Neurosurgical Review (2021) 44:2933–2941
https://doi.org/10.1007/s10143-020-01469-y

ORIGINAL ARTICLE

Diffusion-weighted imaging for predicting tumor consistency and extent of resection in patients with pituitary adenoma

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Received: 5 August 2020 / Revised: 4 December 2020 / Accepted: 28 December 2020 / Published online: 28 January 2021

Abstract

This study aimed to investigate the role of diffusion-weighted imaging (DWI) in predicting tumor consistency, extent of surgical resection, and recurrence in pituitary adenoma (PA). We reviewed a prospectively collected database of surgically treated PA between March 2016 and October 2017. Predictors for extent of resection and recurrence/progression were assessed with logistic and Cox regression analysis. Of the 183 patients, the tumor consistency was found soft in 107 (58.5%) patients, intermediate in 41 (22.4%) patients, and hard in 35 (19.1%) patients. The mean of ADC ratio was 0.92 ± 0.22 for hard tumor, 1.03 ± 0.22 for intermediate tumor, and 1.41 ± 0.62 for soft tumor ($P < 0.001$). The mean collagen content was 25.86% ± 15.00% for hard tumor, 16.05% ± 9.90% for intermediate tumor, and 5.00% ± 6.00% for soft tumor ($P < 0.001$). Spearman analysis showed a significant correlation between ADC ratio and collagen content ($\rho = -0.367$; $P < 0.001$). Gross-total resection (GTR) was obtained in 68.3% of patients, and multivariable logistic regression analysis showed that ADC ratio (OR, 12.135; 95% CI, 4.001–36.804; $P < 0.001$), giant PA (OR, 0.233; 95% CI, 0.105–0.520; $P < 0.001$), and invasion (OR, 0.459; 95% CI, 0.220–0.960; $P = 0.039$) were significantly predictive of GTR. Twenty-seven (14.8%) patients suffered recurrence/progression in the mean follow-up of 35.14 months. Invasion (HR, 2.728; 95% CI, 1.262–5.899; $P = 0.011$) was identified as independent predictors of recurrence/progression. ADC ratio of DWI could be used for preoperative assessment of tumor consistency, tumor collagen content, and extent of surgical resection, which might be useful in preoperative planning for patients with PA.

Keywords Pituitary adenoma · Diffusion-weighted imaging · Tumor consistency · Extent of resection · Recurrence

Introduction

Pituitary adenoma (PA) is the third most common intracranial tumor, and the overall prevalence in general population was 16.7% [2]. Transsphenoidal endonasal surgery is preferred treatment in most patients with PA [13, 38]. Some factors that determine the extent of tumor resection included tumor size, invasion of cavernous sinus (CS), and tumor consistency [3, 16, 20]. Fibrous tumor cannot be easily and sufficiently debulked by curettage and suction via this approach, and second-stage operation, transcranial surgery, or postoperative radiosurgery are often required [1]. Therefore, assessment of tumor consistency would help the clinicians to choose the best therapeutic strategies for patients with PA.

Diffusion-weighted imaging (DWI) in magnetic resonance imaging (MRI) provides information on tissue water diffusion, which is affected by the size and integrity of structures in the brain that normally restrict diffusion. In diffusion MRI, powerful magnetic gradients with echo planar sequence are used. This enables images that are dependent on water diffusion. A diffusion coefficient called apparent diffusion coefficient (ADC) value can be calculated, and ADC maps can be generated [14, 17, 23, 24, 30]. Several studies have reported DWI could be used to evaluate the tumor consistency [3, 4, 19, 26, 28, 32, 35, 36]. However, the relationship between apparent diffusion coefficient (ADC) value and tumor consistency remains uncertain because susceptibility artifacts would

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occur in the sellar region. Moreover, the ADC value used in predicting extent of resection and clinical outcomes was scarcely reported.

In this study, we prospectively collected the clinical, radiological, and histopathological data of patients with PA to discuss the role of DWI in preoperative evaluation of tumor consistency, extent of surgical resection, and recurrence.

Methods

Study design

The study protocol was approved by the Institutional Review Board of Xiangya Hospital. Written informed consent is obtained from all participants at admission. We reviewed a prospectively collected database of PA between March 2016 and October 2017 with the inclusion criteria as follows: (1) PA was diagnosis based on pathology and (2) patients were treated with transsphenoidal endoscopic endonasal surgery or transcranial surgery. Patients who received prior medical therapy, surgery, or radiosurgery were excluded. Recurrent PA, pituitary apoplexy, cystic pituitary adenoma, and microadenoma were also excluded.

