

Original Article

Relationship between pituitary adenoma texture and collagen content revealed by comparative study of MRI and pathology analysis

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Abstract: This study is to reveal the relationship between pituitary adenomas and tumor texture by comparing MRI and pathologic results. Preoperative imaging data of 38 cases of pituitary adenoma patients and collagen content of tumor specimens measured by histopathological were analyzed and compared. T₂WI and diffusion coefficient assessment were used to reveal the relationship between tumor texture and collagen content. There were 13 cases of soft texture, 17 cases of medium texture and 8 cases of tough texture tumors. Signal intensity of different texture Pituitary adenomas had significant difference on T₂WI and ADC map (P < 0.05). The signal intensity ratio of tumor and pons on T₂WI had high consistency with tumor texture. Mean collagen contents of soft, medium and tough texture group were 1.51% ± 0.91%, 7.35% ± 2.99% and 18.10% ± 8.24%, respectively. There were significant differences in collagen content of different texture tumors (P < 0.01). The signal intensity of T₂WI and ADC images have prediction value for pituitary adenomas texture and T₂WI is more reliable.

Keywords: Pituitary adenoma, texture, MRI, T₂WI, ADC, collagen content

Introduction

Pituitary adenoma (PA) is a common benign tumor of neurosurgery and it ranks the third in brain tumors [1]. PA can bring a variety of hazards to human body. Excessive secretion of pituitary hormone can cause a series of metabolic disorders and organ damages. PA can press normal pituitary tissue thus lead to low function of corresponding target glands. Compression and invasion of PA to its surrounding structures such as the sella, optic chiasm, optic nerve, cavernous sinus, skull base and brain-stem can result in serious obstacles to the corresponding organ functions. PA can hamper human growth, development, labor ability and reproductive function, which, causes a series of social psychological impacts. With the rapid development of modern medical technology, progress has been made in the diagnosis and treatment of PA, thereby effectively reduces the harm of PA.

To date, operation resection is the most effective therapeutic method for curing PA. Tumor texture has been considered to be an important factor that affecting the rate of operation resection [2, 3]. Thus, accurately prediction of tumor texture preoperative will play an important role in guiding operative risk evaluation and surgical planning, which, can greatly ensure the operation safety. With the development of medical imaging technology, scholars begin to study the value of preoperative imaging in evaluation of PA texture and the the most watched are T₂WI [4-6] and DWI [4, 7-9]. However, as the methods used are different, there is no unanimous conclusion about the use of PA texture evaluation by T₂WI and DWI.

In this study, T₂WI and ADC images were used for the first time for comparing PA signal intensity with the intensity on the level of pons through bridge arm. Combined with intraoperative tumor texture judgment and collagen con-

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Figure 1. MRI images of 1 case of soft texture PA. A. Enhanced axial MRI image. B. Axial T₂WI image. $T_{2PA} = 0.656 \times 10^{-3} \text{ mm}^2/\text{sec}$, $T_{2ME} = 0.360 \times 10^{-3} \text{ mm}^2/\text{sec}$, $R_{T_2} = 1.82$. C. Axial ADC image. $ADC_{PA} = 0.975 \times 10^{-3} \text{ mm}^2/\text{sec}$, $ADC_{ME} = 0.774 \times 10^{-3} \text{ mm}^2/\text{sec}$, $R_{ADC} = 1.26$.



Figure 2. MRI images of 1 case of medium texture PA. A. Enhanced axial MRI image. B. Axial T₂WI image. $T_{2PA} = 0.657 \times 10^{-3} \text{ mm}^2/\text{sec}$, $T_{2ME} = 0.350 \times 10^{-3} \text{ mm}^2/\text{sec}$, $R_{T_2} = 1.88$. C. Axial ADC image. $ADC_{PA} = 0.721 \times 10^{-3} \text{ mm}^2/\text{sec}$, $ADC_{ME} = 0.784 \times 10^{-3} \text{ mm}^2/\text{sec}$, $R_{ADC} = 0.92$.

