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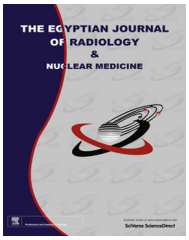

ORIGINAL ARTICLE

Diagnostic value of apparent diffusion coefficient (ADC) in assessment of pituitary macroadenoma consistency

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KEYWORDS

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Abstract *Background:* Pre-operative assessment of macroadenoma consistency is helpful for proper surgical planning. DWI correlated with ADC value adding information about the tumor consistency that cannot be obtained with cMRI.

Patients and methods: Thirty patients with pituitary adenomas were examined by MRI including cMRI (conventional magnetic resonance) and DWI (diffusion weighted imaging) with ADC value measurement. Diagnosis was correlated with intra-operative finding and histopathology.

Results: According to ADC values, we classified our cases into three groups of macroadenoma consistency; Group A (Soft tumors = 22/30) had mean ADC value of 0.482×10^{-3} mm^2/s, Group B (intermediate consistency = 5/30) had mean ADC value of 0.730×10^{-3} mm^2/s and Group C (Firm adenomas = 3/30) with mean ADC value of 0.992×10^{-3} mm^2/s. Diagnostic overlap was detected in one case of group A and 2 cases of group B. The sensitivity, specificity, PPV, NPD and accuracy of ADC values were 80%, 88%, 57.1% and 95.7% at ADC 0.7×10^{-3} mm^2/s and 100%, 88%, 62.5% and 100% at ADC 0.6×10^{-3} mm^2/s respectively.

Conclusion: DWI that correlated with ADC value should be included in routine pre-operative assessment of macroadenoma consistency. We recommend a cut off value of 0.6×10^{-3} mm^2/s, for accurate discrimination of the intermediate/soft macroadenomas from firm adenomas.

1. Introduction

Pituitary adenomas are the most common sellar space occupying lesion and are generally regarded as benign proliferations of cells of the anterior lobe of the pituitary gland. However, some pituitary adenomas demonstrate more aggressive behavior and this affects the success of treatment and disease prognosis (1).

The clinical presentation and classification depend primarily on whether they are functioning (secretory) or

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non-functioning (non secretory). From radiologic perspective, it is best to classify adenomas on the basis of size, those under 1 cm in diameter being considered microadenomas and those greater than 1 cm being considered macroadenomas (1,2).

Macroadenomas are more likely to be nonfunctioning than functioning probably because a lack of hormone-mediated signs and symptoms leads to a relatively late diagnosis. Because they remain clinically silent from a hormonal perspective, the first signs and symptoms produced by nonfunctioning macroadenomas are related to mass effect (e.g., headache and/or visual field defects). By definition, macroadenomas usually extend beyond the sella, and remodeling with enlargement of the sella is almost invariably present (3). The most common pattern is suprasellar extension, in which case the adenoma usually has a polycyclic shape (4).

DWI can provide information about the consistency of macroadenomas that cannot be reliably obtained with conventional MR techniques. Because addition of DW MR imaging to the examination does not change the examination time substantially, it is now suggested that DWI should become part of the routine pre-operative examination of patients with macroadenomas. Pre-operative detection of hard and highly fibrous tumors is important for the planning of the surgical approach and for avoidance of multistage surgical procedures (5–7).

Tumor cellularity and tumor grade have been correlated with ADC values from the ADC maps (The ADC value is inversely proportional to the tumor cellularity). Primary brain tumors with higher cellularity or higher grades typically have lower ADC values with normal brain tissues (8).

In the past decade, surgical treatment of pituitary tumors was performed by using either the direct endonasal trans-sphenoidal approach or trans-septal trans-sphenoidal approach. Both techniques required extensive mucosal dissection and led to long term patient discomfort and rhinologic complications (9). Recently, the endoscopic trans-sphenoidal technique has been applied as a minimally invasive surgical procedure to remove pituitary tumors. An advantage of this technique, compared with the trans-sphenoidal technique, is that postoperative nasal problems may be avoided (10).

