Prediction of the consistency of Pituitary Adenoma: A comparative study on diffusion-weighted imaging and pathological results

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Aims and objectives

As the most common lesion in sellar region, pituitary adenomas rank the third in all brain tumors with the incidence of 73~94 cases / 100,000 inhabitants [1,2]. Because of their possible hormonal secretion and mass effect, pituitary adenomas are always treated by surgery as the first choice [3-5]. There are two kinds of surgery to remove those pituitary adenomas which are resectable basically, named trans-sphenoidal endoscopic surgery and craniotomy, but which surgery to choose depends on the inner feature of the tumors - the consistency [6,7]. Trans-sphenoidal endoscopic surgery is more suitable for the tumors with soft consistency which are easy to pull out, while craniotomy is suitable for the harder ones. So, preoperative evaluation of the tumors` consistency can help to find out the best operation methods and treatments, which will not only increase the possibility of complete tumor removal, but also reduce recurrence rates.

Concerning its high resolution, MRI has shown great advantage in brain imaging and emerged to be the best way for consistency evaluation. Previous studies have attempted to predict pituitary adenomas` consistency by using conventional and some novel MRI sequences, but the results are controversial, especially in terms of Diffusion-Weighted Imaging (DWI) [8]. DWI is used to measure aberrancies in the expected Brownian motion of free water [9,10]. Recent years, DWI has shown utility in predicting the consistency of pituitary adenomas which was verified in several studies [8,11,12]. However, because of the B0-related artefacts in sellar region, their results were not so convincing [13]. BLADE DWI is a turbo spin echo-based diffusion weighted imaging technique and it can oversample the region in the centre of the k-space to correct for heterogeneities prior to combing the data. Depending on the merit of Turbo Spin Echo#TSE#techniques, B0-related artefacts from sinuses and eddy currents can theoretically be dramatically reduced [14]. Therefore, BLADE DWI can enable the visualization of the boundary between sellar lesion and peripheral structures, which is more suitable for preoperative evaluation of tumors in skull base [15].

In clinical practice, we have noticed that pituitary adenomas with soft consistency seem to have higher T2 signal intensity (SI) and ADC value but lower enhancement, which was not aligned with or totally opposite to previous research results [8,11,12,16,17]. So this study was designed to determine the relationship between the consistency and MRI signal intensities of pituitary adenomas and learn about the diagnostic value of MRI techniques.
Methods and materials

Patients:

This study was designed as an observational, comparative investigation with inter-individual comparison between September 2013 and February 2014. All patients were suspected to have pituitary adenomas with clinical manifestations or laboratory abnormality, underwent MRI imaging and then took surgery in our hospital. Subjects who had received previous pituitary surgery and whose MRI imaging strongly indicated haemorrhage or cyst in pituitary adenomas were excluded because of their obviously soft contents. Subjects whose pathological diagnosis were not pituitary adenomas were also excluded in our study.

MR Imaging Protocol:

MR imaging of the sellar region was performed using the following routine sequences: sagittal and coronal pre-contrast T1-weighted images, coronal T2-weighted images, coronal pre-contrast BLADE DWI images and sagittal and coronal contrasted T1-weighted images at 3.0T.

To avoid scaling problems, we calculated SI or ADC ratios for all sequence by following formula:

SI ratio of T1-weighted imaging (rT1) = SI on T1 image of tumor to SI on T1 image of normal grey matter;

SI ratio of T2-weighted imaging (rT2) = SI on T2 image of tumor to SI on T2 image of normal white matter;

SI ratio of contrast enhanced T1-weighted imaging (rT1C+) = SI on T1-enhanced image of tumor to SI on T1-enhanced image of normal grey matter;

ADC ratio (rADC) = ADC on DWI image of tumor to ADC on DWI image of normal brainstem.

The invasiveness of pituitary adenomas were evaluated referred to Knop-Steiner Grading [18]. Pituitary adenomas classified into Grade 3 or 4 were intended to show aggressive activity, so in this study, we defined those pituitary adenomas with Grade 3 or 4 as invasive ones.