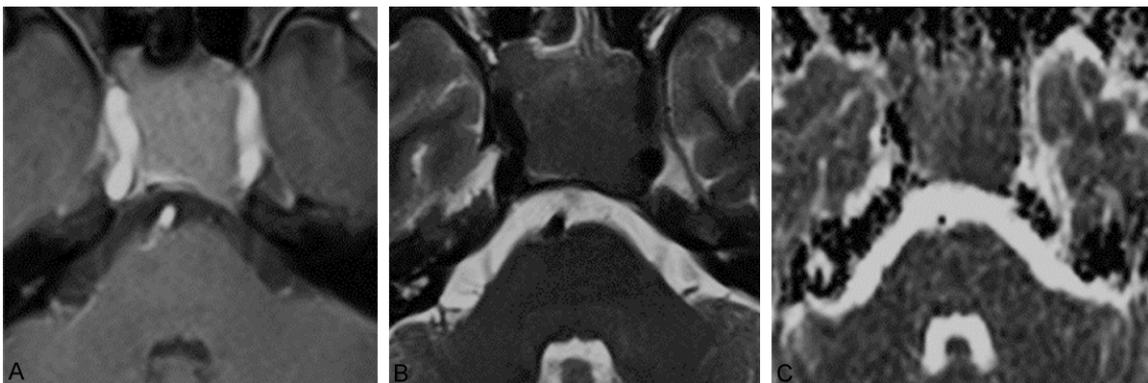


Figure 3. MRI images of 1 case of tough texture PA. A. Enhanced axial MRI image. B. Axial T₂WI image. $T_{2PA} = 0.260 \times 10^{-3} \text{ mm}^2/\text{sec}$, $T_{2ME} = 0.215 \times 10^{-3} \text{ mm}^2/\text{sec}$, $R_{T_2} = 1.21$. C. Axial ADC image. $ADC_{PA} = 0.732 \times 10^{-3} \text{ mm}^2/\text{sec}$, $ADC_{ME} = 0.697 \times 10^{-3} \text{ mm}^2/\text{sec}$, $R_{ADC} = 1.05$.

tent measurement after postoperative, the predicting value of the two parameters had been

investigated and the relationship between them also was discussed in the hope of provid-

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Table 1. Comparison of MRI indexes of different texture of tumors (n = 38)

Texture	T_{2PA} (mm ² /sec)	R_{T_2}	ADC_{PA} (mm ² /sec)	R_{ADC}
Soft	$0.649 \pm 0.130 \times 10^{-3}$	1.92 ± 0.36	$0.987 \pm 0.252 \times 10^{-3}$	1.48 ± 0.43
Medium	$0.570 \pm 0.156 \times 10^{-3}$	1.60 ± 0.45	$0.768 \pm 0.248 \times 10^{-3}$	1.12 ± 0.34
Tough	$0.483 \pm 0.111 \times 10^{-3}$	1.26 ± 0.32	$0.742 \pm 0.190 \times 10^{-3}$	1.09 ± 0.35
<i>P</i>	0.04	0.03	0.02	0.01

Table 2. The AUC of different MRI indexes for tumor texture detection

Index	AUC of different MRI indexes for tumor texture detection		
	Soft	Medium	Tough
T_{2PA}	0.723	0.524	0.767
R_{T_2}	0.790	0.555	0.815
ADC_{PA}	0.763	0.681	0.588
R_{ADC}	0.774	0.654	0.642

ing reference for preoperative evaluation of PA texture.

Materials and methods

Patient' data

A total of 104 cases of patients who were diagnosed as PA and were admitted to our hospital from November 2011 to April 2013 and 38 cases were enrolled in this study. Among the 38 cases, 17 were male and 21 were female. They aged from 21-73 years old, with an average age of (45.3 ± 14.6) years old. The duration was from 14 days to 21 years. The inclusion criteria were defined as follows: patients those taken 3.0-T MRI T_2 WI and DWI examination and were found space-occupying lesions in saddle area; patients those were confirmed as PA by postoperative pathology. The exclusion criteria were described as follows: patients those with inhomogeneous MRI signal intensity in tumor area and patients those with tumor diameter less than 1 cm.

Prior written and informed consent were obtained from every patient and the study was approved by the ethics review board of Fuzhou General Hospital, Fujian Medical University, China.

MRI scanning

Plain and enhanced MRI scanning was performed with 3.0T magnetic resonance scanner

(Tim Trio; Siemens Medical Solutions, Erlangen, Germany). The parameters used for conventional scanning were as follows: conventional T1WI (TR/TE 70-0/8 ms) and T_2 WI (TR/TE 3000/98 ms) in axial, coronal and sagittal;

diffusion sensitivity coefficient (b value) = 100 s/mm²; TR/TE 5100/90 ms. The parameters used for enhanced scanning were as follows: gradin-echo (GRE); TR/TE, 1900/3 ms; Fov, 240 mm × 240 mm; matrix, 256 × 256; layer thickness, 1.0 mm. GD-DTPA was used as contrast agent with the dose of 0.2 ml/kg.

