also reduce recurrence levels [9].

Our study proposes that the consistency of the pituitary macroadenomas can be assessed by DW MR imaging as a prognostic tool of effective transsphenoidal procedure, depending on the correlation between adenomas cellularity and ADC maps where there is an inverted correlation between ADC values & the tumor cellularity; high cellular tumors (soft in consistency) have lower ADC values and those with few cells (firm in consistency) have higher ADC values.

In our study, there were hyperintense and hypointense signal intensities on DWI and ADC map correspondingly in 10 cases, in keeping with restricted diffusion because of the high cellular content the tumor. 9 cases displayed hypointense signal on DWI and hyperintense signal on ADC map that is compatible with unrestricted diffusion due to the low cellular content of the tumor, while

there was a matter of controversy in 5 cases because of their intermediate isointense signal to brain parenchyma on both DWI & ADC map. Also in our study, we found that the mean ADC value of whole cases ( $n = 24$ ) was  $(0.71) \times 10^{-3} \text{ mm}^2/\text{s}$ ; ranging from  $(0.38) \times 10^{-3} \text{ mm}^2/\text{s}$  to  $(1.11) \times 10^{-3} \text{ mm}^2/\text{s}$ . The mean ADC value of cases in accordance with soft macroadenoma ( $n = 10$ ) was  $(0.49) \times 10^{-3} \text{ mm}^2/\text{s}$ ; ranging from  $(0.38) \times 10^{-3} \text{ mm}^2/\text{s}$  to  $(0.60) \times 10^{-3} \text{ mm}^2/\text{s}$  and intermediate macroadenomas ( $n = 5$ ) was  $(0.80) \times 10^{-3} \text{ mm}^2/\text{s}$ ; ranging from  $(0.64) \times 10^{-3} \text{ mm}^2/\text{s}$  to  $(0.90) \times 10^{-3} \text{ mm}^2/\text{s}$  while the mean ADC value of cases consistent with hard macroadenomas ( $n = 9$ ) was  $(0.98) \times 10^{-3} \text{ mm}^2/\text{s}$ ; ranging from  $(0.87) \times 10^{-3} \text{ mm}^2/\text{s}$  to  $(1.11) \times 10^{-3} \text{ mm}^2/\text{s}$ .

Our patients underwent surgery; Soft group was operated well by endoscopic transsphenoidal approach, while the hard and most of intermediate groups weren't totally removable by this method and desired further transcranial surgery. All our joined cases underwent histo-pathological investigation, which categorized macroadenoma regarding its cellularity and collagen content into; Soft (12 cases), intermediate (3 cases) and hard (9 cases). Illuminating the statistical analysis of our DWI & ADC findings with histopathological findings; which exhibited that soft macroadenomas were verified to be 12 cases by histopathology from which DWI & ADC spotted 10 cases only, there were 5 intermediate macroadenomas by DWI & ADC which were proved to be 3 cases only by histopathology and 9 hard macroadenomas were found by both DWI & ADC and histopathology, we reported a shining major association between pituitary macroadenoma consistency and DWI& ADC map signal intensity as well as mean ADC values where P value ( $< 0.001$ ).

Depending on the obvious linkage between macroadenoma consistency and DWI & ADC, ADC cut off value of  $0.61 \times 10^{-3} \text{ mm}^2/\text{s}$  was considered to discriminate tumors that can be aspirated (Soft consistency) from the irresectable ones (intermediate and hard consistency) with sensitivity 100 %, specificity 83.3% , accuracy 91.7 % , PPV 85.7% and NPV 100%.