Radiologic evaluation

All patients underwent magnetic resonance imaging (MRI) before surgery, within 3 days postoperatively, 3 months postoperatively, and then at yearly intervals thereafter. MRI was performed using Signa excite 3.0T system (GE Medical Systems, Systems, Milwaukee, WI) including the following sequences: T1-weighted image with and without contrast, T2-weighted image, diffusion-weighted imaging (DWI) used for tumor consistency, and perfusion-weighted imaging (PWI) used for tumor blood supply [9]. Two experienced neuroradiologists (Gaofeng Zhou and Lang Li) who were blinded to clinical data evaluated MRI separately and resolved disagreement by consensus.

The SS-SE-EPI-DWI scan was acquired with a *b* value of 1000 using the following parameters: repetition time (TR) 5600 ms, echo time (TE) 76 ms, one excitation, matrix size 160 × 160 mm, field of view (FOV) 24 × 24 cm, bandwidth 250 Hz/pixel, thickness 4 mm, and intersection gap 1 mm. The parameters of GRE-PWI scan were as follows: TR1600ms, TE 25 ms, FOV 24 × 24 cm, flip angle (FA) 90, matrix 128 × 128, bandwidth 250 Hz/pixel, thickness 4 mm, and intersection gap 1 mm. MRI data were transferred to a workstation (Advantage Workstation, AW4.2, GE Medical Systems), and the ADC was calculated with the Functool software (GE Medical Systems). Regions of interest (ROI) were placed on the solid parts of pituitary adenomas avoiding cystic or calcified areas and normal brainstem to measure the ADC value on the ADC maps. ROI were placed on tumor and normal frontal white matter to measure values for four parameters, which included cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), and time to peak (TTP). The neuroradiologist drew ROI of uniform shape and size (elliptic, 50 mm^2) for three times and collected the mean value for final data. The ADC ratio was calculated as the ratio between mean ADC value in the tumor and that in the normal brainstem. The CBF ratio was calculated as the ratio between mean CBF value in the tumor and that in the normal frontal white matter.

Tumor size was measured according to maximal tumor diameter in the coronal plane of MRI, and giant adenoma was defined as tumor size over 40 mm. Invasion of the cavernous sinus was considered significant for grades III–IV on the Knosp classification [11, 18]. Sphenoid sinus invasion was defined as tumor growing into the sphenoid sinus confirmed on preoperative MRI or surgery. An invasive PA was considered in tumors with cavernous sinus or sphenoid sinus invasion [21]. The extent of resection was evaluated by comparing MRI before surgery with that within 3 days postoperatively and 3 months after surgery [7, 8, 16]. The extent of resection was categorized, according to the amount of tumor removed, as partial (< 50% volume removed), subtotal (50–80% volume removed), near-total resection (80–99% volume removed), and gross-total (100% volume removed) resection (GTR).

Surgical treatment

Surgical procedures included endoscopic endonasal transsphenoidal surgery and transcranial surgery which were performed by a senior neurosurgeon with over 10 years' experience in pituitary surgery. Transsphenoidal endoscopic endonasal surgery was the preferred approach to the vast majority patients unless patients have the following conditions: (1) parasellar tumor that extend far laterally beyond the internal carotid artery, project anteriorly onto the planum sphenoidale, or project laterally into the middle fossa is inaccessible from the transsphenoidal approach; (2) tumor is fibrous and adheres firmly to critical structures which is difficult to remove totally via the transsphenoidal approach; and (3) prolonged sphenoid sinus inflammation. If tumor cannot be totally removed after surgery, intervention including gamma knife radiosurgery, repeat resection, and medical therapy would be recommended based on patients' condition and tumor characteristics.

Surgical navigation systems (StealthStation® S7; Medtronic, Inc.) and Mini-Doppler (the ES100X MiniDop®; Koven Technology, Inc.) were used to identify the internal carotid artery and guide the extent of bony resection. Soft PA was removed by suction and ring curettes, and for harder tumor, it requires piecemeal resection using a micro-dissector or tumor forceps. The consistency of the tumor was evaluated by the surgeon as soft (easily removable through suction), intermediate (removed by suction with difficulty), or hard (not removable by suction and excised en bloc) [28]. The tumor blood supply was classified as rich (large amount of bleeding during tumor resection that influences the clearance of surgical field), medium (bleeding is observed during tumor section which does not obviously influence the clearance of surgical field), and poor (no obvious bleeding occurred during tumor section) [22].

