



Research Article

Which is More Predictive in the Extent of Resection of Pituitary Adenomas, Cavernous Sinus Invasion or Preoperative Tumor Volume?

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Summary

Objectives. Pituitary adenoma surgery can be challenging and residual tumor tissue avoids complete recovery. A few studies have explored preoperative tumor volume as a predictor of the presence of a residual tumor besides suprasellar and/or parasellar extension. We aimed to predict the existence of residual tumor by measuring preoperative tumor volume.

Materials and Methods. This retrospective study was performed on 118 patients with pituitary macroadenomas who underwent trans-sphenoidal pituitary surgery in Kartal Lutfi Kırdar and Fatih Sultan Mehmet Research and Training Hospitals between January 2011 and August 2014. We explored the effectiveness and reliability of radiologic variables including preoperative tumor volume and cavernous sinus invasion (Knosp grading) on the presence of residual tumor (thus triggering a need for repeat resection).

Results. The most significant correlation noted was between postoperative residual tumor volume and preoperative Knosp grading ($r= 0.800$, $p<0.001$). Also, we recorded a highly significant positive correlation between postoperative residual tumor volume and preoperative tumor volume ($r= 0.551$, $p<0.001$). The preoperative tumor cut-off volume for gross total resection was 3.4 cm^3 .

Conclusion. The most reliable factor predicting a postoperative residual mass was the existence of cavernous sinus invasion. The possibility of gross total resection decreased as the preoperative measured tumor mass exceeded 3.4 cm^3 .

Key words: Cavernous sinus invasion, pituitary adenoma, suprasellar extension, trans-sphenoidal surgery, tumor volume

Hipofiz Adenomlarında Rezeksiyon Genişliğini Belirlemede Hangisi Üstündür; Kavernöz Sinüs Tutulumu ya da Preoperatif Tümör Hacmi?

Özet

Amaç: Hipofiz cerrahisi, rezidüel tümör dokusu tümüyle iyileşmeyi önlediğinden zorlu bir mücadeledir. Çok az çalışmada preoperatif tümör hacmi rezidüel tümör olasılığının önceden tahmininde suprasellar and/or parasellar uzanımın dışında belirteç olarak araştırılmıştır. Çalışmamızda preoperatif tümör hacmini ölçerek rezidüel tümör varlığını önceden tahmin etmeyi amaçladık.

Yöntem ve Gereç. Bu retrospektif çalışma Kartal Lutfi Kırdar ve Fatih Sultan Mehmet Eğitim ve Araştırma Hastanesinde Ocak 2011 ile Ağustos 2014 arasında trans-sfenoidal cerrahi uygulanan hipofiz makroadenomlu 118 hastada gerçekleştirildi. Preoperatif tümör hacmi ve kavernöz sinüs invazyonunu (Knosp derecelendirmesi) da içeren radyolojik değişken verilerin rezidüel tümör varlığı üzerine olan (böylece tekrar rezeksiyon gereğini tetikleyen) etkinliğini ve güvenilirliğini araştırdık.

Bulgular. En belirgin koreasyon postoperatif rezidüel tümör hacmi ile preoperatif Knosp grade leri arasında bulundu ($r=0.800$, $p<0.001$). Ayrıca yüksek derecede belirgin pozitif korelasyon postoperatif rezidüel tümör hacmi ile preoperative tümör hacmi arasında bulundu ($r=0.551$, $p<0.001$). Gross total rezeksiyon için preoperative tümör hacmi eşik değeri 3.4 cm^3 olarak bulundu.

Sonuç. Postoperatif rezidüel kitleyi tahmin etmede en güvenilir factor kavernoöz sinus invazyonu varlığıydı. Preoperatif ölçülen tümör kitlesi 3.4 cm^3 üzerine çıkınca gross total rezeksiyon olasılığı azalmaktadır.

Anahtar Kelimeler: Hipofiz adenomu, kavernoöz sinus invazyonu, suprasellar uzanım, trans-sfenoidal cerrahi, tümör hacmi

INTRODUCTION

For 50 years, the trans-sphenoidal approach has been the treatment of choice for pituitary adenomas. Currently, this approach is used in 96-99% of cases (1-3). Pituitary adenomas are usually benign, slow growing, and well-circumscribed. However, some exhibit peripheral invasion (4). Tumors can extend to the parasellar region, with invasion of the cavernous sinuses, because no bony elements limit the pituitary fossa (5). Similarly, tumors can pass through the diaphragma sella and extend toward the suprasellar area. Such extension renders total resection difficult. Apart from suprasellar and parasellar extensions of the tumor, the tumor volume per se can also be a limiting factor in effective trans-sphenoidal resection (6,7).