MRI signal data processing

T_2 WI and ADC image data of each patient was evaluated. The following adenoma and pons tissue related data were collected (by scanning on the level of brachium pontis) and used for data processing: T_{2PA} (average tumor signal intensity on T_2 WI); T_{2ME} (mean pons signal intensity on T_2 WI); ADC_{PA} (average tumor signal intensity on ADC diagram); ADC_{ME} (mean pons signal intensity on ADC diagram).

The ratios of tumor and pons signal intensity on T_2 WI and ADC were calculated and defined as R_{T_2} (T_{2PA}/T_{2ME}) and R_{ADC} (ADC_{PA}/ADC_{ME}).

Tumor texture judgment

In this study, a total of 34 cases of PA patients underwent transsphenoidal operation while the other 4 cases underwent craniotomy operation. According to Mahmoud [9] classification method, the tumors were divided into three groups. Soft texture group: tumor that is easily suctioned with aspirator. Medium texture group: the tumor that is hard to be removed with aspirator. Tough texture group: the tumor cannot be suctioned with aspirator, and bipolar electrocoagulation or sharp segmentation resection is needed. On the basis of the original grouping method, we classified tumors of soft texture mixed with medium texture into medium texture group and medium texture combined with tough texture into tough texture.

Calculation of collagen content

The operation specimen slices were performed with conventional picric acid- collagen staining

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Table 3. Comparison between MRI indexes and soft texture tumor intraoperative judgment (n = 38)

MRI index	Judgment criteria	Tumor texture		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Youden index
		soft	Medium or tough					
T _{2PA}	≥ 0.562	11	10	84.6	60.0	52.4	88.2	0.446
	< 0.562	2	15					
R _{T2}	≥ 1.77	10	6	76.9	76.0	62.5	86.4	0.529
	< 1.77	3	19					
ADC _{PA}	≥ 0.856	9	7	69.2	72.0	56.3	81.8	0.452
	< 0.856	4	18					
R _{ADC}	≥ 1.23	9	6	69.2	76.0	60.0	82.6	0.452
	< 1.23	4	19					

Table 4. Comparison of judge MRI index and tough texture tumor intraoperative judgment (n = 38)

MRI index	Judgment criteria	Tumor texture		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Youden index
		soft	Medium or tough					
T _{2PA}	< 0.650	8	15	100	50.0	34.8	100	0.500
	≥ 0.650	0	15					
R _{T2}	< 1.72	8	13	100	56.7	38.1	100	0.567
	≥ 1.72	0	17					
ADC _{PA}	< 1.031	8	23	100	23.3	25.8	100	0.233
	≥ 1.031	0	7					
R _{ADC}	< 0.85	3	4	37.5	93.3	42.9	78.8	0.308
	≥ 0.85	5	26					

method followed by taking pictures under the microscope. The images collected were analyzed with Image-Pro Plus 6.0 software and the percentage of each component was calculated with the tools the software provided. The four corners and the central 200 × vision were taken and photographed for collagen content calculation. Collagen content = (total collagen content area under microscope/total slice area under microscope) × 100%.

Statistical analysis

All the statistical analyses were performed using SPSS version 19.0 (SPSS Inc, Chicago, IL, USA) for Windows and *P* value less than 0.05 was considered as statistically significant. The data was expressed as mean ± standard deviation (SD).

The receiver operating characteristic curve (ROC) was used to assess the detecting value

of each index for adenoma texture. Area under the ROC curve (AUC) greater than 0.7 was considered to be with certain detecting value. Kappa coefficient was calculated and the consistency of prejudgment results and tumor texture was assessed. Kappa ≥ 0.75 was considered as good consistency, 0.75 > kappa > 0.4 was regarded as general consistency and kappa < 0.4 was thought to be poor consistency.

Results

Comparisons of MRI indexes of different texture tumors

To identify whether MRI indexes vary among different texture tumors, MRI indexes of different texture tumors were compared. MRI images of soft texture, medium texture and tough texture were shown in **Figures 1-3**.

There were 13 cases of soft texture, 17 cases of medium texture and 8 cases of tough texture tumors. Comparisons of each MRI index of different texture tumors all had significant differences (Kruskal-Wallis H test, *P* < 0.05) (**Table 1**). To sum up, this result indicated that the harder the tumor texture, the lower the MRI index.