Histopathological assessment

Tissue samples were examined histologically by two experienced pathologists (with 10 years of experience in neuropathology), who were blinded to clinical and radiologic data. Histopathologic examination included hematoxylin-eosin (HE) stain, MIB-1 labeling index (Ki-67), and routine immunohistochemical analysis for pituitary hormones. Masson trichrome staining was used for testing collagen content in which collagen fibers stained as blue. Collagen-containing area and the total tumor area were measured with the Image J software, and the percent of collagen content was calculated using the formula: ∑collagen area/∑total tumor area*100%.

Clinical follow-up

Patients were clinically evaluated within 30 days after surgery, in 3 months postoperatively and at the last follow-up. After discharge, the patients were followed up in the outpatient clinic and at home by telephone or visit. All outcomes were evaluated by a trained physician not directly involved in the care of these patients and blinded to the patient's clinical data. The clinical outcome was evaluated based on tumor recurrence and progression [21, 27]. Recurrence of PA was defined as evidence of a tumor mass on MRI scan during follow-up after GTR. Furthermore, the recurrence of functional PA was also determined by the reappearance of hormonal hypersecretion after normalization. Tumor progression was defined as evidence of regrowth of residual on MRI and/or an increase in plasma hormone levels.

Statistical analysis

Data were analyzed using the IBM SPSS Statistics software (Version 20.0). Statistical significance was set at $P < 0.05$. Values were shown in the form of mean ± standard deviation (SD) for normally distributed data or median for data that were skewedly distributed. Fisher's exact test or Pearson χ^2 test was used for comparison of categorical variables, and quantitative variables were compared using independent Student's t test, analysis of variance, or Kruskal–Wallis test. Spearman correlation coefficients were calculated between ADC ratio and collagen content. Predictors for GTR of tumor were analyzed using logistic regression model, and the Cox regression model was used to determine the significance of variables in predicting recurrence and progression.

Results

Patient characteristics

Demographic and radiological baselines are shown in Table 1. A total of 183 patients were enrolled. There were 102 (55.7%) females and 81 (44.3%) males in all patients with mean age of 46.74 years (range, 17–72 years). The most common symptoms were visual impairment in 66 (36.1%) patients, headache in 40 (21.9%) patients, endocrine dysfunction in 53 (29.0%) patients, and incidental finding on MRI in 24 (13.1%) patients. The clinical presentations, preoperative endocrinologic test, and histopathological assessment showed 64 (35.0%) patients with functional PA. Giant tumor was found in 48 (26.2%) patients, and invasiveness of tumor was evident for 38.3% of patients.

Tumor consistency and blood flow

The tumor consistency was found soft in 107 (58.5%) patients, intermediate in 41 (22.4%) patients, and hard in 35 (19.1%) patients (Figs. 1, 2, and 3). The mean ADC value of PA was $0.69 \pm 0.16 mm^2/s$ for patients with hard tumor, $0.76 \pm 0.17 mm^2/s$ for patients with intermediate tumor, and $1.00 \pm 0.39 mm^2/s$ for patients with soft tumor, respectively. The average of ADC ratio was 0.92 ± 0.22 for patients with hard tumor, 1.03 ± 0.22 for patients with intermediate tumor, and 1.41 ± 0.62 for patients with soft tumor, respectively ($P < 0.001$). The mean collagen content was 25.86 ± 15.00% for patients with hard tumor, 16.05 ± 9.90% for patients with intermediate tumor, and 5.00 ± 6.00% for patients with soft tumor, respectively ($P < 0.001$). Spearman showed a significant correlation between rADC and collagen content ($\rho = -0.367$; $P < 0.001$). The tumor blood flow was found rich in 116 (63.4%) patients, medium in 64 (35.0%) patients, and poor in 3 (1.6%) patients. The mean CBF ratio was 1.67 ± 1.03 for patients with rich tumor and 1.05 ± 0.54 for patients with medium and poor tumor ($P < 0.001$).

