Relationship Between Pituitary Adenoma Consistency and Extent of Resection Based on Tumor/Cerebellar Peduncle T2-Weighted Imaging Intensity (TCTI) Ratio of the Point on Preoperative Magnetic Resonance Imaging (MRI) Corresponding to the Residual Point on Postoperative MRI

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Background: Controversies exist in imaging modalities for predicting adenoma consistency. In this study, we proposed a method of predicting consistency by magnetic resonance T2-sequence imaging based on adenoma to cerebellar peduncle signal (TCTI) ratio.

Material/Methods: Between January 2013 and May 2017, 191 consecutive patients with pituitary adenoma diagnosed at our institution were retrospectively studied. The consistency grade for each lesion was assigned. And the TCTI ratio based on preoperative and postoperative T2-weighted imaging was calculated.

Results: The median TCTI ratio was 1.55, 1.28, and 1.25 for soft, fibrous, and hard adenomas, respectively. The differences were significant for all groups (p<0.001). A cutoff value of 1.38 for soft adenomas was found to be 80.2% sensitive and 88.7% specific. The median ratio of the outermost layer of residual tumor was 1.25 (SD±0.408, 95% CI 1.27–1.42). It was less than that ratio of the upper, lower quarter, and middle region of adenoma, respectively, and the inter-group differences were all statistically significant with p≤0.001. The extent of resection for the soft group was significantly greater than that of the hard group (85.3% vs. 70.6%, p=0.011). Analysis of Variance (ANOVA) revealed that the consistency grade was the influencing factor of degree of resection. p=0.003.

Conclusions: The TCTI ratio showed a good correlation with pituitary adenoma consistency. We also determined the optimal ratio of the residual adenoma.

MeSH Keywords: Decision Support Techniques • Magnetic Resonance Imaging • Pituitary Neoplasms

Abbreviations: MRI – magnetic resonance imaging; ANOVA – analysis of variance; FIESTA – fast imaging employing steady-state acquisition; TCTI – tumor/cerebellar peduncle T2-weighted imaging intensity; ROI – region of interest; AUC – area under curve; DWI – diffusion-weighted imaging; ADC – apparent diffusion coefficient

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Background

Pituitary adenomas usually have a soft texture [1–5], and this type of adenoma is easily resected with curettage and suction [6–8]. Approximately 5–13% of pituitary adenomas have a firm consistency [6–9]. Compared with the easy suctioning of soft tumors, firm tumors can pose a great challenge to neurosurgeons because they are more difficult to dissect from critical structures [9–11]. If the texture of a pituitary adenoma is known preoperatively, patients can be informed about the real target, surgical expectations, the risk for second surgeries from above, and any need for post-surgical adjuvant radiotherapy/radiosurgery. Furthermore, it may help surgeons to plan a better operative strategy and to reduce the risk of surgery.

There have been many studies on distinguishing tissues or predicting tumor consistency, including development of a variety of imaging modalities [1–4, 6–8, 10–18]. However, it is unclear whether the signal intensity of a pituitary adenoma in radiologic imaging correlates with its consistency. Some studies suggest that diffusion-weighted imaging and magnetic resonance T2-sequence intensity help to predict the texture of pituitary adenomas [5,7,14,16], while other research did not yield statistically significant results [6,8,13,19]. Ma et al. concluded that the consistency of a pituitary adenoma could be predicted using MR T1-spin echo imaging [15]. Yamamoto et al. obtained a similar conclusion on contrast-enhanced fast imaging employing steady-state acquisition [3]. Although there are controversies, it seems that T2-weighted sequences strongly indicate tumor consistency.

The consistency of an adenoma affects its removal [20]. To the best of our knowledge, there has been no research investigating the relationship between pituitary adenoma consistency and degree of resection based on the tumor/cerebellar peduncle T2-weighted imaging intensity (TCTI) ratio of the point on preoperative MR image corresponding to the residual point on postoperative MR image. We hypothesized that the signal value in T2-weighted sequences predicted the consistency of adenomas. Thus, the signal of the residual adenoma should be different from that of its surrounding tumor measured before surgery. We conducted this study to determine whether TCTI ratio allows prediction of tumor consistency and whether the signal ratio of the residual tumor is different from its surrounding area [16,18].

