**Original Article**

**MRI research of diaphragma sellae in patients with pituitary adenoma**

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**Abstract:** This study is to investigate the clinical significance of diaphragma sellae in patients with pituitary adenoma by MR images. A total of 47 cases of pituitary adenoma patients were enrolled in this study. Preoperative and postoperative MR scanning together with preoperative 3D-GE sequential scanning were performed. A series of parameters of diaphragma sellae were measured and compared. Tumor height was greater in patients with convex diaphragma sellae than that in patients with concave diaphragma sellae. The width and height of diaphragmal opening were positively related to tumor height. Diaphragmal opening width in the invasive group was greater than that of the non invasive group. Diaphragmal opening width in the non total resection group was significantly greater than that in the total resection group. Tumor resection rate was negatively correlated to diaphragmal opening width in the non total resection group. Lift angle of bilateral epidural around diaphragmal opening was positively related to tumor height. Enhanced 3D-GE images can perfectly display diaphragma sellae and parameters of tumor height and tumor invasiveness are related to diaphragmal opening diameter.

**Keywords:** Pituitary adenoma, diaphragma sellae, diaphragmal opening, MRI

**Introduction**

Diaphragma sellae (DS) is a layer of epidural mater structure, covering the above of pituitary and forming the top of pituitary fossa. For patients with pituitary adenoma (PA), DS has a special meaning in both tumor growth and transsphenoidal approach operation [1, 2]. Anatomy studies on DS morphology of normal people are conducted [1, 3-6], however, no in-depth reports of DS are published for patients with PA. As early as 1986, Daniels et al. [7] firstly observed DS in patients with PA in MR images and they described it as a low shadow signal line above pituitary. Because contrast agent was not widely used in clinical at that time, nor did the existence of the sequence concept, the image displaying effect for DS was not ideal. With the development of MR technology, many scholars have focused on epiepidural-all structures such as DS using MR [8-10]. However, they all paid attention to DS displaying effect but did not further analyze DS morphology not to mention compare PA patients with normal people. Farn et al. [11] found that while compared with the conventional spin echo (SE) enhanced images, epidural structures displaying in 3D gradient echo (GE) sequential enhanced images was with a higher percentage, longer fragments and better continuity. Based on previous studies, in order to better display DS in patients with PA, 3D-GE sequential enhanced scanning was used and the scanning parameters had been adjusted in this study. The accurate parameters were measured to investigate the clinical application value of DS in patients with PA.

**Materials and methods**

**Patients’ data**

A total of 47 cases of patients admitted to our hospital and diagnosed as PA from March 2012 to April 2013 were enrolled. Among them, 22 were male and 25 were female. They were aged from 23-70 years old, with an average age of 45.1 years old. Among them, 1 case was micro...
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Figure 1. Measurement markers of all parameters used in 3D-GE sequential enhanced MRI coronal scanning. A. The right bordering of diaphragma sellae dura connecting to the lateral wall of cavernous sinus. B. Diaphragma sellae dura end on the right of diaphragmal opening. C. Diaphragma sellae dura end on the left of diaphragmal opening. D. The left starting point of diaphragma sellae dura. The distance between “b” and “c” was diaphragmal opening width. The sum of the distance of “a”-“b” and “c”-“d” was the width of diaphragma sellae dura on both sides of diaphragmal opening. The average value of the angle between “a”-“b”, “c”-“d” and the horizontal line was the lift angle of diaphragma sellae dura on both sides of diaphragmal opening. The arrows showed the pituitary stalk.

Adenoma (diameter < 10 mm), 41 cases were large adenoma (10 mm < diameter < 40 mm) and 5 cases were giant adenoma (diameter > 40 mm). Tumor height was 8.90-60.11 mm, with an average height of 26.40 ± 11.59 mm. The main symptoms included headaches, blurred vision, amenorrhea, lactation, acromegaly, loss of libido, etc. The longest duration was 10 years and the shortest was less than 1 month. Postoperative immunohistochemistry confirmed that there were 18 cases of nonfunctional adenoma, 7 cases of prolactin type, 7 cases of growth hormone type, 2 cases of adrenocorticotropic hormone type, 7 cases of gonadotropin type, 1 case of thyroid stimulating hormone type and 5 cases of multiple hormone type.