Outcomes

All patients underwent surgical treatment including 169 patients treated with endoscopic endonasal transsphenoidal surgery and 14 patients treated with transcranial approach. GTR was obtained in 68.3% of patients, near-total resection in 28.4% of patients, and subtotal resection in 3.3% of patients. Clinical and radiological features on extent of resection are shown in Supplementary Table S1. There was one (0.5%)

Table 1 Clinical characteristics in 183 patients with pituitary adenoma

Variables	*n* (%)
Age (years)	49.00 ± 20.00*
Sex (female/male)	
Female	102 (55.7%)
Male	81 (44.3%)
Initial clinical presentations	
Headache	40 (21.8%)
Visual disorder	66 (36.1%)
Endocrine dysfunction	53 (29.0%)
Asymptomatically	24 (13.1%)
Hormone type (functional PA)	64 (35.2%)
Knosp classification	
0	56 (30.6%)
1	34 (18.6%)
2	36 (19.7%)
3	22 (12.0%)
4	35 (19.1%)
Sphenoid sinus invasion	43 (23.5%)
Invasive pituitary adenoma	70 (38.2%)
Tumor size	
< 40 mm	135 (73.8%)
≥ 40 mm	48 (26.2%)
Tumor consistency	
Hard	35 (19.1%)
Intermediate	41 (22.4%)
Soft	107 (58.5%)
ADC_{tumor} (mm^2/s)	0.87 ± 0.44*
ADC ratio	1.19 ± 0.60*
Masson's trichrome staining (%)	9.00 ± 14.00
Tumor blood flow	
Rich	116 (63.4%)
Medium and poor	67 (36.6%)
CBF ratio	1.41 ± 1.05*
Surgical approach	
Transsphenoidal endoscopic surgery	169 (93.35%)
Transcranial surgery	14 (7.65%)
Extent of resection	
Gross-total resection	125 (68.3%)
Near-total resection	52 (28.4%)
Subtotal resection	6 (3.3%)
Follow-up outcome	
Recurrence	14 (7.7%)
Progression	13 (7.1%)

*Values are presented with median ± QR

CI confidence interval, *PA* pituitary adenoma

perioperative death due to intracranial infection, and the tumor of this patient was near-total resection. Complications included five patients (2.7%) with cerebrospinal fluid leaks, two patients (1.1%) with bleeding, one (0.5%) patient with intracranial infection, one (0.5%) patient with visual deterioration, twelve (6.6%) patients with diabetes insipidus, and seven (3.8%) patients with new hypopituitarism.

The mean follow-up period was 35.14 months (range, 24–42 months). Twenty-seven (14.8%) patients suffered recurrence or progression (Supplementary Table S2). Of these patients, 4 patients were performed with second surgery, 16 patients underwent adjuvant gamma knife radiosurgery, 2 patients treated with medical therapy, and 5 patients chose observation.

Predictors for extent of surgical resection and recurrence/progression

The predictors for extent of surgical resection and recurrence/progression are shown in Table 2. Multivariable logistic regression analysis showed that ADC ratio (OR, 12.135; 95% CI, 4.001–36.804; $P < 0.001$), giant PA (OR, 0.233; 95% CI, 0.105–0.520; $P < 0.001$), and invasion (OR, 0.459; 95% CI, 0.220–0.960; $P = 0.039$) were significantly predictive of GTR. Invasion (HR, 2.728; 95% CI, 1.262–5.899; $P = 0.011$) was identified as independent predictors of recurrence or progression at the last follow-up.

Discussion

Surgical resection is the main treatment for patient with PA [13, 38]. Previous studies revealed that 26.3–40.1% patients suffered recurrence or progression after surgery [12, 29], and incomplete resection was one of the predictors for recurrence [21]. Some tumor characteristics, such as soft consistency, were significantly associated with gross total resection [5]. Therefore, identification of tumor characteristics related to GTR and postoperative recurrence/progression is important to facilitate clinical decision making. Our study reviewed 183 patients with PA and revealed that ADC ratio of DWI could be used for preoperative assessment of tumor consistency, tumor collagen content, and extent of surgical resection, which might be useful in preoperative planning for patients with PA.

It is still controversial the relationship between the tumor consistency and ADC value in DWI. Suzuki et al. [32], Yiping et al. [36], and Alimohamadi et al. [4] found no significant correction between tumor consistency and ADC value. Mohamed et al. [26] found that higher absolute ADC value was associated with hard consistency. Pierallini et al. [28] and Wei et al. [35] reported that higher ADC ratio value was significantly predictive of soft tumor, which was consistent with our study, while Boxerman et al. [10] found that higher ADC ratio was associated with hard tumor. The reasons on different results of abovementioned studies are as follows. First, besides our study, the sample size in other studies was small. In addition, due to low incidence of hard PA (the