In the present study, the influence of preoperative tumor volume on the likelihood of tumor extension was explored in patients who underwent trans-sphenoidal microsurgery.

MATERIAL AND METHODS

In this retrospective study, data were analyzed on 118 patients who underwent trans-sphenoidal microsurgery via the sublabial route, in Kartal Lutfi Kırdar and Fatih Sultan Mehmet Research and Training Hospitals, between January 2011 and August 2014. All operations were performed by the same senior surgeon (EÇ).

The epidemiologic and clinical findings recorded were age, sex, symptoms at presentation, eye-field test results, hormonal functional deficiencies, and/or excessive hormone production, which are indicative of functional adenomas.

Radiologic evaluations were performed using dynamically enhanced T1-weighted images obtained via hypophyseal magnetic resonance imaging (MRI) on a Philips 1.5-Tesla Aciva device. Measurements of postoperative residual tumor volumes were performed on enhanced, hypophyseal, MRI dynamic scans taken within the first 24 h after surgery. Histopathologic data including those from immuno-histochemical staining and improvements in hormonal problems (if they existed) were also recorded.

Parasellar/cavernous sinus invasion was graded using the Knosp system. This system focuses on the extent to which the adenoma exceeds lines drawn tangential to the medial and lateral edges of the supra- and intra-cavernous segments of the internal carotid artery. After statistical evaluation, all grades except Knosp Grade I are accepted as reflecting cavernous sinus invasion. Volume measurements were performed using Sante DICOM Editor 3.1.24 software (a DICOM imaging and arrangement software). When calculating the volume of an adenoma or a residual tumor, the software first sums the ellipsoid surface areas of chosen sequences obtained during anteroposterior and craniocaudal movement, and multiplies these areas by

the scan thicknesses. The method does not differ from the Cavalieri method commonly used for radiologic area and volume measurements. The advantage of Sante software is that ellipsoids and user-designated areas marked with a freehand tool may be considered, which allows volume measurements to be performed in an almost real-time manner.

While analyzing surgical results, we considered that patients with postoperative tumor volumes of 0 cm³ had undergone gross total resection (GTR), whereas those with any residual tumor volume had undergone subtotal resection (STR).

Statistical methods

The Statistical Package for the Social Sciences (SPSS) version 19 and MedCalc 9 were used for data analysis. The Kolmogorov-Smirnov test was used to explore whether quantitative data were normally distributed. Parametric methods were used to analyze variables that were normally distributed, and nonparametric methods were used to compare data that were not normally distributed. The Mann-Whitney U test was used to compare data between two independent groups, and Spearman's rho test was employed to define intercorrelations between quantitative data sets. Receiver operator characteristics (ROCs) curves were drawn to identify borderline (cut-off) values. We used Pearson Chi-squared testing to compare categorical data. Quantitative data are shown as means \pm standard deviations (SD), or as medians \pm interquartile ranges (IQR). Categorical data are shown as frequencies (n) with percentages (%). The 95% confidence intervals were calculated, and a P value <0.05 was considered to reflect statistical significance.

RESULTS

Baseline characteristics

We studied a total of 118 patients of mean age of 50.8 ± 14 years (range, 21 - 77 years). Of all patients, 60 (51%) were female and 50 (49%) male; the

female:male ratio was thus $\sim 1:1$. A total of 34 patients (28%) had functional adenomas. Of these, 22 were growth hormone (GH)-secreting tumors and 12 prolactin (PRL)-secreting tumors. The most common symptoms at presentation were visual disturbance (62 cases, 52%) and headache (50 cases, 42%). Prevailing symptoms were impotence in males and amenorrhea in females. In the functional adenoma subgroup, although GH-secreting tumors were in the majority, signs and symptoms of acromegaly were dominant.

Characteristics of Tumors

The mean preoperative tumor volume of all patients was 7.75 ± 5.47 cm³. The mean postoperative tumor volume was 0.62 ± 1.04 cm³. When the entire series was subjected to preoperative Knosp grading, 28 (23.7%) patients were grade 0, 36 (30.5%) were grade I, 20 (16.9%) were grade II, 22 (18.6%) were grade III, and 12 (10.2%) patients were grade IV.

