**Sphenoid sinus anatomy and suprasellar extension of pituitary tumors**

Clinical article

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**Object.** As tumors enlarge, they generally grow along paths of least resistance. For pituitary macroadenomas, extrasellar extension into the suprasellar region, cavernous sinus, or sphenoid sinus may occur. The sphenoid sinus is known to have a variable anatomical configuration, and the authors hypothesize that certain anatomical factors may resist tumor expansion into the sphenoid sinus, thereby directing tumor growth into the suprasellar space. In this paper the authors’ goal was to determine if sphenoid anatomy influences pituitary tumor growth.

**Methods.** The authors conducted a retrospective analysis of 106 consecutive surgical cases of pituitary macroadenoma. Patient demographics, suprasellar extension, sellar width, and features of the sphenoid intersinus septum were recorded on radiographic review. The chi-square test, t-test, logistic regression, and classification and regression tree analysis were used for statistical analysis.

**Results.** Of the 106 patients included in the study, 71 (67%) demonstrated suprasellar extension of their tumor. Patients with suprasellar tumor extension had significantly greater intersinus septum width (width > 1.27 mm: OR = 14.32; p = 0.0012) and were significantly older (age > 54 yrs: OR = 3.33; p = 0.0176). They also tended to be male and to have two or more sphenoid partitions (OR = 6.58; p = 0.0306). While patients with suprasellar extension tended to be more likely to have a midline partition and a larger sellar width than their counterparts, these differences did not reach statistical significance.

**Conclusions.** Certain aspects of the sphenoid sinus anatomy may function to resist pituitary tumor growth into the sphenoid sinus. Progressive enlargement of pituitary macroadenomas may extend in a suprasellar direction, in part, as a consequence of the sphenoid sinus anatomy.

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**Key Words** • pituitary tumor • macroadenoma • suprasellar • sphenoid sinus • intersinus septum • pituitary surgery • skull base

**Abbreviation used in this paper:** CART = classification and regression tree.
sinus and its partitions may aid in resistance of downward growth into the sinus, thereby directing an enlarging sellar lesion to spread into the suprasellar space. The aim of this study is to determine if particular sphenoid anatomical features are associated with suprasellar extension of pituitary tumors.

**Methods**

This study was approved by the University of Pennsylvania Institutional Review Board. A retrospective review of consecutive transnasal endoscopic surgeries performed for pituitary macroadenoma between 2006 and 2011 was performed at a tertiary care institution (University of Pennsylvania). Patients with a prior history of sphenoid or pituitary surgery were excluded. Patients with presellar or conchal pneumatization patterns of the sphenoid sinus were also excluded. Patient medical charts, preoperative pituitary MR images, and preoperative sinon CT scans were reviewed. Patient demographics and anatomical features of the sella and sphenoid sinus were recorded.

**Radiographic Review**

Preoperative CT scans were reviewed in the coronal and axial planes. The presence and number of sphenoid intersinus septations were recorded. The location of insertion of the main intersinus septum was recorded as midline into the sellar floor or lateral. Measurements were taken of the maximal width of the main intersinus septum in the coronal plane and the width of the sella in the coronal plane at the junction of the anterior and middle clinoid processes (Fig. 2). In some cases, the middle clinoid process is not visible, and this measurement was taken at the posterior aspect of the anterior clinoid process. Three observers (V.R.R., J.D.S., and J.Y.L.) blinded to the tumor extension status reviewed each CT scan together and agreed on the specific coronal and axial slice and measurement using the radiographic workstation analysis ruler tool. Preoperative MR images were reviewed, and the presence or absence of suprasellar extension of the macroadenoma was defined by extension above the line drawn from the tuberculum sella to the posterior clinoid process in the sagittal/parasagittal plane.

**Statistical Analysis**

We analyzed the association between tumor growth and the 6 recorded variables: age, sex, number of sphenoid partitions, midline insertion of the main intersinus septum, width of the main intersinus septum, and sellar width before and after adjusting for covariates. Categorical variables were summarized by frequency and continuous variables by mean and standard deviation. The chi-square test was used for comparing categorical variables and the t-test for comparing means for continuous variables.

We used 2 methods of adjusting for covariates. First, we used logistic regression, and we report the adjusted odds ratios obtained under this model. Linearity tests for the relationship between each continuous predictor variable and the outcome variable on the log odds scale were performed by fitting splines. Predictor variables were selected into the final logistic model using backward stepwise selection with liberal p < 0.25 as the retention criteria, as this is an exploratory study and we did not wish to miss a potentially important predictor. Since the sample size may have been inadequate to formally detect departures from linearity for the continuous predictors including age, septum width, and sellar width, the above variables were modeled in 2 ways: 1) in continuous form assuming linearity and 2) as binary variables using the best thresholds. For the latter analysis, the best threshold was defined as the value of the continuous predictor that maximized the chi-square statistic for the odds ratio. The latter analysis does not impose a linear relationship. Prediction accuracy was assessed by a receiver operating curve analysis under the final logistic model. The concordance statistic for the 2 models was compared. The categorical model using thresholds was found to be more accurate, and these results are provided. Since the sample size was assumed to be too small to formally assess potential interaction effects among the 6 predictor variables using the logistic model, all effects in the model were assumed to be additive on the log odds scale.