Not all macroadenomas are amenable to resection with the trans-sphenoidal endoscopic technique. In cases in which a trans-nasal approach is contraindicated, such as cases of sphenoid sinusitis or ecstatic midline (“Kissing”) carotid arteries, a trans-cranial approach may be warranted. Some patients who harbor pituitary macroadenomas with significant lateral suprasellar extension that cannot be adequately removed trans-sphenoidally may benefit from a trans-cranial approach (11).

Furthermore, the main limitation of the endoscopic trans-sphenoidal technique, as is the limitation of traditional trans-sphenoidal techniques, may be tumor consistency. Most macroadenomas are soft and easily resectable, whereas about 10% of large pituitary tumors may be fibrous and exhibit increased consistency. Macroadenomas with hard components cannot be successfully removed with the endoscopic technique and may require a more extensive trans-sphenoidal approach (12).

2. Patients and methods

The study was carried out in the time frame between February 2011 and March 2013, included 30 patients (16 females and 14 males), their age ranged between 16 and 54 years, they were referred from Neurology and Neurosurgery Departments to MR unit, Radiology Department, Zagazig University. All our patients were suspected to have pituitary adenoma on clinical basis, except six cases that were previously diagnosed with macroadenoma and referred for post-treatment follow-up.

Our study protocol was explained to our patients and informed consent was obtained.

2.1. Imaging sequences

1- Conventional MRI (cMRI) with a 1.5 T clinical imager (Philips Achieva class IIa Medical System) equipped with a standard head coil. The following protocol was used:
   - Non contrast axial, coronal and sagittal T1WIs (TR 400–550 m/s, TE 15 m/s, FOV 250, matrix 256×256, section thickness 3 mm, interslice gap 1 mm).
   - Axial T2WI (TR 3500–4800 m/s, TE 110 m/s, FOV 250, matrix 256×256, slice thickness 3 mm, interslice gap 1 mm).
   - Post contrast coronal and sagittal T1WI after administration of gadolinium 0.1 mm/kg body weight.
2- Prior to contrast agent administration, breath hold DWI was done with a single-shot spin-echo echo-planner sequence (TR/TE: 2000/33–55, matrix size 128×128, section thickness 6 mm, interslice gap 1 mm, FOV 38 cm, b values 0 and 1000 s/mm^2).
3- ADC maps were calculated automatically and ADC values were measured by using circumferential ROI (8–50 mm^2) in the central and solid appearing portion of macroadenomas.

2.2. Operative data

All patients had been treated in the Neurosurgery Department using the endoscopic trans-sphenoidal approach in 12 cases while the trans-cranial approach has been used in 18 cases as well as all recurrent cases and in cases with small sphenoid sinuses or in cases with para-sellar extension.

The consistency of the tumor has been evaluated by the surgeon as soft tumor which was easily succable without the need for dissection and as firm type which was not succable at all and removed by the peace meal technique using the pituitary forceps while there was an intermediate type which has been removed by dissection and ring curette.

2.3. Histopathological diagnosis

Our diagnosis was confirmed pathologically after surgical treatment.

2.4. Statistical analysis

It was performed by using the Roc curve, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) to detect validity of ADC in assessment of tumor consistency.

A difference with a threshold P value of < 0.001 was considered statistically significant.

3. Results

Pituitary macroadenoma was detected in different age groups. The most common age group was 20 to <40 years in 17 patients (56.6%) (Table 1). The most frequent clinical presentation was headache with or without visual disturbances as seen in 19 out of 30 cases (63%) while the 2nd common complaint was headache and recurrent resistant vomiting in 6 cases (20%) (Table 2).

Hormonal Status was evaluated in all cases. The hormonal profile was abnormal in 18 cases (Table 3), included hypopituitarism in six cases, elevated prolactin in eight cases, elevated growth hormone in three cases and low growth hormone level in one case.

Conventional MR imaging revealed 26 cases with hypointense signal and four cases with hyperintense signal relative to the adjacent temporal lobe gray matter on T1WI while on T2WI, isointense signal to gray matter was detected in two cases, hypointense signal in 18 cases and heterogeneous hyperintense signal in 10 cases. Cystic degeneration was detected in seven cases while hemorrhage was found in two cases. On post Gd DTPA images, 22/30 cases exhibited intense homogeneous enhancement while heterogeneous enhancement was detected in 8/30 cases (Table 4).