Relationships between preoperative volume, cavernous sinus invasion and extent of resection In terms of postoperative tumor volume, 54 (45.7%) patients experienced GTR and 64 (54.3%) STR. The preoperative volumes of various postoperative volume subgroups were recorded. The median preoperative volume of the GTR group was 4.9 ± 4.6 cm³, significantly lower ($P = .001$) than that of the STR group (7.2 ± 10.55 cm³).

A significant association was evident between preoperative Knosp grade and postoperative tumor volume (GTR-STR) ($p < 0.001$). Of the 28 patients with preoperative Knosp grade 0, 24 (85.7%) achieved GTR and 4 (14.3%) had STR; of the 36 patients with preoperative Knosp grade I, 26 (72.2%) achieved GTR and 10 (27.8%) had STR; of the 20 patients with a preoperative Knosp grade II, 4 (20%) achieved GTR and 16 (80%) had STR; of the 22 patients with preoperative Knosp grade III, all achieved STR; and, of the 12 patients with preoperative Knosp grade IV, all achieved STR. The GTR rate was

higher in patients with grades 0, I, and II, whereas the STR rate was higher in patients with grades III and IV.

The highest correlation was between postoperative volume and preoperative Knosp grade. The cut-off (predictive) values of preoperative volume, Knosp grade, and modified Hardy grade in terms of postoperative GTR or STR status, and preoperative Knosp grade (in the absence of invasion) were assessed.

The cut-off value for preoperative volume determined by the extent of GTR/STR was 3.4 cm³, with 48.15% sensitivity and 93.75% specificity. The area under the ROC curve (AUC) was 0.750±0.063, which was highly significant (p<0.001; Fig. 1). When the preoperative tumor volume exceeded 3.4 cm³, the possibility of

GTR attainment was reduced markedly (Figure 1).

The cut-off value of preoperative volume by Knosp grade invasion status was 4.9 cm³ with a sensitivity of 78.57% and a specificity of 75.56%; the AUC was 0.817±0.057, which was highly significant (p<0.001). When the preoperative volume exceeded 4.9 cm³, the likelihood of cavernous sinus invasion increased (Figure 2).

The cut-off value for preoperative Knosp grading in terms of postoperative volume (GTR/STR) status was grade I, with a sensitivity of 92.59% and a specificity of 78.12%; the AUC value was 0.893±0.042 and was highly significant (p<0.001). As the preoperative Knosp grade exceeded I, the probability of GTR status decreased.

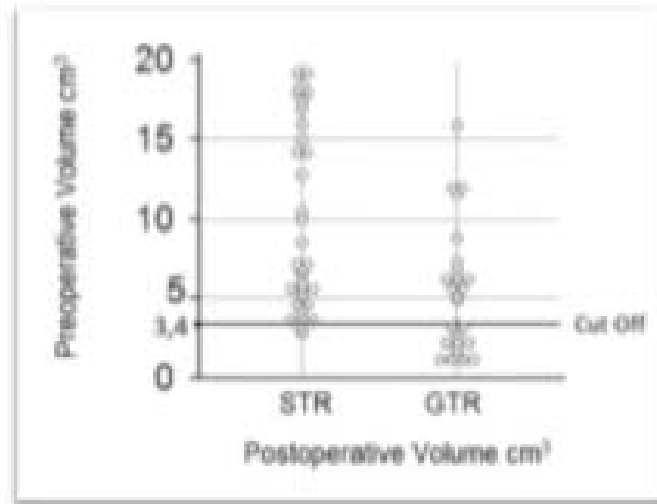


Fig 1. Preoperative volume according to postoperative volume.