Material and Methods

Patients and study outline

Between January 2013 and May 2017, 191 consecutive patients who met the inclusion and exclusion criteria with pituitary adenoma diagnosed at the First Affiliated Hospital of Fujian Medical University were retrospectively included in our study. Patient data, including clinical assessment (at admission, during the immediate postoperative period), and preoperative and postoperative images were collected. The inclusion criteria included the MRI consistent with pituitary adenoma, which was done within 1 month before surgery. The exclusion criteria included previous surgery, history of radiotherapy, and history of bromocriptine or other drugs therapy.

Clinical setting

All patients who underwent microscopic transsphenoidal surgery or neuroendoscopic surgery were operated on by a senior surgeon and his assistant at our institution. Utilizing the most widely used classification method for pituitary adenomas, a consistency grade was assigned based on the surgical instruments used and surgeons’ unanimous identification [8]. Based on their consistency, all tumors included in our study were categorized as soft (easily removed by suction), fibrous (removed with difficulty by suction), or hard (not removable by suction, and excised en bloc), as determined by the primary neurosurgeon during surgery.

Image analysis

All imaging evaluations were conducted by a senior neurosurgical expert who was blind to patient information and has focused on the comprehensive treatment of pituitary adenoma for over 10 years (C.Z.J.). The postoperative 1.5T MR images of these patients were all scanned 3 to 7 days after surgery. A region of interest (ROI) was selected from the cerebellar peduncle in axial sequence [16,18] (Figure 1A). This peduncle ROI, which was circular and of fixed size, was selected by the neurosurgeon blinded to patient information. Three ROIs was selected in a circular shape within the adenoma for representative samplings in coronal sequencing of homogenous tumors [14,16,18] (Figure 1B). Alternatively, for heterogeneous adenomas, multiple ROIs were selected and a representative mean ratio was calculated for the lesion. Microhemorrhagic, necrotic, and microcystic areas were excluded from the ROIs [14]. Utilizing preoperative T2-weighted MR images, TCTI ratios were calculated with the upper and lower quarter regions and middle region of the adenoma. The residual tumor descended or moved in the horizontal line. Thus, the distance from the residual stump to the unresected margin was relatively fixed. In our study, we localized the residual tumor stump in pre-/post-operative MR images with the help of the cavernous segment of the internal carotid artery and the relative distance from the residual stump to the opposite margin. Using postoperative MR images, the distance between the incisal margin and the opposite margin of the residual adenoma was calculated (Figure 1C, 1E). Then, the point of the residual tumor stump was found on the preoperative MR image (Figure 1D, 1F). Similarly, the TCTI ratio using this...
A point was calculated. In this manner, we reduced sampling error. Using MR T2-weighted sequence ROIs, adenomas of different consistencies had corresponding signal ratios. Tumor size was defined as the maximum diameter of the pituitary adenoma in 3 relative planes (axial, coronal, and sagittal). Then, consistency categories and ratios were analyzed.

**Statistical analysis**

The independent-samples t test was used to compare mean ratios of pituitary adenomas to brainstem signal intensity on MR T2-weighted sequences. Receiver operating characteristic analysis was performed to determine an optimal ratio of pituitary adenoma to brainstem T2-weighted signal intensity threshold, for which the Youden index is theoretically the maximum. Using 1-way ANOVA, we compared TCTI ratios and consistency grades. Dunnett’s test was used to analyze variance (degree of resection) on the 3 consistency groups. For all statistics of patient’s characteristics related to consistency grade, 1-way ANOVA and chi-square test were used to assess statistically significant differences. Statistical analysis was performed with SPSS version 19.0. P values less than 0.05 were considered as statistically significant.

**Results**

**Demographic and clinical data**

Patient characteristics are displayed in Table 1. There were 161 (85.3%) patients with adenoma size of 1 to 4 cm. Symptoms of 118 (62.1%) patients were associated with compressed...
17 (8.9%) patients had complications and 2 (1.0%) of them had reoperation; 64 (38.3%) patients had residual adenoma invading the cavernous sinus, and the other 103 did not. Immunohistochemical subtypes in the 3 groups were significantly different (p=0.001). The preoperative and postoperative hematological indexes are shown in detail in Table 1.