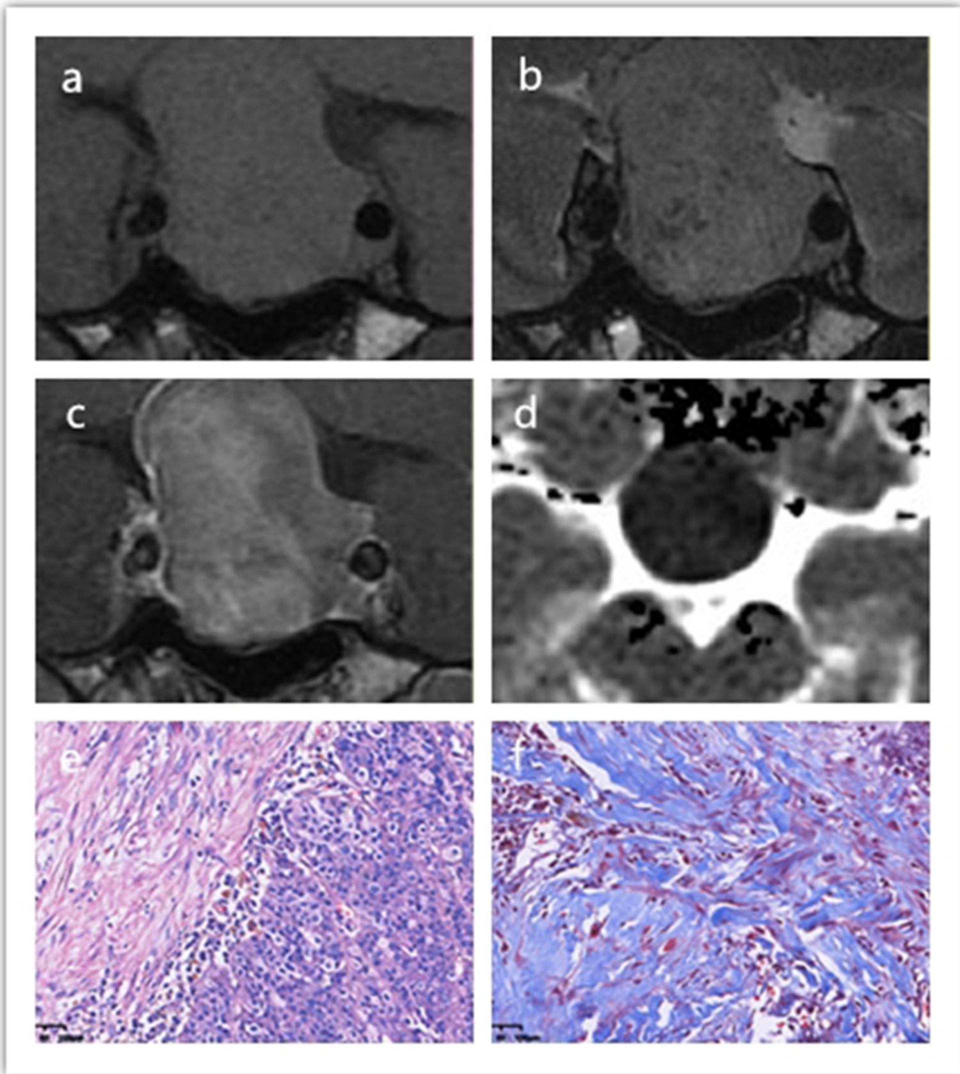

Fig. 1 A 27-year-old male with a hard pituitary adenoma. The tumor in the sellar region is isointense on coronal T1-weighted imaging (**a**), relatively hyperintense on coronal T2-weighted imaging (**b**), slightly enhanced on coronal enhanced T1-wighted imaging (**c**), and relatively hypointense on apparent diffusion coefficient map (**d**). Pituitary adenoma is confirmed by postoperative hematoxylin-eosin staining (**e**), and abundant collagen content (in blue) is found in Masson trichrome staining showed (**f**)

reported incidence of 10–24.5%) [4, 25, 37], the number of patients with hard tumor in most studies was limited. Second, different DWI techniques and parameters were used in these studies. Su et al. discussed DWI at a standard *b* value (b = 1000s/mm^2) and a high *b* value (b = 2000s/mm^2) for their ability to assess the tumor consistency of pituitary macroadenomas and found ADC at a high *b* value may facilitate better type discrimination [31]. Third, values on ADC map for predicting tumor consistency were differently calculated in these studies. Absolute value of ADC might not be appropriately used to compare because signal intensity of MRI is influenced by many factors [35]. Hence, it is necessary to take another reference for comparison to reduce the bias. In addition, some studies applied relative value of ADC (ADC ratio), but the reference was differently chosen from brainstem to brain white matter tissue. Based on above findings, difference selection of MRI techniques and parameters may lead to different results among these studies. Development of standard measures of tumor consistency, standard MRI quantification metrics, and further exploration of MRI technique may improve the predictive ability of neuroimaging for PA in the future.