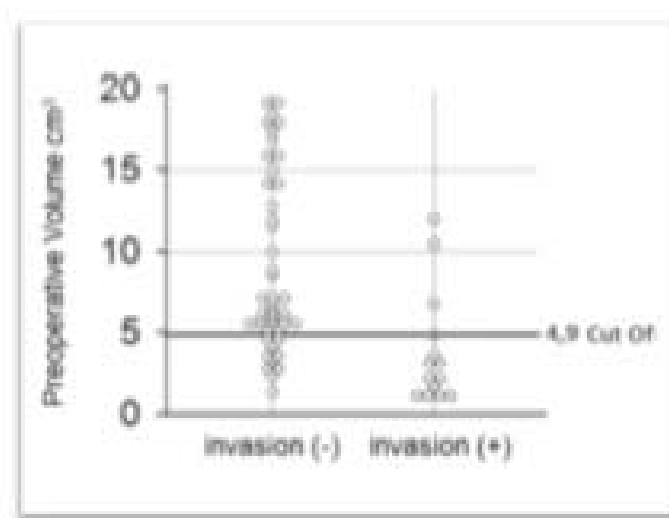


Fig 2. Preoperative volume according to cavernous sinus invasion status.

DISCUSSION

The trans-sphenoidal approach is the most common technique used for excision of pituitary adenomas. Today, the procedure is employed in 96-99% of all cases (2,3). Although the vast majority of patients have very small microadenomas, trans-sphenoidal surgery is indicated for almost all patients with Cushing's disease and patients with acromegaly who over-secrete growth hormone (8,9). In both conditions, the adenoma is usually small, which renders trans-sphenoidal surgery possible (10). In the time since their discovery in the early 1970s, dopamine agonists (DAs) have been considered as options to treat prolactinomas (11). DAs are currently preferred to treat large prolactinomas because adenomas exhibiting suprasellar extensions (SSEs) cannot be surgically excised (12).

Unlike functional adenomas, non-functional tumors are usually very large by the time of diagnosis. Thus, many symptoms are associated with compression of neighboring tissues by the lesion. Prevailing symptoms at presentation include compression of the chiasm,

followed by symptoms of endocrine deficiency. Chiasmal syndromes may be present if lesions have SSEs exceeding 10 mm in length (13). The surgical treatment of non-functional adenomas is rather complex. Functional pituitary adenomas are usually diagnosed before they reach a size that requires transcranial surgery (14).

The frequency of use of trans-sphenoidal and transcranial techniques varies widely between series of patients with non-functional adenoma (2,3,14-19). Surgeon preference and experience play roles, in addition to patient requirements. The literature contains descriptive data on indications for trans-sphenoidal surgery; however, objective (quantitative) criteria are lacking. Also, MRI studies on the resection rates of adenomas with SSEs are few in number. Therefore, we sought to develop a predictive model using tumor size, the extent of SSE, and cavernous sinus invasion status to predict resectability.

Factors influencing adenoma resection

- When limitations of trans-sphenoidal surgery are discussed in the literature,

irregular and asymmetric growth are considered more problematic than SSE (3,17,20,21). We found that total tumor volume and cavernous sinus invasion grade (the Knosp grade) affected tumor resectability to varying extents. Mohr et al. subclassified adenomas into four grades in terms of SSE and claimed that about 39.5% of grade C and D adenomas with extensions over 20 mm recurred or were associated with residual tumors (22).

- It has been claimed that adenomas with irregular SSEs or of multilobular appearance are difficult to resect totally, because the tumors grow by perforating or eroding the diaphragma sellae. Honneger et al. stated that despite such an unfavorable predictor, 39% of patients achieved total resection via trans-sphenoidal surgery and only 11% of patients required repeat surgical interventions (23). The cited authors emphasized that, in such cases, trans-sphenoidal surgery should precede transcranial surgery.

- Several authors found it difficult to safely remove tumors with dumbbell or hourglass-shaped SSEs in trans-sphenoidal surgery (2,3,17,21). Such an appearance is characteristic of tumors that perforate the diaphragma sellae. A similar picture may also be present in patients with small interclinoid distances or narrow intercarotid spaces (24). Honneger et al. reported that the hourglass shape developed as the SSE grew (24). However, the cited authors did not consider that the hourglass shape alone was a significant predictor of incomplete resection.

- The dimensions of the pituitary fossa are important when a trans-sphenoidal approach is considered (17,25). Non-adenomatous lesions (e.g., hypophysitis or craniopharyngioma) have normal sellar dimensions (23,26). Therefore, it is almost impossible that pituitary fossa dimensions are independent factors predictive of GTR status (24).

- Preliminary information on tumor fibrosis or stiffness can also affect the

choice of surgical approach. MRI scans yield information on tumor hardness (27). Trans-sphenoidal surgery can be difficult if resection of a fibrous adenoma is required (17,21). However, identical difficulties are encountered using a transcranial approach.