Relationship between preoperative images and adenoma consistency

Data were collected for 191 consecutive patients (Table 1); 111 tumors were categorized as soft, 40 as fibrous, and 40 as hard. Figure 2 illustrates the frequency distribution of tumor consistency groups. The TCTI ratio for all pituitary adenoma was from 0.6 to 3.01, with a mean ratio of 1.46. For soft adenomas ratios, the mean value was 1.64 (SD±0.400, 95% CI 1.56–1.71); for fibrous adenomas, the mean ratio was 1.25 (SD±0.128, 95% CI 1.21–1.29); and for hard adenomas, the mean ratio was 1.20 (SD±0.388, 95% CI 1.13–1.29).

The consistency grades of pituitary adenomas and TCTI ratios were compared with 1-way ANOVA. The mean TCTI ratio of soft adenomas was significantly different from that of the other groups (p<0.001) (Table 2). A correlation was determined between consistency ratings and TCTI ratios.

ROC curve analysis was done to determine an exact number that could quickly verify the consistency of the adenoma. The optimal cutoff value of TCTI ratios was determined to be 1.38, with soft adenomas ≥1.38. The value of area under the curve (AUC) was 0.862. This ratio cutoff is 80.2% sensitive and 88.7% specific. The point of residual adenoma on the preoperative image and its TICI ratio on the preoperative image

The preoperative and postoperative imaging data were obtained for 157 consecutive patients, with 49 patients received total resection. The residual tumor volume for the other 108 patients was calculated. Two patients, whose MR image files were not loaded, were eliminated as well. Thus, the distance...
Table 1. Summary of characteristics of 191 patients.

| Characteristic       | Value   | Soft     | Fibrous  | Hard    | p       |
|----------------------|---------|----------|----------|---------|---------|
| Mean age±SD, years   | 47.9±14 | 47.5±14  | 49.8±14  | 47.2±14 | 0.641   |
| Sex                  |         |          |          |         | 0.772   |
| Male                 | 91 (47.6%) | 59 (53.2%) | 19 (47.5%) | 22 (55%) |         |
| Female               | 100 (52.4%) | 52 (46.8%) | 21 (52.5%) | 18 (45%) |         |
| Size                 |         |          |          |         | 0.255   |
| Micro ≤1 cm          | 4 (2.1%)  | 2 (1.8%)  | 0 (0.0%)  | 2 (5.0%) |         |
| Large 1–4 cm         | 163 (85.3%) | 91 (82.0%) | 37 (92.5%) | 35 (87.5%) |         |
| Giant >4 cm          | 24 (12.6%) | 18 (16.2%) | 3 (7.5%)  | 3 (7.5%) |         |
| Knosp grade          |         |          |          |         | 0.369   |
| 0                    | 11 (5.8%)  | 5 (4.5%)  | 4 (10.0%) | 2 (5.0%) |         |
| 1                    | 38 (19.9%) | 22 (19.8%) | 9 (22.5%) | 17 (17.5%) |         |
| 2                    | 44 (23.0%) | 21 (18.9%) | 9 (22.5%) | 14 (35.0%) |         |
| 3                    | 33 (17.3%) | 18 (16.2%) | 8 (20.0%) | 7 (17.5%) |         |
| 4                    | 65 (34.0%) | 45 (40.5%) | 10 (25.0%) | 10 (25.0%) |         |
| Preoperative hematological parameters |         |          |          |         |         |
| ACTH 8am pg/mL       | 37.96±32.23 | 36.90±34.78 | 38.39±27.56 | 40.70±29.51 | 0.859   |
| ACTH 4pm pg/mL       | 22.03±22.13 | 20.95±17.43 | 26.13±30.25 | 20.63±24.31 | 0.497   |
| PRL mIU/L            | (20.46–830.00) | (197.10–803.00) | (296.35–967.65) | (204.50–844.00) | 0.387   |
| GH ug/L              | 92.37±1058 | 147.71±1378 | 7.41±17.09 | 18.35±52.12 | 0.721   |
| TSH mIU/L            | 2.34±3.90  | 2.03±2.71  | 3.39±6.92 | 2.21±2.31 | 0.198   |
| FSH IU/L             | 15.64±26.87 | 16.56±30.65 | 12.81±16.43 | 15.96±24.24 | 0.768   |
| LH IU/L              | 5.26±7.66  | 5.52±8.94  | 4.76±5.72 | 5.01±5.1 | 0.857   |
| Main complain         |         |          |          |         |         |
| Excessive hormone secretion | 25 (13.2%) | 13 (11.8%) | 6 (15.0%) | 6 (15.0%) |         |
| Insufficient hormone secretion | 26 (13.7%) | 15 (13.6%) | 4 (10.0%) | 7 (17.5%) |         |
| Compression of surrounding structure | 118 (62.1%) | 75 (68.2%) | 22 (55.0%) | 21 (52.5%) |         |
| Tumor stroke         | 5 (2.6%)   | 1 (0.9%)   | 2 (5.0%)  | 2 (5.0%)  |         |
| Absence of symptoms  | 16 (8.4%)  | 6 (5.5%)   | 6 (15.0%) | 4 (10.0%) |         |
| Hematological index after surgery (Day 1) |         |          |          |         |         |
| ACTH 8 am pg/mL      | 41.33±77.64 | 35.72±52.61 | 62.02±131.05 | 28.00±18.93 | 0.329   |
| ACTH 4 pm pg/mL      | 59.86±101.11 | 75.71±114.78 | 55.38±77.99 | 68.09±57.28 | 0.739   |
| PRL mIU/L            | (91.90–524.80) | (178.09–531.08) | (187.65–570.50) | (45.94–305.40) | 0.604   |
| GH ug/L              | 5.95±10.89 | 5.74±11.26 | 6.54±12.08 | 5.96±8.08 | 0.962   |
of the residual adenoma from stump to top was calculated for 106 patients, as well as the TICI ratio, using the point where the residual tumor stump was in found in the preoperative MR image as a reference.