Hypointensity of pituitary tumors on T2WI (18/30) correlates with high cellularity, but it is not specific for accurate assessment of tumoral cellularity.

Table 1 Age and sex distribution of the 30 studied cases.

Age group	Number	Male	Female
0 to <20	4	4	–
20 to <40	17	6	11
40 to <60	9	4	5
Total	30	14	16

Table 2 Main clinical presentations in the 30 studied cases.

Clinical presentation	No. of patients	Percent (%)
Headache (severe ± persistent) with visual disturbances	19	63.3
Headache with recurrent resistant vomiting	6	20
Isolated bilateral visual disturbance	2	6.6
Gigantism	1	3.3
Acromegaly	2	6.6

Table 3 Other clinical and laboratory findings in the 30 studied cases.

Clinical or Lab findings	No. of patients	Percent (%)
Obesity (BMI > 20)	6	20
Hypertension	8	26.6
Diabetes mellitus	5	16.6
Diabetes insipidus	1	3.3
Disturbed pituitary hormonal profile	18	60
Vision loss & squint	1	3.3
Amenorrhea	2	6.6

On diffusion imaging, the signal intensity was hyperintense and hypointense on DWI and ADC map respectively in 22 cases which is consistent with restricted diffusion as a result of high tumoral cellularity, while five cases revealed hyperintense signal on DWI and less hypointense signal on ADC map compared to the hypointensity seen in group A. Three cases displayed hypo- to isointense signal on DWI and high signal intensity on ADC map denoting unrestricted diffusion, subsequent to low tumoral cellularity.

The signal intensity on DWI was correlated with ADC value measured on ADC map, according to these values we classified our cases into three groups of macroadenoma cellularity (Table 5).

- *Group A (Soft pituitary tumors = 22/30):* they are hyperintense on DWI showing restricted diffusion as a result of high cellularity and exhibited a mean ADC value of 0.482×10^{-3} mm^2/s. (Fig. 1).
- *Group B (macroadenomas with intermediate consistency = 5/30):* they are hyperintense on DWI and had mean ADC value of 0.730×10^{-3} mm^2/s. (Fig. 2).
- *Group C (Firm adenomas = 3/30):* they displayed hypointense signal on DWI which is consistent with unrestricted diffusion due to low cellularity and had mean ADC value of $.0.992 \times 10^{-3}$ mm^2/s. (Fig. 3).
- After surgical resection and histopathological analysis, we found false positive finding in one case of the soft group as its ADC value revealed high cellularity and restricted diffusion while it was proved to be firm macroadenoma on histpathological analysis. Additionally,

Table 4 cMRI findings in the 30 cases of pituitary macroadenoma.

MR findings	No. of cases
Borders:	
Well defined	19
Ill defined	11
Intensity:	
T1-WIs	
Isointense	–
Hypointense	26
Hyperintense	-4
T2-WI	
Isointense	2
Hypointense	18
Hyperintense	10
Contrast enhancement:	
No enhancement	–
Enhancement	
Marginal	–
Homogeneous	22
Heterogeneous	8
Mass effect:	
Third ventricle	6
Optic chiasma	11
Other findings:	
Hydrocephalus	6
Calcification	3
Cystic changes	7
Hemorrhage	2

Table 5 Findings of the DWI & ADC map in the 30 cases.

Group	No	DWI (b1000)	ADC map	ADC mean ($\times 10^{-3}$ mm^2/s)
A	22	Hyperintense	Hypointense	0.482
B	5	Hyperintense	Slightly hypointense	0.730
C	3	Hypointense-Isointense	Hyperintense	0.992

ADC value was calculated in comparison to ADC value in normal white matter of temporal lobe which is $0.93 \pm 0.31 \times 10^{-3}$ mm^2/s.

Table 6 Validity of ADC value in diagnosis of pituitary macroadenoma consistency at ADC = 0.7×10^{-3} mm^2/s.