The inclusion criteria were described as follows. PA patients who had not taken surgery before admission. Patients who could cooperate with MR checking preoperative and postoperative. Patients those taken endonasal transsphenoidal operation of tumor resection and the operators were the corresponding authors of this study. Patients with PA confirmed by sur-
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Figure 2. Diaphragma sellae morphology in 3D-GE sequential enhanced MRI coronal images. A. Concave type. B. Horizontal type. The white arrow showed the pituitary stalk. C. Convex type. The sellar was pushed upward by the tumor and diaphragmal opening was expanded. The white arrow showed the pituitary stalk.

Table 1. Measuring data of pituitary adenoma and diaphragma sellae of the 47 cases of patients

<table>
<thead>
<tr>
<th>Measurement parameters</th>
<th>Measurement result</th>
</tr>
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<tbody>
<tr>
<td>SE sequence</td>
<td></td>
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<tr>
<td>Tumor height</td>
<td>(26.40 ± 11.59) mm</td>
</tr>
<tr>
<td>Tumor resection extent</td>
<td>(91.10 ± 13.80)%</td>
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<tr>
<td>3D-GE sequence (refer to each marker of Figure 1)</td>
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<tr>
<td>Diaphragmal opening width</td>
<td>(7.67 ± 5.11) mm</td>
</tr>
<tr>
<td>Lift angle of diaphragmal opening bilateral dura</td>
<td>(46.53 ± 31.95)°</td>
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<tr>
<td>Diaphragmal opening bilateral dura width</td>
<td>(18.37 ± 6.60) mm</td>
</tr>
<tr>
<td>Diaphragmal opening bilateral dura thickness</td>
<td>(0.94 ± 0.20) mm</td>
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</table>

Figure 3. Scatter diagram of the relationship between tumor height and the width of the diaphragm sellae opening.

MRI examination

All the patients received MRI examination before and after surgery with Siemens trio 3.0T MR (Global Siemens Healthcare Headquarters, Erlangen, Germany). Axial, coronal and sagittal plain and enhanced scan images of SE sequential T1WI and T2W were collected. Coronal 3D-GE enhanced scan was taken preoperatively. The parameters employed were as follows: TR/TE, 7/2 ms; Fov, 180 mm × 180 mm; matrix, 448 × 305; slice thickness, 0.8 mm. At 30 s after the injection of contrast agent, uninterrupted continuous scanning was carried out. The contrast agent was GD DTPA, with a dosage of 0.1 mmol/kg, i.v.

Image analysis

The collected MRI images were read by at least two attending or rather seniority physicians and an attending or rather seniority neurosurgeon. DS morphology was observed in 3D-GE coronal enhanced images. DS was the inward extended enhancing shadow line between bilateral cavernous segment of internal carotid artery and supraclinoid segment. In most cases, DS extended inward to bilateral sides of surgery. The exclusion criteria were PA patients taking operation because of recurrence. Prior written and informed consent were obtained from all patients and the study was approved by the ethics review board of the Fuzhou General Hospital, Fujian Medical University.
hypophyseal stalk and combined with it. In some cases, there might be no hypophyseal stalk, leaving the free epidural border. The surrounding part of the ellipse edge, i.e, the central part of diaphragma sellae dura that without dura covered, was identified as the diaphragmal opening. The layer that maximally displayed diaphragmal opening was selected. The width, thickness, and lift angle of bilateral epiepidural together with diaphragmal opening width were measured with PACS system (Figures 1 and 2). Tumor morphology was observed in SE enhanced images, meanwhile, grading indexes like tumor height and SIPAP [12] were recorded (Table 1). In the enhanced images before and after operation, tumor boundary was artificially outlined and tumor area of each layer was automatically measured with computer. Tumor volume was calculated by adding thickness of each layer preoperative and postoperative, thereby, the degree of tumor resection was calculated. The correlation among DS, diaphragmal opening indexes and tumor markers was compared.

Statistical analysis

All data were analyzed by SPSS19.0 software (SPSS Inc, Chicago, IL, USA) and P < 0.05 was considered as statistically significant. All data were analyzed with Kolmogorov-Smirnov test and data met normal distribution were expressed as x ± s. A linear regression was performed between the two variables. An independent-sample t test was carried to compare the difference between groups. χ²/Fisher exact probability was used for ranked data comparison. Nonparametric test was performed for data that did not meet normal distribution.

Results

Comparison of DS morphology

In order to understand the growth characteristics of PA, DS morphology of the patients were recorded and compared. DS were integrity in all the 47 cases and fell into concave type, horizontal type and convex type. The cases of the three types were 3 (6.4%), 10 (21.3%) and 34 (72.3%), respectively. Tumor height of the three types were (13.57 ± 4.42) mm, (22.03 ± 10.77) mm and (28.82 ± 11.29) mm, respectively. Tumor height of the convex type was significantly larger than that of concave type (P < 0.05). However, there were no significant difference in tumor height neither between the convex type and horizontal type or between horizontal type and concave type. In summary, these results indicated that the tumor could lift up diaphragma sellae dura while it grew upward, however, there was no direct evidence showing that diaphragmal opening could expand.