- After internal decompression, it is our experience that an intact capsule is required if the tumor is to be pulled slightly sideways/downwards into the sellar space, prior to peeling the tumor off the diaphragma sellae and the arachnoid.

- A massive SSE was formerly regarded as a contra-indication to using the trans-sphenoidal approach (2). Nowadays, however, such an approach to even giant adenomas is favored by some who claim that transcranial surgery is associated with high mortality and morbidity rates (18,19,28,29). In experienced hands, however, the complication rates of trans-sphenoidal surgery are low (30). Takakura and Teramoto achieved better results in patients with giant pituitary adenomas if the initial surgical approach was trans-sphenoidal, and very good results were reported in Hardys remarkable series (19,22). Although resection of giant adenomas is often subtotal or partial, it seems appropriate to commence with trans-sphenoidal surgery (24). Such surgery has been revolutionized over the last 10-15 years to incorporate endoscopic approaches; it is no longer controversial to use trans-sphenoidal techniques to treat giant pituitary adenomas larger than 10 cm³ (14,18,22,31-34). Craniotomy is no longer necessary for most patients with giant pituitary adenoma (30). Zada et al. reported that the trans-sphenoidal approach might limit resection of lateral tumor extensions, and concluded that the approach used must be decided by the surgeon (35). Many studies have shown that the outcomes of trans-sphenoidal surgery and craniotomy are similar, but the former technique is less risky and almost always yields better outcomes (30). Ideally, any cut-off value predicting giant

adenoma resectability should not depend on tumor length, but rather volume (30).

In the past, systems were developed to predict the surgical morbidity and likelihood of cure for patients with pituitary adenoma. Over time, the definition of a "giant adenoma" evolved to reflect technical developments. Earlier systematic reviews discussed three principal morphologic characteristics of an adenoma: SSEs, shape irregularity, and invasion of the cavernous sinus. In 1940, Jefferson and Bakay first described SSEs and emphasized their influence on perioperative mortality and surgical outcomes (31,33). Hardy classified adenomas into types A to D by reference to the pneumoencephalography (36). Using CT and MRI data, Mohr et al. considered that a 3-cm-long SSE was a useful cut-off to distinguish type C and D lesions (22). Symon et al. proposed that a 4-cm-long SSE should serve as a cut-off between macroadenoma and giant adenoma (18). Such early classifications sought to predict the effects of SSEs on tumor resectability and mortality/morbidity; this was in the era of classic microsurgery. In the past, presence of a massive SSE was accepted as a contra-indication for trans-sphenoidal surgery (1). Mohr et al. reported that 40% of patients who were Hardy grade C and D had residual tumors, or experienced recurrence (22). Recently, work with a large series of 105 patients indicated that the extent of SSE was the strongest determinant of STR (24). Hofstetter et al. claimed to have ruled out SSE as an independent variable determining the degree of resection by combining extracapsular dissection methods (termed transplanum and transtuberculum) with an endoscopic technique (30).

An irregular/multilobular shape predicts STR (24). A recent study reported a GTR rate of only 39% for such tumors. Interestingly, Symon et al. explored the effects of tumor morphology on surgical outcomes almost 30 years ago (18). In the

cited study, lesions longer than 4 cm, or those with more than two lobules extending to the suprasellar cisterna, were termed giant pituitary tumors (18). In older studies that used two-dimensional measurements, 3 or 4 cm was used as the cut-off diameter for a giant pituitary tumor (32,34). According to the cited studies, adenomas of maximal diameter more than 3 cm were associated with a higher prevalence of residual tumor tissue and increased perioperative morbidity. Thus, in a recent study, Hofstetter et al. used 10 cm³ as the cut-off volume determining STR status and perioperative morbidity (30). In terms of SSEs, the cited authors claimed that volumetric measurements were more predictive than areas, because this was the only way in which SSEs and irregular tumor protrusions be considered. However, Jain et al. considered that 5 cm³ was the limit for incomplete resection (STR status) (6). Hofstetter et al. gathered both two- and three-dimensional data and showed that the correlations between the two types of measurement fell when volumes were large (30). Thus, both volumes and diameters of larger tumors should be measured. It is obvious that a small threshold volume (5 cm³) will not be superior to a two-dimensional measurement. For a 5-cm³ volume, the Pearson correlation coefficient between volume and diameter is 0.84. If the threshold were 17 cm³, the correlation coefficient would be as low as 0.66. In the cohorts of Hofstetter et al. a volume of 5 cm³ corresponded to a maximum diameter of 2 cm (30). In contrast, a 10 cm³ threshold would equate to a maximum diameter of 3 cm. Therefore, a cut-off volume of 10 cm³ seems to be more reasonable for defining giant pituitary adenomas (18,32,34).