Surgery:
All patients had received surgery in the Neurosurgery Department and all were performed by the same skilled neurosurgeon with experience in brain surgery over 10 years. Endoscopic trans-sphenoidal or trans-cranial approach was used depending on the size of tumours. The surgeon together with another experienced neurosurgeon who assisted during surgeries recorded tumor consistency by negotiation immediately after surgeries. Pituitary adeonomas were classified into 2 groups: tumor with soft consistency (easily removable by aspiration or curettage) and tumors with hard consistency (not removable by aspiration or curettage and requiring piecemeal resection by use of a microdissector or tumor forceps).

**Histologic Study:**

The specimens were examined for collagen contents by both Masson trichrome staining and H.E. staining.

1) Qualitative Evaluation:

Since after the process of H.E. staining, collagen is the main contents of extra-cellular matrix (ECM) in pituitary adenomas, so the percentage of ECM in H.E. staining slice approximately equals to collagen content. Therefore, 2 pathologists judged collagen contents in the H.E. staining slices respectively, then after negotiation they separated pituitary adenomas into different groups according to the criteria below:

Collagen Content (+): the extra-cellular matrix portion accounts for less than 5% of the the whole area of the stained tissue.

Collagen Content (++): the extra-cellular matrix portion accounts for 5~15% of the whole area of the stain tissue.

Collagen Content (+++): the extra-cellular matrix portion accounts for over 15% of the whole area of the stain tissue.

2) Quantitative Evaluation:

A quantitative estimation of fibrous tissue was performed on histologic slices stained with Masson trichrome staining method by using an interactive image analysis system (Olympus BX51, Japan). Each area of collagen and the total tumor area was measured and the percentage of collagen content (PCC) was calculated by using the following equation: 

\[
PCC = \frac{A_{coll}}{(A_{tumor} - A_{bv})} \times 100\%,
\]

where \(A_{coll}\) is area of collagen, \(A_{tumor}\) is area of total tumor, and \(A_{bv}\) is the area occupied by blood vessels.

**Statistical Analyses**
Statistical analysis was performed by using statistical software (SPSS, release 19.0, IBM, China). Correlations between MRI results and tumor consistency were also tested by use of Fisher exact probability tests. For pathological findings, the relationship between collagen contents and tumor consistency were tested by Fisher exact probability tests and correlation between collagen contents and MRI findings were tests by liner regression. A $P$ value of $<0.05$ was considered statistically significant.

Diagnostic value of MRI finds in predicting tumor consistency and clinical function were evaluated by analysing Receiver Operating Characteristic (ROC) Curve which was also used in evaluation the value of collagen contents in differentiation tumor consistency with calculation of sensitivity, specificity, positive predictive value, negative predictive value and cut-off line for MRI prediction of harder adenomas.
Results

Tumor`s consistency vs. clinical data

Between September and December 2013, a total of 34 patients. The tumor consistency at surgery was divided into soft group in 29 (85%) patients and hard group in five (15%) patients. There was no significant correlation of tumor`s consistency with patient`s age, gender, age of onset, invasiveness of pituitary adenomas, the size of tumor or tumor`s function. All demographic data were listed in Table 1.

<table>
<thead>
<tr>
<th>Number of Subjects (N and %)</th>
<th>Total</th>
<th>Soft Group</th>
<th>Hard Group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
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<td>13/16</td>
<td>2/3</td>
<td>0.616</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>49.74 ± 12.8</td>
<td>50.34 ± 2.37</td>
<td>46.20 ± 6.82</td>
<td>0.518</td>
</tr>
<tr>
<td>Onset Age (mean ± SD)</td>
<td>46.96 ± 13.2</td>
<td>47.47 ± 2.46</td>
<td>44.00 ± 7.16</td>
<td>0.602</td>
</tr>
<tr>
<td>Months since onset (mean ± SD)</td>
<td>33.31 ± 36.6</td>
<td>34.50 ± 6.96</td>
<td>24.60 ± 17.61</td>
<td>0.660</td>
</tr>
</tbody>
</table>

Table 1: Demographic Data on Subjects: hard and soft group

References: Radiology, Huashan Hospital, Fudan University, Huashan Hospital, Fudan University - Shanghai/CN
Tumor`s consistency vs. radiological findings:

The SI ratio on T1-weighted, T2-weighted, enhanced T1-weighted and BLADE DWI images in the ROI in soft and hard group are shown in the Table 2.