Although there was a definite cut off value, the minor changes in the fixed values using standard deviations has its impact on our results as the intermediate consistency cases were 5 cases based on ADC value measurements with a range between  $(0.64) \times 10^{-3} \text{ mm}^2/\text{s}$  to  $(0.90) \times 10^{-3} \text{ mm}^2/\text{s}$  and a mean ADC value equals  $(0.80) \times 10^{-3} \text{ mm}^2/\text{s}$  while on histopathology, 3 cases were proved to be of intermediate consistency as two cases were soft, one case was hard and on the other hand one case from the hard was proved to be intermediate, so

this group was controversy in surgical planning but we considered if the ADC values into different tumoral locations were near to the value of soft consistency, so it will be amenable for endoscopy. While if the ADC values approaching that of the hard one so it is not accessible for endoscopic section. Our study was in agreement with the study reported by Mohamed and Abouhashem. [4] considering a linear relationship between ADC values and tumors consistency from soft to the harder side; soft tumors exhibit low ADC values and the hard ones exhibit high ADC values as well as they suggest a cut off value of  $0.6 \times 10^{-3} \text{ mm}^2/\text{sec}$  to discriminate macroadenomas that are liable to be aspirated from the others.

Also, our study was broadly consistent with Mohamed and Abouhashem. [4] who found that the soft macroadenomas mean ADC value was  $0.482 \times 10^{-3} \text{ mm}^2/\text{s}$ ; in the intermediate category was  $0.730 \times 10^{-3} \text{ mm}^2/\text{s}$ ; and in the hard category was  $0.992 \times 10^{-3} \text{ mm}^2/\text{s}$ . Statistical analysis revealed a major association between DWI signal intensity, ADC values, tumor consistency & the proportion of the collagen content with sensitivity 100%, specificity 88. However, they showed interfere between soft and intermediate groups and we found overlap between intermediate and hard groups.

As well, Alashwah et al. [2], showed in a study carried out on twenty cases with pituitary macroadenoma that the mean value of ADC in the soft group was  $0.54 \times 10^{-3} \text{ mm}^2/\text{s}$ ; in the intermediate group was  $0.82 \times 10^{-3} \text{ mm}^2/\text{s}$ ; and in the hard group was  $1.11 \times 10^{-3} \text{ mm}^2/\text{s}$  and suggested cut off value  $1.0 \times 10^{-3} \text{ mm}^2/\text{s}$  to discriminate macroadenomas that can be aspirated. Pierallini et al. [10], stated that the mean value of ADC in the soft macroadenomas was  $0.663 \pm 0.109 \times 10^{-3} \text{ mm}^2/\text{s}$ ; in the intermediate tumors was  $0.842 \pm 0.081 \times 10^{-3} \text{ mm}^2/\text{s}$ ; and in the hard tumors was  $1.363 \pm 0.259 \times 10^{-3} \text{ mm}^2/\text{s}$ .

A significant association between tumor consistency and ADC values, DWI signal intensity and the ratio of the collagen ( $p < 0.001$ , analysis of variance) was revealed by statistical analysis. They found in their study that the ADC value of  $1.0 \times 10^{-3} \text{ mm}^2/\text{s}$  was the cut off value to discriminate soft tumors liable for suctioning from hard ones.

Our results have been found consistent with Pierallini et al., and Alashwah et al. [10, 2], who found that there is a significant correlation between the tumor consistency and the ADC values with recommendation of using DW MR images to afford details about the tumor consistency, but there is dissimilarity in the cut off value between our study and theirs, that may be due to the sample size variance. We were in conflict with the results

of the study of Suzuki et al. [11], where cases at their study were limited to soft and intermediate consistencies, with no encountered cases of hard macroadenoma and the mean ADC of the intermediate consistency was found faintly lower than that of the soft tumors, but the between group ADCs were not considerably different. Suzuki et al. [11] reported that two tumors (one soft and one intermediate) that had ADC values greater than  $1.0 \times 10^{-3} \text{ mm}^2/\text{s}$  were found.

These disparities between the findings can be related to consuming altered DWI techniques and limited sample size in their study, which was restricted to soft and intermediate consistencies.

## CONCLUSION

In our study, we established that as a routine of the preoperative assessment of the macroadenoma, DWI associated with ADC value should be used to guarantee the most convenient surgical approach and we advise a cut off value of  $0.61 \times 10^{-3} \text{ mm}^2/\text{s}$ , for accurate discrimination of the soft macroadenomas from intermediate/hard adenomas.

**Conflict of interest:** None

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