Finally, as an alternative multivariable strategy to predict the direction of tumor growth, we used the CART method of binary recursive partitioning using the same 6 predictor variables as above. The accuracies under the final tree model were computed, including the percentage
of suprasellar patients correctly predicted by the model, the percentage of nonsuprasellar patients correctly predicted by the model, and the corresponding overall accuracy. Calculations were done using SAS version 9.2 (SAS Institute, Inc.).

**Results**

A total of 106 patients were included in the study; the mean age was 53.2 ± 14.1 years and 53% were men. There were 71 tumors (67%) with suprasellar extension. A descriptive analysis is shown in Table 1. Fifteen (14.2%) of the 106 patients had more than 1 intersinus septation; 69 (65.1%) of the 106 patients had a midline insertion of the main intersinus septum. The mean thickness of the main intersinus septum was 1.15 ± 0.39 mm, and the mean sellar width was 18.05 ± 3.95 mm.

In logistic regression, the following factors were significantly associated with higher odds of having suprasellar tumor growth: larger intersinus septum width (width > 1.27 mm: OR 14.32; p = 0.0012), older age (age > 54 years: OR 3.33; p = 0.0176), and presence of 2 or more sphenoid partitions (OR 6.58, p = 0.0306). Presence of a midline partition and larger sellar width also tended to be associated with higher odds of having suprasellar tumor growth, whereas female sex tended to be associated with smaller odds of having suprasellar tumor growth, but these findings did not reach statistical significance. These results are shown in Table 2. Accuracy in the use of this model is demonstrated with a concordance statistic of 0.82.

To assess linearity, we plotted the relationship between intersinus septum width and age versus the odds of having suprasellar growth on the logit scale (Fig. 3). Although there was no formal evidence to reject linearity at p < 0.05, these plots indicate a trend toward nonlinearity for each of the above predictors. Figure 3 left demonstrates the increased odds of having suprasellar tumor growth as the intersinus septum width reaches a threshold of approximately 1.2 mm. In Fig. 3 right, the curve is relatively flat in the lower age range of 30–50 years, after which there is a considerable increase in the fitted spline. In logistic regression, the best threshold of intersinus septum width that maximized the chi-square statistic for the odds ratio was 1.27 mm, and the corresponding best threshold for age was 54 years.

In the CART analysis, the tree shows that intersinus septum width was the most important predictor of tumor growth direction, followed by age and lastly by sellar width (Fig. 4). Once these 3 predictors were known, the addition of the other 3 predictors in the model did not further improve the prediction of tumor growth direction. Patients who had a septum width greater than 1.22 mm were predicted to have suprasellar tumor growth regardless of the other factors. Patients who had a septum width of 1.22 mm or less were also predicted to have suprasellar tumor growth.

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**TABLE 1: Descriptive analysis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>sex</td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>56 (52.8)</td>
</tr>
<tr>
<td>female</td>
<td>50 (47.2)</td>
</tr>
<tr>
<td>no. of partitions</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>91 (85.8)</td>
</tr>
<tr>
<td>≥2</td>
<td>15 (14.2)</td>
</tr>
<tr>
<td>midline partition</td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>37 (34.9)</td>
</tr>
<tr>
<td>yes</td>
<td>69 (65.1)</td>
</tr>
<tr>
<td>mean age (yrs)</td>
<td>53.22 ± 14.14</td>
</tr>
<tr>
<td>mean septum width (mm)</td>
<td>1.15 ± 0.39</td>
</tr>
<tr>
<td>mean sellar width (mm)</td>
<td>18.05 ± 3.95</td>
</tr>
</tbody>
</table>

* A total of 106 patients were included in the study, of whom 71 had suprasellar tumor extension.
† Mean values are presented as the mean ± SD. Other values are presented as the number of patients (%).

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**TABLE 2: Logistic regression analysis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>Lower CL</th>
<th>Upper CL</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>intercept</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.1095</td>
</tr>
<tr>
<td>female (vs male)</td>
<td>0.48</td>
<td>0.18</td>
<td>1.29</td>
<td>0.1460</td>
</tr>
<tr>
<td>midline partition</td>
<td>1.94</td>
<td>0.70</td>
<td>5.36</td>
<td>0.2013</td>
</tr>
<tr>
<td>no. of partitions (≥2 vs 1)</td>
<td>6.58</td>
<td>1.19</td>
<td>36.33</td>
<td>0.0306</td>
</tr>
<tr>
<td>sellar width &gt;20.08 mm</td>
<td>2.49</td>
<td>0.82</td>
<td>7.61</td>
<td>0.1083</td>
</tr>
<tr>
<td>septum width &gt;1.27 mm</td>
<td>14.32</td>
<td>2.87</td>
<td>71.45</td>
<td>0.0012</td>
</tr>
<tr>
<td>age &gt;54 yrs</td>
<td>3.33</td>
<td>1.23</td>
<td>9.00</td>
<td>0.0176</td>
</tr>
</tbody>
</table>