The mean residual tumor volume was 4.03±7.803 cm³ (95% CI 2.73–5.67). The mean degree of resection was 79.9±25.9% (95% CI 75.8–83.6%), and the mean distance between the incisal margin and the opposite margin of the residual adenoma was 1.54 cm (SD±0.76, 95% CI 1.40–1.69 cm). The ratio for the residual point was 1.34 (SD±0.408, 95% CI 1.27–1.42). The ratio was less than the ratio of the upper quarter, lower quarter, and middle regions of adenomas, and the differences were all statistically significant (p £ 0.001).

According to the Knosp E’s classification system, the degrees of resection for grade 0-4 adenomas were 84.0%, 81.0%, 86.6%, 78.2%, and 74.2%, respectively, but there was no significant difference between them. When they were divided into 2 groups (grade 0–2 and grade 3–4), degree of resection of the former group was greater than that of the latter group (83.8% vs. 75.6%, p=0.045). The degree of resection for adenomas in which there was a residual tumor invading the cavernous sinus after resection was less than in the ones without such invasion, at 69.9% vs. 85.6%, respectively (p<0.001). The mean preoperative adenoma volume of the total resection group was less than that of the partial resection group (4.23 cm³ vs. 13.10 cm³) (p<0.001). The degree of resection for the soft group was significantly greater than that of the

Table 1 continued. Summary of characteristics of 191 patients.

| Characteristic                        | Soft          | Fibrous       | Hard        | p     |
|---------------------------------------|---------------|---------------|-------------|-------|
| TSH mIU/L                             | 5.39±40.63    | 7.94±52.17    | 1.83±3.42   | 1.02±1.00 | 0.702 |
| FSH IU/L                              | 10.40±11.98   | 10.37±12.98   | 9.78±9.75   | 11.66±11.87 | 0.896 |
| LH IU/L                               | 4.84±6.32     | 4.37±6.15     | 4.60±5.79   | 7.50±7.87   | 0.263 |
| Immunohistochemical subtypes           |               |               |             | 0.001*   |
| ACTH positive                         | 6 (3.1%)      | 5 (4.5%)      | 1 (2.5%)    | 0 (0.0%)  |
| FSH positive                          | 30 (15.7%)    | 8 (7.2%)      | 14 (35.0%)  | 8 (20.0%)  |
| GH positive                           | 4 (2.1%)      | 3 (2.7%)      | 0 (0.0%)    | 1 (2.5%)   |
| LH positive                           | 1 (0.5%)      | 1 (0.9%)      | 0 (0.0%)    | 0 (0.0%)   |
| PRL positive                          | 18 (9.4%)     | 11 (9.9%)     | 5 (12.5%)   | 2 (5.0%)   |
| TSH positive                          | 1 (0.5%)      | 0 (0.0%)      | 0 (0.0%)    | 1 (2.5%)   |
| Multiple items positive               | 17 (8.9%)     | 9 (8.1%)      | 4 (10.0%)   | 4 (10.0%)  |
| Negative                              | 110 (57.6%)   | 71 (64.0%)    | 15 (37.5%)  | 24 (60.0%) |
| Residual adenoma invading cavernous sinus |            |               |             | 0.912    |
| No                                    | 104 (61.5%)   | 60 (60.6%)    | 22 (61.1%)  | 22 (64.7%) |
| Yes                                   | 65 (38.5%)    | 39 (39.4%)    | 14 (38.9%)  | 12 (35.3%) |
| Complication                          |               |               |             | 0.333    |
| No                                    | 174 (91.1%)   | 103 (92.8%)   | 34 (85.0%)  | 37 (92.5%) |
| Yes                                   | 17 (8.9%)     | 8 (7.2%)      | 6 (15.0%)   | 3 (7.5%)   |