It has been reported that collagen deposition is a significant pathological feature in fibrous pituitary adenomas of PA [33, 34]. Masson trichrome staining in our study demonstrated that the collagen content in the hard tumor was about five times than that in the soft tumor. Moreover, ADC values for predicting consistency was confirmed by postoperative Masson trichrome staining, which showed that lower ADC ratio was significantly associated with higher collagen content. Therefore, assessing tumor consistency, preoperative DWI characteristics were consistent with intraoperative findings and postoperative histopathological features.

Higher GTR rate might lead to better clinical outcome for patients with PA [6]. Tumor consistency based on intraoperative observation has been reported to be a key determinant of extent of resection in intracranial tumor [15, 39]. However, the correlation between radiologic variable for evaluating tumor

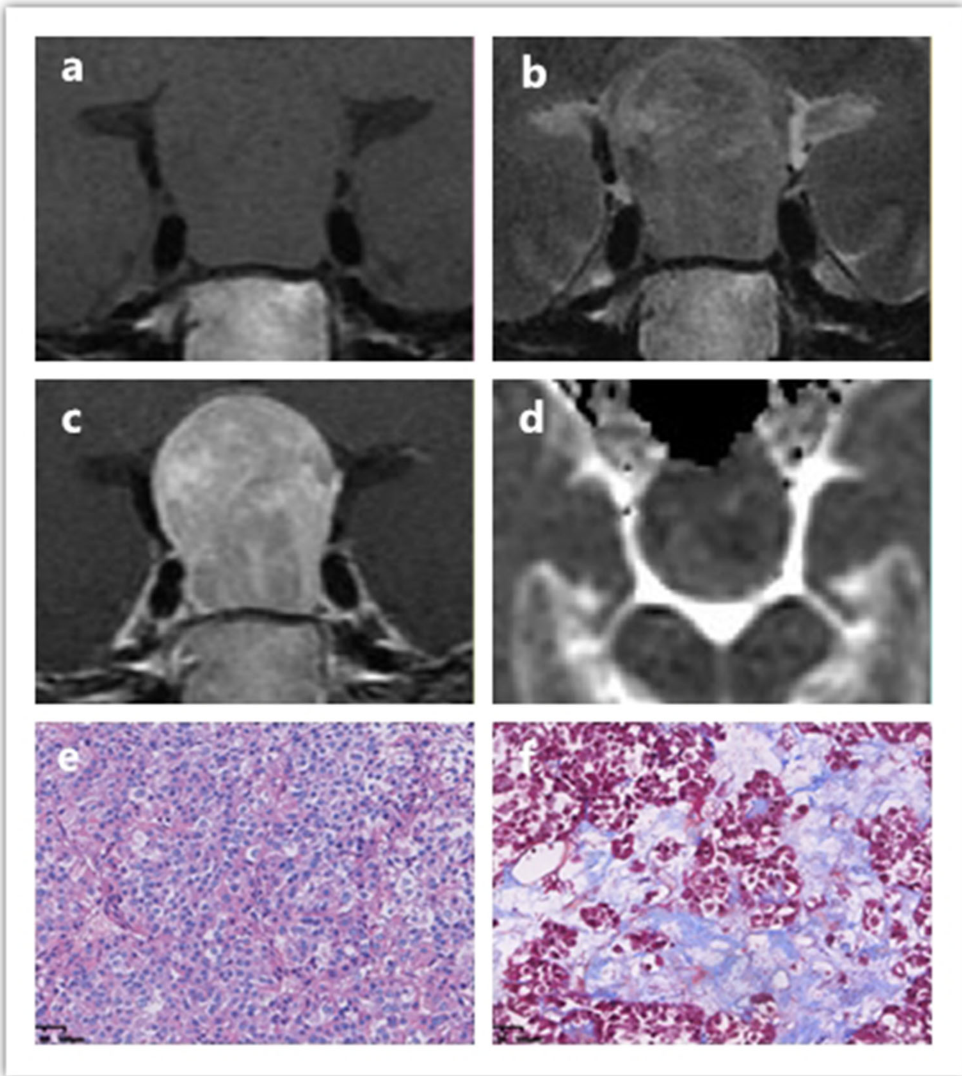

Fig. 2 A 47-year-old female with an intermediate pituitary adenoma. The tumor in the sellar region is isointense on coronal T1-weighted imaging (**a**), hyperintense on coronal T2-weighted imaging (**b**), obviously enhanced on coronal enhanced T1-wighted imaging (**c**), and relatively isointense on apparent diffusion coefficient map (**d**). **e** Pituitary adenoma is confirmed by postoperative hematoxylin-eosin staining (**e**), and moderate collagen content (in blue) is found in Masson trichrome staining showed (**f**)