Differences of diaphragmal opening width

In order to identify whether diaphragmal opening was related to tumor growth, diaphragmal opening widths in different groups were compared. Diaphragmal opening width of the 47 cases of PA patients was 1.45-21.87 mm with an average of (7.67 ± 5.11) mm. Diaphragmal opening width and tumor height were made into scatter plot and analyzed with linear regression, and the result showed positive correlation between the two parameters (r = 0.224, P = 0.003) (Figure 3). According to Hardy-Wilson staging [13] and Knosp grading [14] classification, preoperative MRI of W-Hardy staging above stage C and Knosp grading higher than level 3 were considered as invasive PA group and the conversely were taken as non invasive PA group. There were 21 cases (44.7%) in invasive group and 26 cases (55.3%) in non invasion group. Diaphragmal opening width of the invasive group was significantly higher than that of non invasive group, with statistically significant difference (Table 2). There were 29
cases of tumor complete resection (61.7%) and 18 cases (38.3%) of incomplete resection. The incomplete resection cases all were from the invasive group. Diaphragmal opening width of incomplete resection cases was significantly larger than that of the complete resection cases, with statistically significant differences (Table 3). In the 18 cases of non complete resection patients, tumor resection rate and diaphragmal opening width were negatively correlated ($r = -0.576, P = 0.02$). As a conclusion, the above results argued that the larger the diaphragmal opening, the easier the tumor grows upward to diaphragmal opening and the harder the tumor to be removed.

**Comparison of the lift angle of bilateral epidural around diaphragmal opening**

To find out whether lift angle of diaphragmal opening caused by tumor was positively linked to tumor height, the lift angle of bilateral epidural around diaphragmal opening was measured and compared. The average degree of the lift angle of bilateral epidural around diaphragmal opening (i.e. bilateral diaphragma sellae around diaphragmal opening) of the 47 cases of patients was $(46.53 ± 31.95)$. Lift angle and tumor height were made into scatter plot and analyzed with linear regression and the result indicated positive correlation between the two parameters ($r = 0.586, P = 0.000$) (Figure 4). There was no significant difference in lift angle of bilateral epidural around diaphragmal opening ($P > 0.5$) neither between the invasive group and non invasive group nor between complete and incomplete groups. These results indicated that the tumor had upward pushing force all the time it grows even if it has passed the diaphragmal opening.

**Comparison of bilateral epidural around diaphragmal opening width and thickness**

To identify whether there was biological invasion or phagocytosis existed, bilateral epidural around diaphragmal opening width and thickness were measured and compared. Average width of bilateral epidural around diaphragmal opening of the 47 cases was $(18.37 ± 6.60)$ mm and there was no significant correlation ($r = 0.277, P = 0.059$) between epidural width and tumor height. Bilateral epidural around diaphragmal opening width of invasive group and non invasion group were $(18.59 ± 6.33)$ mm and $(18.19 ± 6.93)$ mm, respectively, with no significant difference between them. The width of bilateral epidural around diaphragmal opening in complete resection group and incomplete resection group were $(19.10 ± 6.58)$ mm and $(17.18 ± 6.63)$ mm, and there was no significant difference. Average thickness of bilateral epidural around diaphragmal opening in the 47 cases was $(0.94 ± 0.20)$ mm, and there was no significant correlation ($r = 0.050, P = 0.740$) between epidural thickness and tumor height. There was no significant difference neither between invasive group and non invasive group nor between complete resection group and incomplete resection group. To sum up, these results suggested that no invasion or phagocytosis was found no matter the PA was invasive or non invasive.

**Discussion**

In this study, 3D-GE sequential MRI was adopted to show DS and this method had received good results. Based on previous reports [7-11, 14, 15], a series of parameters used in this study had been modified. Short TR and TE were
used to shorten the time of a single excitation in order to adjust matrix and vision thus improving signal to noise ratio. A 0.8 mm ultrathin layer thickness and continuous scanning was adopted to increase DS appearing layer numbers as far as possible. Image collection was started 30 s after injection of contrast agent so as to achieve rich intravenous development of DS epidural structures using the circulation period within contrast agents into the venous. Besides, the image scanning was taken sing 3.0T MRI with high resolution, thus observing satisfactory DS morphology. One minor short coming was that sagittal and axial images were not collected lacking of three-dimensional observation effect. The method of measuring and analyzing DS morphology in patients with PA after DS on MRI has not been reported.