<table>
<thead>
<tr>
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<th>rT2</th>
<th>rT1C+</th>
<th>rADC</th>
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<td>Hard Group</td>
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<td>P value</td>
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<td>0.942</td>
<td>0.508</td>
<td>0.100</td>
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</tbody>
</table>

Table 3: Collagen Content on Subjects: hard and soft groups

References: Radiology, Huashan Hospital, Fudan University, Huashan Hospital, Fudan University - Shanghai/CN

These parameters showed no significant relation with consistency, $P>0.05$. ROC curve was done to evaluate the diagnostic value of MRI sequence on predict tumor`s consistency, area under the curve of T1, T2, enhanced T1 and ADC was 0.6483, 0.5724, 0.6071 and 0.7724 respectively.

We found a cutoff value of rADC that separates hard type from soft type which was 1.077 with sensitivity of 80%, specificity of 62.7%, PPV of 26.67%, NPV of 94.74% and Youden index of 0.4207 in diagnosis (Figure 1).
**Fig. 1:** ROC Curve in Diagnosis of Hard Consistency in Pituitary Adenomas

**References:** Radiology, Huashan Hospital, Fudan University, Huashan Hospital, Fudan University - Shanghai/CN

**Tumor`s consistency vs. collagen content**

At histologic examination, 15 tumors were confirmed to be hormone-negative pituitary adenomas, 19 contained functional cells by immunochemistry analysis. Collagen content was evaluated qualitatively after H.E. staining and calculated quantitatively after Masson staining. In qualitative analysis, 16 cases were categorized into (+) group while 6 into (++) group and 12 into (+++) group. The mean collagen content (±SD) in these groups were 2.69±0.34%, 11.43±1.52% and 16.61±1.11% with a \( P \) value <0.0001. Pituitary adenomas with different consistency exhibited a wide variation in architecture: soft ones were always composed of cells arranged very closely to each other with a small amount of extra-cellular matrix in between while cells were scattered in abundant extra-cellular matrix in tumor with harder consistency. Most soft tumors were categorized into (+) group and harder ones were in (+++) group (Table 3). The collagen content in pituitary adenomas with soft consistency and hard consistency were 7.27±1.81% and 17.72±2.00% (mean ± SD).
Table 3: Collagen Content on Subjects: hard and soft groups

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<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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References: Radiology, Huashan Hospital, Fudan University, Huashan Hospital, Fudan University - Shanghai/CN

ROC curve was done to evaluate the diagnostic value of collagen content on tumor’s consistency, area under the curve was 0.8966 with a cutoff value of 15.39% that separates hard type from soft type with a sensitivity of 89.66%, specificity of 80%, PPV of 57.14%, NPV of 96.30% and Youden Index of 0.6966 in diagnosis (Figure 2).
Fig. 2: ROC Curve of Collagen Content in Diagnosis of Hard Consistency in Pituitary Adenomas

**References:** Radiology, Huashan Hospital, Fudan University, Huashan Hospital, Fudan University - Shanghai/CN

**Collagen Content vs. Radiological Findings:**

Since grouping of collagen content by H.E. staining was compliance with the actual collagen content calculated after Masson staining, we tried to discover the difference of MRI parameters in different collagen groups (Table 4).
### Table 4: Radiological Findings on Subjects: different collagen groups

**References:** Radiology, Huashan Hospital, Fudan University, Huashan Hospital, Fudan University - Shanghai/CN

ADC ratio exhibited difference in 3 collagen groups, the more collagen, the lower rADC value. But there was no linear regression relationship between rADC and actual collagen content. Other MRI parameters could not reflect collagen details in pituitary tumors.

Classical pituitary adenoma with soft and hard consistency were exhibited in Figure 3 and 4 along with MRI images, pathological staining slices.