Detecting value of MRI indexes for different texture tumors

To investigate the detecting value of MRI indexes for different texture tumors, MRI indexes including T_{2PA}, R_{T2}, ADC_{PA} and R_{ADC} were compared with intraoperative texture judgment by ROC curve. It was found that for soft and tough texture tumors, AUC all were greater than 0.7 while each AUC of medium texture tumor was less than 0.7 (**Table 2**). According to ROC curve analysis, the critical value of MRI indexes for

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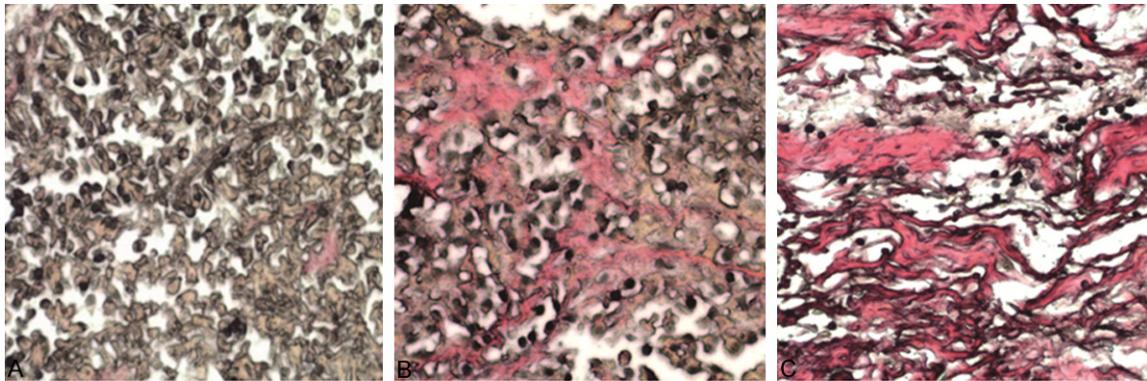


Figure 4. Picric acid-collagen staining of three PA cases of different texture. A. Soft texture PA under microscope. A large number of tumor cells (black), a small amount of fresh red collagen tissue (arrows) and rich cytoplasm (brown yellow) were seen. B. Medium texture PA under microscope. Moderate strip or bundle collagen fiber (red), tumor cells (black), and rich cytoplasm (brown yellow) was seen. C. Tough texture PA under microscope. A large number of collagen fibers (red), a small amount of tumor cells (black) and little cytoplasm (brown yellow) was seen.

Table 5. Comparison of collagen content and tumor intraoperative judgment (n = 38)

Pre judgment results	Collagen judgment standard	Intraoperative findings and cases		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Youden index
		Soft	medium/tough					
Soft	≤ 3.74%	13	2	100.0	92.0	86.7	100.0	0.920
	> 3.74%	0	23					
Tough	≥ 8.93%	7	5	87.5	83.3	58.3	96.2	0.708
	< 8.93%	1	25					

Table 6. Comparison of tumor type and tumor texture (n = 38)

Grouping	Texture (cases)		
	Soft	Medium	Tough
Clinical endocrine type			
Functional type	4	7	2
Non functional type	9	10	6
Immunohistochemical types			
Hormone active adenoma	9	14	6
Null cell adenoma	4	3	2

soft texture tumor detecting was calculated and compared with intraoperative judgment (Table 3). The kappa coefficients of T_{2PA} , R_{T2} , ADC_{PA} and R_{ADC} were 0.389, 0.501, 0.391 and 0.436, all with $P < 0.05$ while compared with tumor texture. Meanwhile, the same comparison of tough texture tumor was carried out (Table 4). The kappa coefficients of T_{2PA} , R_{T2} , ADC_{PA} and R_{ADC} were 0.379, 0.401, 0.245 and 0.118 and the P value were 0.013, 0.005, 0.307 and 0.146. In conclusion, it was notable

that compared to other indexes, R_{T2} had high consistency with intraoperative judgment.

Relationship between tumor texture and collagen content

To identify the relationship between tumor texture and collagen content, collagen contents in different texture tumors were tested. Mean collagen contents of soft, medium and tough texture group were $1.51\% \pm 0.91\%$, $7.35\% \pm 2.99\%$ and $18.10\% \pm 8.24\%$, respectively. The schematic tissue slices of soft, medium and tough texture tumor were shown in Figure 4. There were significant differences in collagen content of different texture tumors (Kruskal-Wallis H test, $P < 0.01$). According to the ROC curve analysis, AUC of collagen content detection for soft, medium and tough texture tumors were 0.972, 0.655 and 0.908. Hence, one can see that collagen content had higher detection value for soft and tough texture tumors. Further calculation showed that the critical values of collagen content in soft and tough texture

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tumors were 3.74% and 8.93%, this result was compared with intraoperative judgment (**Table 5**). The kappa coefficients of detecting values of collagen content for soft and tough texture tumors were 0.887 and 0.599, all had statistical correlation ($P < 0.01$). Given all this, it is possible to assume that collagen content is positively correlated to tumor texture and the harder the texture, the more collagen content the tumor contains.