	Pathology		Total
ADC 0.7	Hard 4	Soft/intermediate 3	7
	57.1%	42.9%	100%
	80.0%	12.0%	23.3%
	1	22	23
	4.3%	95.7%	100.0%
	20.0%	88.0%	76.7%
	5	25	30
Total	16.7%	83.3%	100.0%
	100.0%	100.0%	100.0%

Sensitivity = 80%, Specificity = 88%, PPV = 57.1%, NPV = 95.7%, Kappa value = 0.586 and P value < 0.001

false positive ADC diagnosis was detected in two cases of the intermediate consistency group, one of them was considered soft and the other one was firm on histopathological finding.

3.1. Statistical analysis

Roc curve was done (Fig. 4), area under the curve was 0.97 (0.92–1.03).

- Statistical analysis revealed a significant correlation between the pituitary macroadenoma consistency and the ADC values which can assess tumoral consistency (p value < 0.001) at ADC values of 0.6 and

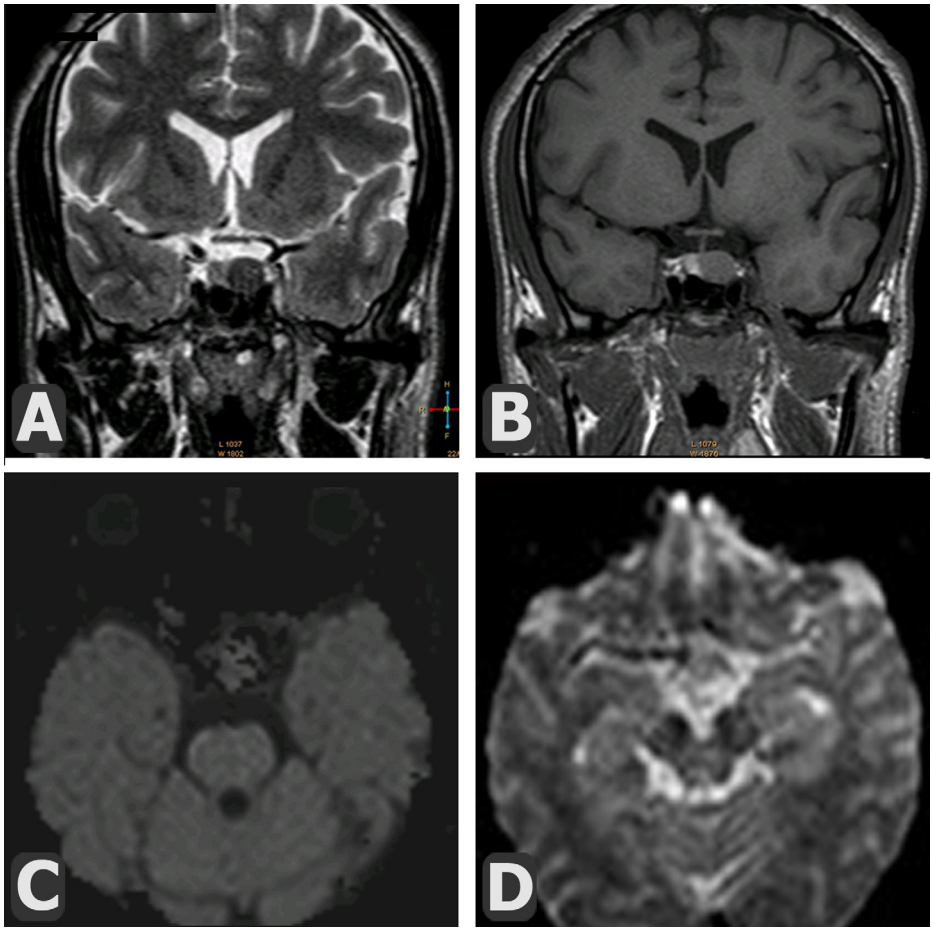

Figure 1 A- Coronal T2WI revealed hypointense sellar lesion. B- Coronal T1WI Post Gd DTPA revealed homogeneous enhancement of the sellar lesion. C- Axial DWI displayed hyperintensity of the lesion which is consistent with restricted diffusion. D- ADC map revealed hypointensity of the lesion with ADC value: 0.49×10^{-3} mm^2/s.