consistency and extent of resection and recurrence is rarely reported. Our study further discussed the role of DWI in predicting extent of surgical resection and postoperative recurrence/progression. Multivariable logistic regression analysis showed that higher ADC ratio was associated with higher rate of resection, which presented that soft tumor was more likely to be totally removed. Thus, ADC ratio could be used routinely in preoperative evaluation for PA. Our results did not clarify the relationship between ADC ratio and recurrence/progression. Further interventions were recommended for patients with residual tumor after surgery in our hospital. Of 57 patients without GTR, 23 (40.3%) patients were performed with interventions, and statistical analysis showed, compared with patients without interventions, patients with interventions have lower progression rate (32.3% vs 8.7%, P = 0.037; Supplementary table S3). Therefore, due to postoperative interventions for residual PA, progression rate was decreased in our cohort, which may explain why ADC ratio was not effective in predicting recurrence/progression. Long-term follow-up would be needed to clarify the role of ADC ratio in predicting tumor recurrence/progression.

Limitations

There were several limitations in the study. First, although the same neurosurgeon used uniform standard to evaluate the tumor consistency and blood flow at surgery, it may still be subjective. More accurate methods should be used in the future study. Second, tumor removal by suction makes it difficult to preserve the same tissue for histopathological assessment as it is for evaluation of ADC value. Third, to reduce the effect of tumor size and heterogeneity on assessment of ADC and CBF value, some types of PA, such as microadenomas, were excluded from our study. Thus, the results may not be generalizable to all patients and should be interpreted with caution. Further studies are required to and thus develop grading system for preoperative risk assessment and clinical decision making.