<table>
<thead>
<tr>
<th>Collagen Content</th>
<th>rT1 (mean ± SD)</th>
<th>rT2 (mean ± SD)</th>
<th>rT1C+ (mean ± SD)</th>
<th>rADC (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+)</td>
<td>1.197±0.240</td>
<td>2.028±0.831</td>
<td>2.584±0.604</td>
<td>1.517 ± 0.126</td>
</tr>
<tr>
<td>(++)</td>
<td>1.307±0.156</td>
<td>2.116±0.954</td>
<td>2.481±0.548</td>
<td>1.100 ±0.296</td>
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<tr>
<td>(+++)</td>
<td>1.330±0.248</td>
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<td>1.043 ± 0.084</td>
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P value:  0.328  0.218  0.808  0.036
Fig. 3: Pituitary Adenoma with soft consistency in a 30-year-old male patient whose complaint was weight-gaining accompanied by vision loss for 1 year. A) Coronal spin-echo T1-weighted MR image (2000/18) shows large inhomogeneous hypointense pituitary mass (hollow arrow) with rT1=0.90. B) Coronal spin-echo T2-weighted MR image (4000/94) shows a slightly hyperintense lesion (hollow arrow) with rT2=1.50. C) Coronal enhanced T1-weighted MR image (2000/18) shows an obvious enhanced pituitary adenoma (hollow arrow) with rT1C+=2.12. D) Coronal ADC map by BLADE DWI technique (b=1000, 0) shows a relatively hyperintense mass (hollow arrow) with rADC=1.27. E) Specimen of mass by H.E. staining shows plenty of small cells (in blue) and pink fibrous stroma and categorized into collagen content (+) group. F) Specimen of mass by Masson trichrome staining shows small cells (in purple) and collagen (in blue) with a collagen content of 3.89%.

References: Radiology, Huashan Hospital, Fudan University, Huashan Hospital, Fudan University - Shanghai/CN
Fig. 4: Pituitary Adenoma with hard consistency in a 30-year-old female patient who was diagnosed as acromegaly a year ago. A) Coronal spin-echo T1-weighted MR image (2000/18) shows large homogeneous hypointense pituitary mass (hollow arrow) with rT1=1.07. B) Coronal spin-echo T2-weighted MR image (4000/94) shows an isointense lesion (hollow arrow) with rT2=1.35. C) Coronal enhanced T1-weighted MR image (2000/18) shows an homogeneous enhanced pituitary adenoma (hollow arrow) with rT1C+=2.23. D) Coronal ADC map by BLADE DWI technique (b=1000, 0) shows a relatively hypointense mass (hollow arrow) with rADC=0.68. E) Specimen of mass by H.E. staining shows small cells (in blue) scattering in pink fibrous stroma and was categorized into collagen content (+++) group. F) Specimen of mass by Masson trichrome staining shows small cells (in purple) and collagen (in blue) with a collagen content of 20.62%.

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Number of Subjects (N and %)</strong></td>
<td>34 (100%)</td>
<td>29 (85%)</td>
<td>5 (15%)</td>
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<tr>
<td><strong>Clinical Manifestations:</strong></td>
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<td></td>
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<tr>
<td>Visual Disturbance (N)</td>
<td>18</td>
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<td>2</td>
<td></td>
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<tr>
<td>Appearance Changing (N)</td>
<td>8</td>
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<td>Chronic Headache (N)</td>
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<td>Abnormal Menstruation (N)</td>
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<tr>
<td>Others (N)</td>
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<tr>
<td>Maximal Diameter on coronal plane (mean ± SD/mm)</td>
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<td>Knop-Steiner Grading Grade 0-2 (N)</td>
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<td>Grade 3-4 (N)</td>
<td>14</td>
<td>11</td>
<td>3</td>
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**Table 3:** Collagen Content on Subjects: hard and soft groups
Table 2: ROC Curve in Diagnosis of Hard Consistency in Pituitary Adenomas

<table>
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<th>Collagen Content (+)</th>
<th>Collagen Content (++)</th>
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<th>P value</th>
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<tbody>
<tr>
<td>Soft Group (N)</td>
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<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Hard Group (N)</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Collagen Content (mean ± SD)</td>
<td>2.69 ± 0.34</td>
<td>11.43 ± 1.52</td>
<td>16.61 ± 1.11</td>
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Table 4: Radiological Findings on Subjects: different collagen groups

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Fig. 1: ROC Curve in Diagnosis of Hard Consistency in Pituitary Adenomas

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Fig. 2: ROC Curve of Collagen Content in Diagnosis of Hard Consistency in Pituitary Adenomas