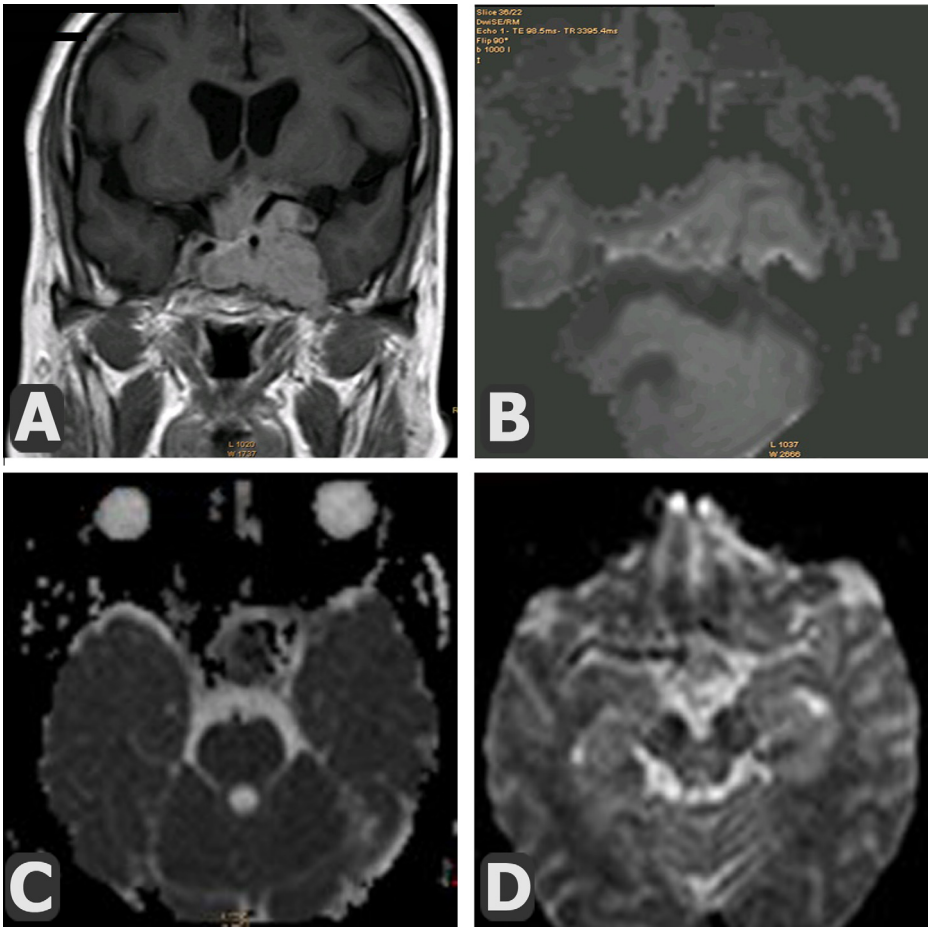

Figure 2 A- T1WI Coronal post Gd DTPA revealed homogeneously enhanced sellar lesion with supra- and para-sellar extension, more on the left side. B- Axial DWI revealed relative hyperintensity of the lesion. C&D- Axial ADC map showed hypointensity of the lesion with ADC value 0.66×10^{-3} mm^2/s.

0.7×10^{-3} mm^2/s. Higher sensitivity and specificity were detected at 0.6×10^{-3} mm^2/s as seen in Table 6 and Table 7.

- We found a cutoff value of ADC that separates between high/intermediate tumoral cellularity from one side and low cellularity macroadenomas (Firm fibrous type) which was 0.6×10^{-3} mm^2/s which provided high sensitivity and specificity in diagnosis. Macroadenomas with high ADC value above this value should be considered firm adenomas with low cellularity and low collagen content which are accessible by endoscopic procedure, while those with ADC value at or below this cut off value were considered soft to intermediate adenomas with the lowest ADC values in the soft tumors that were easily to be suctioned during surgery as conformed by histopathological findings (Table 8).