* Overall accuracy 74%, concordance 0.822. Abbreviation: CL = confidence limit.
† Values in boldface are significant.
growth provided that they were also 1) older than 58.5 years or 2) 58.5 years or younger and had a sellar width greater than 20.47 mm. This tree model identified 62 (87%) of 71 patients with suprasellar extension correctly and 22 (63%) of 35 patients without suprasellar extension correctly, for an overall accuracy of approximately 75%.

Discussion

In the current study, we examined demographic and anatomical factors that may contribute to extrasellar extension of pituitary macroadenomas in the superior direction. One potential challenge in radiographic studies of such a small area is the accuracy of the measurements taken. Reproducibility of our measurements was confirmed by general agreement on comparison with established norms in the literature.5,8 The mean sellar width in this study of 18 mm is in the high range of that found in prior cadaver studies (10–18 mm) and appears consistent given that this population should have an enlarged sella.2,5

In prior anatomical studies, a single major intersinus septum was found in 68% of specimens and inserted as far as 8 mm off from the midline.5 Our data indicate that it is not simply the presence of this midline septum, but its thickness that acts as a buttress to resist inferior extrasellar tumor extension into the sphenoid sinus. It is unclear why advanced age and increased sellar diameter may be risk factors. Advanced age may play a factor in subclinical bony sclerosis and bone deposition within the sphenoid, or perhaps may indicate a prolonged growth period prior to presentation and surgical intervention.7 Tanaka and colleagues6 performed an observational study of 40 patients with residual nonfunctioning adenomas after surgery, showing that tumor volume doubling time is significantly shorter in patients younger than 61 years, and that rapidly growing tumors occurred in patients with a mean age of 51 years. We initially examined the thickness of the sellar floor in addition to the other parameters, but we found this to be so thin in most cases that reliable measurements were not feasible.

Both the logistic model and the tree model agreed that septum width and age were the most significant predictors of suprasellar tumor growth. Sellar width was also a significant factor by the tree model, although it did not reach statistical significance by the logistic model, whereas a higher number of partitions (≥ 2 vs 1) was significant by the logistic model, but not by the tree model. Both of the models had similar overall accuracy (tree 75% vs logistic 74%). Although the statistical findings are very interesting, one must remember that as the sample size is relatively small, some of the findings may not be statistically significant but they may still be clinically significant. For example, based on the current sample size of 106 patients, the presence of a midline partition tended to be associated with higher odds of suprasellar tumor growth (OR 1.94), a finding that was not significant (p = 0.2013). To confirm the above odds ratio with 80% power at p < 0.05, at least 348 patients would be required, assuming that the proportion of patients with suprasellar tumor growth would remain the same as in the current sample.

One limitation of this study lies within its retrospective design. This continuous cohort of patients was selected from the operative experience of a combined otolaryngology-neurosurgery team. It is possible that there was inherent selection bias for more challenging cases or those with significant suprasellar extension to be referred to a tertiary care facility, although our 67% prevalence of suprasellar extension has been similar to that found in the literature in the past. A more definitive study could be performed with a larger prospective cohort of patients on presentation, rather than those surgically managed. To be sure, the applicability of these findings would manifest in patients who undergo observation rather than surgical management. Our data suggest that sphenoid anatomy should be examined in patients who are satisfactorily managed nonsurgically to help predict the likelihood of suprasellar growth and compression of the optic apparatus, which could influence the decision for early surgical intervention.

Conclusions

Sphenoid sinus anatomical variants are clearly im-
Important for surgeons to recognize for the operative management of sellar lesions but may also play a role in the evolution of pituitary macroadenomas. Unique features of the sphenoid sinus may function to resist pituitary tumor growth into the sphenoid sinus, most notably a thick intersinus septum that inserts on the midline. Progressive enlargement of pituitary macroadenomas may extend in a suprasellar direction, in part, as a consequence of the sphenoid sinus anatomy. Additionally, age and sex may be predisposing factors for suprasellar tumor extension.

**Fig. 4.** CART analysis demonstrates that intersinus septum width is the most important predictor of tumor growth, followed by age and sellar width. This model accurately predicted suprasellar extension in 75% of the cohort.
Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Ramakrishnan, Suh, O’Malley, Palmer. Acquisition of data: Ramakrishnan, Suh, Lee. Analysis and interpretation of data: Ramakrishnan, Suh, O’Malley, Grady, Palmer. Drafting the article: Ramakrishnan, Suh. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Ramakrishnan. Statistical analysis: Suh. Administrative/technical/material support: Lee. Study supervision: Ramakrishnan, Palmer.

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