Data are n (%), mean±SD, and median (25–75%).

Figure 2. Frequency distribution for TCTI ratio by consistency.
Table 2. Pituitary adenoma consistency groups statistics.

| Category | Overall TCTI Ratio | Pituitary adenoma Consistency Grade |
|----------|--------------------|------------------------------------|
|          | Mean               | Median                            |
|          | Max                | Min                               |
| Soft     | 1.46               | 1.64                              |
| Fibrous  | 1.25               | 1.55                              |
| Hard     | 1.21               | 0.83                              |

Discussion

Prediction of consistency carries implications for the neurosurgeon. However, it is clinically valuable to reliably evaluate consistency as it can lead to better counseling of surgical risks.

Several research studies had shown that pituitary adenoma texture is one of the factors affecting resection rate [10,14]. We also found that the consistency rate was correlated with degree of resection. In the subgroups analysis, we divided the patients into higher Knosp grades (3–4) and lower Knosp grades (0–2), and we got the same result in the lower Knosp grades group (90.7% vs. 69.3%, p=0.003). In the higher Knosp grades group, there was no significant difference between the soft group and hard group (80.0% vs. 66.6%, p=0.17).

In this study, we investigated the relationship between pituitary adenoma consistency and extent of resection based on TCTI ratio of the point on the preoperative MR images corresponding to the residual point on the postoperative MR image. TCTI ratios of fibrous and hard adenomas were significantly lower than that of soft adenomas. A TCTI of 1.38 was 80.2% sensitive and 88.7% specific for soft adenomas (≥1.38).
Pathological studies suggest that collagen content in firm adenomas is greater than that of soft ones [3,7,10,11,14]. It has been proven that the percentage of collagen content is reversely associated with T2-sequence intensity of adenomas and other relevant tissues [7,9,21–24]. Furthermore, fibrous tumors with low water content would have lower T2-weighted signal intensity than soft resectable tumors. Other studies also showed that increased vascularity and expression of TGFβ1 play an important role in adenoma consistency [11,25]. For our study, the lower ratio of hard adenomas was a reasonable result. Prediction of adenoma consistency helps plan better operative strategies and reduces the risk of surgery.

There were also limitations regarding our consistency analysis. Different researchers graded tumor consistency differently. Our consistency categories were classified into 3 groups, while some authors rate into only soft and firm groups. In addition, there is a continuum of consistency in clinical practice. Although we used standard criteria to assess texture by the same surgeon, this method for assessment is subjective and can cause bias. Although we utilized the postoperative MRI scan performed 3 to 7 days after surgery, results may be affected by artifacts or other effects. Intraoperative MRI, which precisely assesses the degree of tumor removal, could minimize the bias.

Conclusions

The TCTI ratio on MR T2-sequence imaging showed good correlation with adenoma consistency. A cutoff ratio of 1.38 showed good sensitivity and specificity for predicting soft consistency. Also, the residual adenoma had a signal ratio lower than that of its surrounding region, which meant hard consistency in our study. The consistency rate was correlated with degree of resection, especially in the patients with lower Knosp grades. Further prospective and large-scale studies should be conducted to validate our conclusions.

Conflict of interest

None.

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