4. Discussion

Radiological imaging of the pituitary gland and parasellar region is challenging because the pituitary gland is a very small organ near many important structures. Magnetic resonance imaging (MRI) is the modality of choice; it provides multiplanar high-contrast images of the pituitary gland and adjacent structures (13). Typical MRI protocols used for the evaluation of sellar masses include pre- and post-gadolinium-enhanced T1-weighted and T2-weighted coronal and sagittal sequences with a section thickness of 3 mm or less. However, it can be very difficult to distinguish between the sellar and parasellar tumors even with high-field MRI. DWI provides information on water mobility or diffusion within tissues by demonstrating Brownian motion in those tissues (14).

Knowledge of the consistency of macroadenoma may help the clinician to plan the proper surgical technique before the procedure; thus, the clinician can avoid conversion from an endoscopic to a full trans-sphenoidal technique during the procedure. This strategy may prove to be cost effective and psychologically valuable for both the patient and the neurosurgeon (15).

Tumor characterization with DW MR images and ADC maps has a direct relationship with tumor respectability with minimally invasive surgical techniques. Pre-operative detection of hard and highly fibrous tumors is important for the planning of the surgical approach and for avoidance of multistage surgical procedure (15).

The MRI signal characteristics of macroadenomas are quite variable. They may be homogeneous or heterogeneous and can have cystic components, but generally are hypointense relative

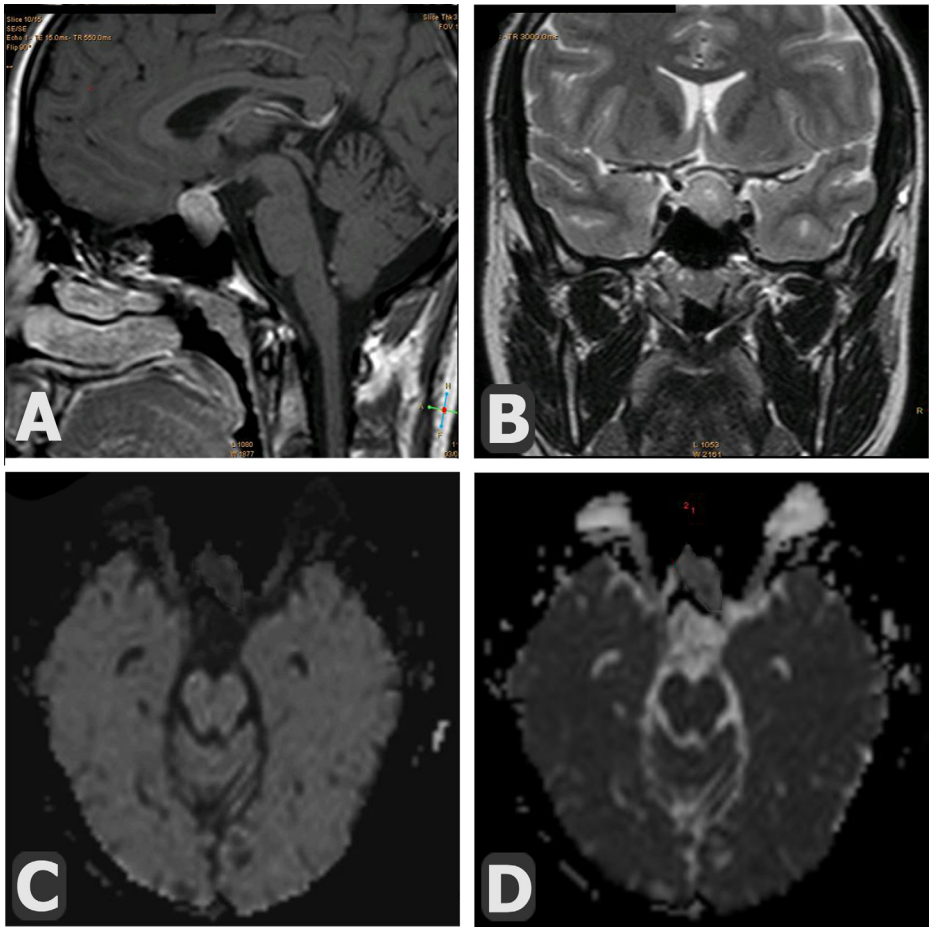

Figure 3 A- Post Gd DTPA sagittal T1WI revealed intense homogeneous enhancement of sellar lesion with supra-sellar extension. B- Coronal T2WI revealed relatively hyperintense sellar and supra-sellar lesion. C & D- DWI and ADC map revealed isointensity of the lesion to CSF denoting unrestricted diffusion with ADC value 1.1×10^{-3} mm^2/s.