Relationship between tumor type and tumor texture

To identify the relationship between tumor type and tumor texture, texture of different PA types was compared. PA clinical endocrine diagnosis was performed according to the 2004 WHO classification criteria [10]. There were 25 cases of non functional adenoma, 8 cases of growth hormone adenoma, 3 cases of lactotroph adenoma, 1 case of thyrotroph adenoma and 1 case of adrenocorticotrophic hormone adenoma. As shown in **Table 6**, 75.0% (6/8) of patients in tough texture group were non functional adenoma. All the samples were subjected to immunohistochemical examination and there were 11 cases of gonadotropin adenomas, 9 cases of null cell adenoma, 7 cases of growth hormone adenoma, 6 cases of PRL adenoma, 2 cases of TSH adenoma, 1 case of ACTH adenoma and 2 cases of plurihormonal adenoma. It was shown by **Table 6** that in tough texture group, most of the patients were hormone-active adenoma. Together, the results argued that non functional adenoma and hormone-active adenoma were common in tough texture PA.

Discussion

In this study, signal intensity of tumor and pons in MRI images was firstly compared and the result showed that T_2WI had quit high reliability in tumor texture detecting. In previous studies, some scholars compared adenoma signal intensity directly. Influenced by movement and tissue density, even with the same scanning parameters, there are differences of MRI signal intensity in the same parts of different patients. Hence, it is necessary to take another reference for comparative study to reduce the disturbance. Some scholars [4, 7, 9] have compared the MRI signal intensity in adenoma and cerebral white matter, however, there was no

detailed description of which parts of the brain white matter scanned. In this study, we found that there was difference in signal intensity in the same patient because tissue density of different parts of the brain white matter tissue was not unified. Magnetic susceptibility artifacts induced by cerebrospinal fluid and brain gray matter can interfere with DWI and ADC images, as a result, the acquisition error was larger when scanning brain white matter. It was found that the signal intensity of pons on bridge arm level was relatively homogeneous and stable on axial MRI, and the result calculated with taking this part as a reference was less disturbed by magnetic susceptibility artifacts.

Previous reports compared MRI indexes of different texture tumors directly, ignoring the prediction value of each index for single texture tumor. In this study, ROC curve was used to evaluate the detecting value of each MRI index for different texture tumors. The result showed that T_{2PA} , R_{T_2} , ADC_{ME} and R_{ADC} had certain predictive value for soft and tough texture adenomas. However, forecast results were not highly in accordance with intraoperative judgment results, only R_{T_2} was more reliable. Studies with more samples should be taken for further confirmation.

It was pointed that collagen content is the main factor that influences the texture of PA [4, 7-9, 11-13]. Pierallini et al. [7] showed that the collagen content in three groups of PA were $1.34\% \pm 1.21\%$, $6.89\% \pm 1.91\%$ and $7.23\% \pm 4.80\%$. Naganuma et al. [6] recommended that adenoma with collagen content more than 5% be defined as "fibrosis" adenoma. In this study, collagen content of the three kinds of texture tumors were $1.51\% \pm 0.91\%$, $7.34\% \pm 3.10\%$ and $15.45\% \pm 8.58\%$. Meanwhile, collagen content of 3.74% and 8.93% were considered as critical value in the detection of soft and tough texture tumors respectively. The prediction results were highly consistent with tumor texture. There were certain differences among our results and those of the other scholars. This might be caused by uneven distribution of collagen tissue in tumor, also it might be affected by different experimental methods and sample sizes. In the present study, most of the tough texture PA were nonfunctional adenoma and this was consistent with previous reports [6, 14]. However, it was reported that in prolactinoma patients, the degree of tumor fibrosis

was independent of tumor shrinkage and prolactin secretion. This difference might be due to the diverse measurement standard and further research remained to be carried.

Because of tough texture adenoma only accounts for 10% of all PA cases [15], and DWI imaging is prone to be affected by movement and tissue density, in this study, cases those with inconsistent MRI signal intensity were excluded, which, making the small sample size further reduced. There is certain subjectivity in intraoperative judgment of PA texture and different operator may have different judgment results. At the same time, collagen distribution was not uniform in most tumors although the imaging signal was uniform and most of the tumors were removed by suction method. This made it difficult to guarantee the integrity of the operation samples, further affected collagen region measurement under the microscope. As a result of the forementioned reasons, there were some errors in collagen content calculation. More accurate detection methods remain further investigation.

In conclusion, the signal intensity of T_2 WI and ADC images had prediction value for PA texture and T_2 WI was more reliable. Collagen content of most soft texture adenoma was less than 3.74% and more than 8.93% in tough texture adenoma.

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Disclosure of conflict of interest

None.

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