Cavernous sinus (CS) invasion is another determinant of surgical resectability and morbidity. Wilson identified the importance of such invasion three decades ago (37). The author modified Hardy's classification through the addition of "type E", which describes a cavernous sinus

extension of the tumor (2). One of the first studies that described endoscope-assisted trans-sphenoidal surgery to treat pituitary adenomas stated that subtotal resection was inevitable for every lesion extending into the cavernous sinus (38). However, Kitano et al. performed a cohort study of 36 patients with pituitary macroadenomas exhibiting such invasion, and found that 72% attained GTR status (39). In the same series of patients, 67% of those with functional adenomas attained hormonal remission (39). The cited authors used an endoscope-assisted trans-sphenoidal microsurgical approach.

Frank et al. stated that 59% of patients with non-functional adenomas attained GTR status, and 43% of patients with functional adenomas experienced endocrinologic remission, in a series of 65 patients with pituitary adenoma and cavernous sinus invasion who were underwent endoscopic-endonasal surgery (40). De Pavia et al. reported that 3 (9.7%) of 31 patients with cavernous sinus invasion attained GTR status when treated via endoscopically-assisted trans-sphenoidal microsurgery (41).

Reduction in tumor volume is the principal goal of treatment in patients with large pituitary adenomas. Such reduction improves visual, endocrinologic, and neurologic symptoms. Further, a reduced tumor volume enhances responses to medical therapy and radiotherapy. Subtotal resection of functional tumors can enhance the response to pharmacologic therapy. However, in a recent series of giant pituitary adenomas, little radiologic or endocrinologic evidence was obtained to indicate curative success. Mortini et al. treated a series of 26 giant pituitary adenomas of diameter over 4 cm; only one patient attained GTR status (4%) (34). In the same series, the GTR rate of 85 giant adenomas operated via the trans-sphenoidal route was 15%.

A similar GTR rate was reported by Zhang et al. Of 54 patients with grades C and D

disease (SSEs of 20-30 mm and > 30mm), the GTR rate was 17% (14). Garibi et al. worked with a series of 43 patients with giant pituitary adenoma whose maximum diameter was over 3 cm, and found that 27% of those who underwent trans-sphenoidal surgery attained GTR (32). Recently, de Pavia Neto worked with a series of 51 giant pituitary adenomas of maximum diameter >4 cm, and found that the trans-sphenoidal approach was associated with attainment of GTR status in 41.2% of patients. Hofstetter et al. used a threshold of 10 cm³ to define giant adenomas and found that 8 of 20 patients (40%) attained GTR status (30).

In our series, 70 patients had giant adenomas (grades C and D), 24 of whom (34%) attained GTR status. If it is accepted that the giant pituitary adenoma cut-off value is 10 cm³, only 8 (23%) of our 34 patients attained GTR status. However, the cut-off value for GTR was 3.4 cm³. When this value was exceeded, the likelihood of GTR decreased.

In our study on associations between the extent of tumor resection and preoperative variables, the most significant relationship was with cavernous sinus invasion ($r=0.800$, $P < .001$). The next most significant variable was preoperative volume, followed by the preoperative modified Hardy grade.

CONCLUSION

We sought to predict the extent of resection during trans-sphenoidal surgery using preoperative radiologic criteria. We did not consider tumor configuration because this is difficult to grade and quantitate. In terms of postoperative tumor mass, the most significant predictive factor was cavernous sinus invasion. As the preoperative tumor mass exceeded 3.4 cm³, the likelihood of attainment of GTR status decreased. When we compared preoperative tumor volume and cavernous sinus invasion status, we found that as the volume increased the invasion rate also rose. The cut-off value of the volume-

invasion relationship was 4.9 cm³. When this tumor volume was exceeded, the possibility of cavernous sinus invasion increased markedly.

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