Due to the limitation of specimens, previous anatomical study on DS and PA was difficult to be linked together. As a result, there was no direct evidence for mutual influence between PA growth and DS, and the relationship was mainly remained on theoretical speculation. None of the sporadical imaging researches on DS in patients with PA [7, 8, 15] measured the accurate parameters of DS. Daniels et al. [7] has studied DS structure with MRI plain scan, however, DS were observed only in some cases. In addition, the researchers focused mainly on DS displaying effect. In this study, enhanced MRI was used and DS displaying received ideal result in each case. Cattin et al. [8] have compared SE sequential sagittal enhanced MRI of PA and normal people. They found that DS epidural thickness in some patients with PA was thickened. However, they did not compare the data systematically and they just observed from one point of view, which was not a comprehensive understanding. Nomura et al. [15] used transsphenoidal approach parallel level scanning for observing sellar region. Pituitary stalk and diaphragmal opening were discovered in MRI images in some pituitary micro adenoma patients and were measured. However, pituitary macro adenomas and giant adenoma were not observed, thus, it was difficult to analyze the effect of tumor growth on DS. In this study, not only 1 case of micro adenoma but more macro adenomas and giant adenomas were included, which, can comprehensively reflect the interaction between tumor and DS. A short coming of this study was that relatively few cases were collected in this study.

It is reported that 35% PA are diagnosed as invasive adenoma [16]. During the growth, invasive PA can destroy the medial wall of cavernous sinus, sellar epidural, even the floor of sella bone structure. As the pituitary fossa top, DS is the only way by which PA growing to the saddle. The middle of DS is diaphragmal opening, which is a natural passage that leading to saddle. Just as the existence of diaphragmal opening, making the relationship of DS with tumor different from the medial wall of cavernous sinus and sellar epidural. To date, whether the contact mean is infiltrating growth or just a simple expansion process, there is controversy. In this study, histological technique had not been used to test whether there was infiltration of tumor on DS, however, MR observation itself also had some persuasion. One short coming was that as DS is relatively thin and currently MRI precision is limited, as a result, there are certain errors in actual measurement process.

Yao Yiqun et al. [17] have taken biopsy of DS during surgery, and their results showed that there was infiltration of PA on part of DS. As DS is an important structure for preventing the leakage of cerebrospinal fluid, direct biopsy is not widely recognized. Wang Jianxin et al. [18] proposed that invasive PA growth might not play a destructive role by means of infiltration, but by expansion, which causing the thinning of surrounding structures. They also argued that PA was monoclonal origin. Their conclusion could be applied to other parts including DS. Defects of the medial wall of cavernous sinus, sellar epidural and bone were seen and even cavernous sinus top wall defect appeared in this study, however, all DS were complete. There was no statistic difference between invasive group and non invasive group in DS thickness and bilateral epidural around diaphragmal opening comparison, which could not support the existence of DS infiltration. Lift angle of bilateral epidural around diaphragmal opening was positively related to tumor height, suggesting that tumor growth had the effect of upward process. Diaphragmal opening width in invasive group was significantly higher than that of non invasive group indicated that invasive PA could expand diaphragmal opening while passing from diaphragmal opening into saddle. Hence one can see that as the tumor grows upward, the main effect is squeezing DS upward and the evidence of whether there is infiltration is not sufficient.
It was reported that postoperative residual rate of non functioning adenomas was 50% [19]. Another researcher reported non functional giant PA growing to saddle in 68 patients receiving transsphenoidal operation. One stage complete resection accounted for only 20.6% (20 cases), and the other 48 cases all had residual tumors [20]. Postoperative tumor residual of cavernous sinus was common in clinical, and suprasellar part residual was often seen. Besides tumor texture, DS is another reason that causing tumor difficult to settle into intrasellar. The larger the preoperative imaging of diaphragmal opening, the more difficulty the tumor to be totally extracted.

In conclusion, 3D-GE enhanced imaging was used to display DS and edipaphragmal opening, and this method could be popularized in related research in the future. During the growth of PA, it could push DS upward. diaaphragmal opening width and lift angle of diaphragmal opening bilateral epidural were positively related to tumor height. The diaaphragmal opening of invasive PA was larger than non invasive PA and the larger the tumor, the harder the tumor to be totally extracted.

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Disclosure of conflict of interest

None.

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