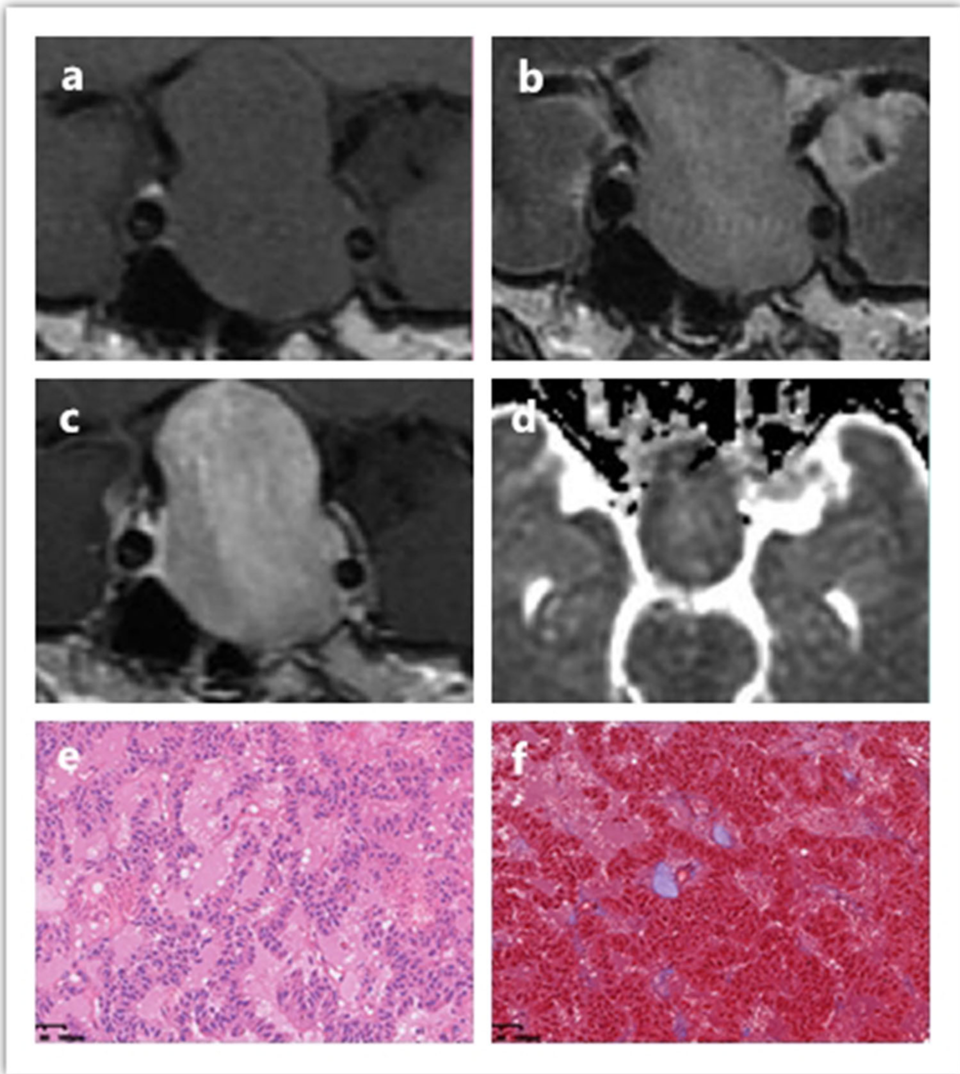

Fig. 3 A 57-year-old female with a soft pituitary adenoma. The tumor in the sellar region is relatively hypointense on coronal T1-weighted imaging (**a**), relatively hyperintense on coronal T2-weighted imaging (**b**), homogeneously enhanced on coronal enhanced T1-wighted imaging (**c**), and hyperintense on apparent diffusion coefficient map (**d**). Pituitary adenoma is confirmed by postoperative hematoxylin-eosin staining (**e**), and scanty collagen content (in blue) is found in Masson trichrome staining showed (**f**)

Table 2 Predictors for extent of resection and recurrence/progression in patients with pituitary adenoma

Characteristics	Univariate logistic regression (gross-total resection)			Multivariate logistic regression (gross-total resection)			Univariate Cox proportional (recurrence/progression)			Multivariate Cox proportional (recurrence/progression)		
	OR	95% CI	*P* value	OR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (years)	1.017	0.988–1.048	0.251	-	-	-	0.978	0.949–1.008	0.151	-	-	-
Sex, female	1.402	0.656–2.994	0.383	-	-	-	0.622	0.274–1.410	0.256	-	-	-
Hormone type (functional PA)	1.877	0.780–4.517	0.160	-	-	-	0.782	0.326–1.876	0.582	-	-	-
Invasive pituitary adenoma	0.414	0.188–0.908	0.028	0.459	0.220–0.960	0.039	2.576	1.124–5.905	0.025	2.728	1.262–5.899	0.011
Tumor size (≥ 40 mm)	0.221	0.096–0.509	0.000	0.233	0.105–0.520	0.000	1.375	0.619–3.053	0.434	-	-	-
ADC ratio	11.726	3.697–37.186	0.000	12.135	4.001–36.804	0.000	0.741	0.295–1.864	0.524	-	-	-
CBF ratio	0.889	0.670–1.181	0.417	-	-	-	0.751	0.456–1.238	0.262	-	-	-

CI confidence interval, *PA* pituitary adenoma

Conclusions

ADC ratio of DWI could be used for preoperative assessment of tumor consistency, tumor collagen content, and extent of surgical resection, which might be useful in preoperative planning for patients with PA. Long-term follow-up would be needed to clarify the role of ADC ratio in predicting tumor recurrence/progression.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10143-020-01469-y.

Acknowledgments The authors would like to thank Dr. Zhongliang Hu and Dr. Zhenghao Deng of the Department of Pathology at Xiangya hospital for their assistance with the histopathological assessment.

Author contributions W D, Z H, and ZY L contributed to the study conception and design. W D, Z H, and MY Z collected clinical data.GF Z and L L collected radiological data. W D and Z H performed the statistical analysis and drafted the manuscript. All authors contributed to the interpretation of results, all revised the manuscript critically for important intellectual content, and all approved the final manuscript. ZY L is the guarantor.

Funding This study was funded by the Natural Science Foundation of Hunan Province of China (Grant No.2018jj6139) and the Innovation-oriented Provinces Construction Project of Hunan Province (Grant No. 2019ZK4004).

Data availability Data of this study are available from the corresponding author upon reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval The current study was approved by the ethical committee of our hospital.

Consent to participate Informed consent was obtained from all enrolled patients.

Consent for publication All authors of this manuscript consent to the publication of the manuscript in Neurosurgical Review journal.

Code availability Not applicable

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