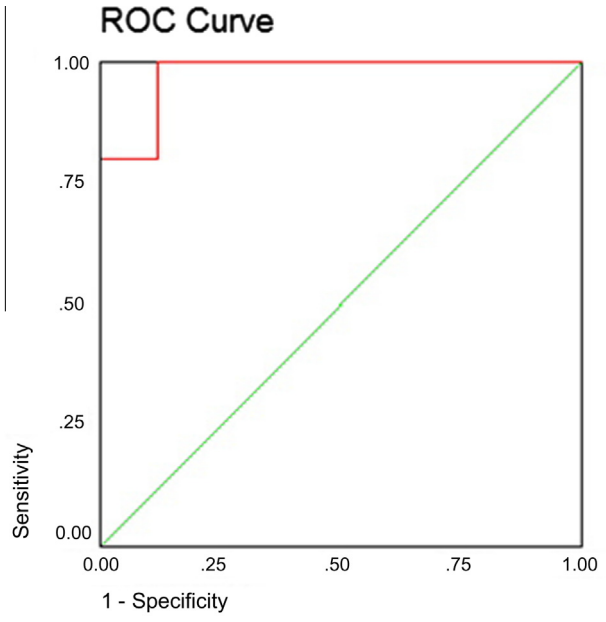

Figure 4 Roc curve.

to normal pituitary tissue on both non enhanced and enhanced T1-weighted images and are relatively hyperintense on T2-weighted images. DWI with apparent diffusion coefficient (ADC) maps can provide information about the consistency of macroadenomas. Relatively lower ADC values have been correlated with softer tumor consistency at surgery and higher cellularity at pathology (15).

DW MR imaging allows the measurement of tissue water diffusion, which is affected by the size and integrity of structures that normally restrict diffusion. The ADC can be increased as a result of pathologic processes that modify tissue integrity and thus these processes reduce 'restricting' barriers (5).

In our study, we examined 30 cases of macroadenoma (24 primary and 6 residual cases) by cMRI and DWI with ADC value calculation for prediction of the macroadenoma consistency. We found that hypointense signal on T2WI cannot accurately predict tumoral cellularity as seen in 18/30 cases in disagreement with Pierallini et al., 2006 (15), who found a correlation between tumor consistency and the signal intensity on T2WI and soft tumors displayed a lower SI than did intermediate and hard tumors. Inverse correlation between the SI on T2WI and the percentage of collagen in macroadenoma was concluded by Luchi et al., 1998 (16).

Table 7 Validity of ADC value in diagnosis of pituitary macroadenoma consistency at ADC = 0.6×10^{-3} mm^2/s.

	Pathology		Total
ADC.64	Hard	Soft/intermediate	8
	5	3	
	62.5%	37.5%	100.0%
	100.0%	12.0%	26.7%
	–	22	22
	–	100.0%	100.0%
	–	88.0%	73.3%
	5	25	30
Total	16.7%	83.3%	100.0%
	100.0%	100.0%	100.0%

Sensitivity = 100%, Specificity = 88%, PPV = 62.5%, NPV = 100%, Kappa value = 0.710 and P value < 0.001.

Table 8 Mean value of ADC in the three groups of macroadenoma consistency after histopathological analysis.