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Conclusion

Although the prevalence is severely underestimated, pituitary adenomas are still the most common pathology encountered in sellar region [1,2,19,20]. There are several therapeutic regimen including surgery, medicine or radiotherapy while surgery is the radical choice, however, according to previous reports, 6-21% patients encountered recurrence after surgery, which brought about sufferings to patients physiologically and psychologically [6,21-24]. There are two kinds of surgery to remove resectable pituitary adenomas, named trans-sphenoidal endoscopic surgery and craniotomy and which to choose depends on the inner feature of the tumors - the consistency. Trans-sphenoidal endoscopic surgery is more suitable for the tumors with soft consistency which are easy to pull out, while craniotomy is suitable for the harder ones. Knowledge of the consistency of pituitary adenomas may help surgeons plan the proper surgical technique which can significantly decrease the risk of incomplete resection and minimalize the possibility of recurrence.

Given the multiplanar high-contrast images of the pituitary gland and adjacent structures, magnetic resonance imaging (MRI) is the modality choice to predict the consistency of pituitary adenomas. Conventional MRI sequences used for the evaluation of sellar masses include pre- and post-enhanced T1-weighted and T2-weighted coronal and sagittal sequences [16,17,25,26]. Recent researches also found DWI images might provide information about tumors` consistency by demonstrating Brownian motion in abnormal tissues [8,11,12]. However, in clinical practice, the use of echo-planar diffusion-weighted MRI is severely limited for imaging sellar lesions due to its high sensitivity to off-resonance effects. In this study, we used BLADE DWI technique which could dramatically reduce B0-related artefacts and enhances the image quality in sellar region especially when the minimal diameter of lesion was larger than 12mm which was demonstrated by our previous study (published) [14, 15]. So in this study, we also used BLADE DWI technique to guarantee the acquisition of exact ADC value in pituitary adenomas which meant to make results more reliable.

Pituitary adenomas are generally hypointense relatively to normal grey matter on both pre-enhanced and enhanced T1-weighted images and are relatively hyperintense on T2-weighted images. According to previous reports, SI ratio of T2-weighted images (SI on T2 image of tumor to SI on T2 image of normal white matter) is related to tumor’s consistency, while SI ratio increases with soft consistency and decreases with hard consistency [25]. In this study, however, there was no relationship between tumor’s consistency and the SI ratio of pre-enhanced, enhanced T1-weighted or T2-weighted images which was not aligned with previous results [27]. There is a hypothesis that adenomas with soft consistency contain more water than hard ones, which cause increased SI on T2-weighted images. But on the other hand, functional pituitary adenomas secret proteins which will decrease SI on T2-weighted images. After
separating pituitary adenomas into functional and non-functional ones, we found no SI
difference in each group in terms of consistency, however, SI ratio of T2-weighted images
was significant lower in functional adenomas than non-functional ones. It seems that the
content of protein has much more effects on T2-weighted images than water content
which might limit the usage of T2-weighted images only in non-functional adenomas.

It is still controversial whether DWI with apparent diffusion coef#cient (ADC) maps can
provide information about the consistency of pituitary adenomas. Although ADC ratio
showed no relation with tumor`s consistency in our study, it was relevant to collagen
content. The more collagen in adenomas, the lower ADC ratio correspondingly. In
addition, collagen content is aligned with tumor`s consistency: the collagen content
of pituitary adenomas with hard consistency is 17.72±2.00% (mean ± SD) which is
significant higher than the one in adenomas with soft consistency (7.27±1.18%). Since
ADC ratio can reflect the collagen content which is relevant to tumor`s consistency, it
should have correlation with consistency of pituitary adenomas at surgery which hasn`t
been proved in our study. It may due to subject factors at surgery, small samples or other
reasons.

There remains a certain capacity for improvement: First, the manual judgment of
consistency at surgery was subjective and would definitely cause bias, which may bring
about a different result. Second, the size of sample is small relatively so that a further
research should be carried out. Third, since the consistency of tumor is not homogenous,
the pathological tissues of pituitary adenomas are randomized selected from whole
tumors which might not the section surgeon used for judgement at surgery. Fourth,
during the process of preparing specimens, tumor tissue was dehydrated, so the collagen
content calculated can not represent the accurate one, which means it is hard to correlate
water content with SI on T2-weighted images from pathological view.

Because of the connection between ADC ratio and collagen content of pituitary
adenomas, further research could be conducted to explore the possible relation between
ADC ratio and consistency of pituitary adenomas with a large sample.
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