Pathology	N	Mean	Std. deviation
Hard	5	0.9920	0.2535
Intermediate	3	0.7300	0.1015
Soft	22	0.4820	0.1433
Total	30	0.5918	0.2513

Pierallini et al., 2006, (15), stated that the mean value of ADC in the soft group was $0.663 \pm 0.109 \times 10^{-3}$ mm^2/s; in the intermediate group was $0.842 \pm 0.081 \times 10^{-3}$ mm^2/s; and in the hard group was $1.363 \pm 0.259 \times 10^{-3}$ mm^2/s. Statistical analysis revealed a significant correlation between tumor consistency and ADC values, DW image SI, T2WI SI ratios and the percentage of collagen content ($p < .001$, analysis of variance).

Mahmoud et al. 2009 (17), studied 24 cases of macroadenoma by propeller DWI and calculated their ADC as minimum (MIN), mean and maximum (MAX). Lesions appeared hyperintense ($n = 9$), isointense ($n = 8$), hypointense ($n = 2$), and as mixed intensity ($n = 5$). ADC MIN, ADC MEAN, and ADC-MAX values were 0.953 ± 0.181 (range 0.717–1.37), 1.08 ± 0.190 (range 0.787–1.50), and 1.20 ± 0.205 (range $0.911–1.67) \times 10 - 3$ mm^2/s, respectively.

In our study, the signal intensity of macroadenoma on DWI was correlated to the ADC value obtained from the 30 cases. We found that the majority of our cases (Group A 22/30 = 70.4%) are pituitary tumors with soft consistency that displayed hyperintense signal on DWI and had low ADC values and the lowest mean ADC value (mean = 0.482×10^{-3} mm^2/s) among the three groups. Slightly higher ADC values were detected in group B (5/30 = 16.1%) with intermediate consistency adenomas with mean ADC value of 0.730×10^{-3} mm^2/s which is considered higher than in group A, but some overlapping between the two groups were encountered. Higher ADC values were detected in group C adenomas (3/30 = 13.5%) that displayed hypointense signal on DWI and had mean ADC value of 0.992×10^{-3} mm^2/s denoting low cellularity and low collagen content.

Our results are consistent with Pierallini et al., 2006 (15), regarding the correlation of ADC values and the tumor consistency, who found their results indicate that DW MR images can provide information about the consistency of macroadenoma that cannot be reliably obtained with conventional MR techniques and tumor characterization with DWI and ADC maps has a direct relationship with tumor respectability with minimally invasive surgical techniques.

Our findings were supported after surgical management and histopathological correlation, but we found that false positive finding in one of the soft groups which was proved to be firm adenoma on pathology and false positive diagnosis in two cases of the intermediate group, one of them was proved to be soft and the other was firm on histopathology.

After statistical analysis, we found that ADC value measurement had a high sensitivity and specificity in assessing the pituitary macroadenoma consistency ($P = < 0.001$) with a significant correlation between the adenoma consistency and the detected ADC values. We found sensitivity, specificity, PPV and NPV of 80%, 88%, 57.1%, 95.7% respectively at 0.7×10^{-3} mm^2/s ADC value and 100%, 88%, 62.5%, and 100% respectively at 0.6×10^{-3} mm^2/s, but some overlapping in ADC values was detected as seen in one case of group A and two cases of group B.

Pierallini et al., (15), stated that the small number of hard tumors in their series did not allow a formal estimation of the most accurate cutoff value for the ADC. In consideration of the correlation between tumor consistency and ADC and the small overlap between ADC values for the hard and soft or intermediate groups, however, a cutoff value of 1 mm^2/s could be considered for differentiation of tumors amenable to aspiration.

In our study, we found a cutoff ADC value with higher sensitivity and specificity in differentiating the soft versus intermediate consistency adenoma types from firm adenoma from which was 0.6×10^{-3} mm^2/s. This value confidently detected the soft/intermediate consistency adenoma which showed low ADC values with the lowest ADC value in the soft consistency group due to high cellularity allowing them liable for endoscopic suction.

The difference in the cutoff value between our study and the study made by Pierallini et al., (15) may be related to the difference in the sample size.

5. Conclusion

DWI that correlated with ADC value should be a part of the routine pre-operative assessment of macroadenoma consistency to ensure proper planning of the surgical approach and we recommend a cut off value of 0.6×10^{-3} mm^2/s, for accurate discrimination of the intermediate/soft macroadenomas from firm adenomas.

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