Original article

Prospective study of transsphenoidal pituitary surgery: is tumor volume a predictor for the residual tumor?

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Keywords: *pituitary neoplasms; transsphenoidal approach; tumor volume; residual volume; predictor*

Background The presence of residual tumor after surgery for pituitary adenoma may necessitate further treatment. The suprasellar and parasellar extension of the tumor have been widely considered as the predictors for residual tumor. However there is scarcity of studies regarding the preoperative tumor volume and residual tumor. This study was conducted to evaluate if tumor volume could predict the outcome of transsphenoidal pituitary surgery.

Methods A prospective study was designed and 48 patients who underwent transsphenoidal pituitary surgery within 1 year in the First Affiliated Hospital of Xi'an Jiaotong University were included in this study. The preoperative tumor volume and immediate postoperative tumor volume (within 4–7 days) were calculated in the contrast magnetic resonance imaging by using the formula of ellipsoid. All these volumes were divided into three subgroups, i.e. group 1, group 2 and group 3 with preoperative volume of less than 4 cm^3, 4–8 cm^3, and more than 8 cm^3 respectively. The parasellar and suprasellar extension of the tumor were also classified by Knosp and modified Hardy's classifications.

Results Baseline characteristics were comparable. The preoperative tumor volume of more than 8 cm^3 (group 3, (12.1±1.1) cm^3) had increased risk on postoperative tumor residue (P <0.01) than the other two groups ((2.1±0.3) cm^3 and (6.1±0.3) cm^3 in groups 1 and 2). The mean postoperative volume in group 3 patients ((2.2±0.1) cm^3) was significantly higher than the other two groups (P <0.01).

Conclusion Preoperative volume of more than 8 cm^3 can be considered as a predictor for postoperative residual volume.

Chin Med J 2012;125(14):2444-2448

Since half a century, transsphenoidal surgery has become the preferred surgical approach for most pituitary tumors[1] and is adopted in 90% of pituitary tumor surgeries. Pituitary adenomas can extend to the parasellar region and invade into the cavernous sinus due to the absence of bony interface in the lateral limits of the pituitary fossa.[2] Similarly they can also frequently extend from the sella through the diaphragm sella to reach the suprasellar regions. These extensions of the tumor result in difficulty in total resection of the tumor. Besides the suprasellar and parasellar extension of the tumor, the volume of the tumor in itself can also influence the outcome of the transsphenoidal surgery.[3,4] It is believed that the volume of the tumor provides the three dimensional status of the tumor.[3] However, the relationship between preoperative volume and postoperative residual volume has not been investigated, which is important in the continuation of therapy and prognosis. We are presenting this study to evaluate whether tumor volume could predict the presence of the residual tumor with the assistance of contrast magnetic resonance imaging (MRI).

METHODS

Patients

This prospective study was conducted in the Department of Neurosurgery of the First Affiliated Hospital of Xi'an Jiaotong University. A total of 48 patients with pituitary adenomas were included in this study who underwent transsphenoidal surgery from January 2011 to December 2011. The baseline parameters including age, gender, complaints, hormonal status, and visual symptoms were recorded. The preoperative volume of the tumor was calculated in the gadolinium-contrast MRI scan (Philips Ingenia 1.5 T; Philips Healthcare, Eindhoven, Netherlands). All the patients were also sent for postoperative contrast MRI scans within 4–7 days postoperatively and postoperative tumor volumes were also calculated. The patients' histopathological diagnosis and hormonal correction were also recorded.

Pituitary volume calculation

Pituitary volume was calculated using the formula for the volume calculation of ellipsoid.[5,6] Pituitary volume (PV) = 0.5×PH×PL×PW, where PH is pituitary tumor height and PL is pituitary tumor length taken in sagittal MRI, and PW is pituitary tumor width taken in coronal MRI. In our study we used contrast MRI to calculate both

DOI: 10.3760/cma.j.issn.0366-6999.2012.14.009
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The authors declare no conflicts of interest in this work.

preoperative and postoperative volumes. Contrast MRI in the immediate postoperative period also allows us to differentiate between the residual tumor and other postoperative changes in the sellar region. It is believed that any mass that shows nodular and combined enhancement must be a residual tumor as the normal gland does not fully expand in the early postoperative period.[7]

Grouping and classification

Based upon the preoperative volumes, the cases were divided into three groups, i.e. group 1, group 2 and group 3 with preoperative volume of less than 4 cm^3, 4–8 cm^3 and more than 8 cm^3 respectively. Similarly, the parasellar extension of the tumor was classified according to Knosp classification and the suprasellar extension of the tumor was classified according to Modified Hardy's classification.

Knosp classification is based upon parasellar extension of the tumor in the coronal section of MRI scans with internal carotid artery (ICA) serving as the radiological landmark.[8] It consists of five grades. Grade 0 means that the adenoma does not encroach into the cavernous sinus space or cross the medial aspect of intra- and supra-cavernous ICA. Grade I means that the tumor crossed the medial tangent but does not extend beyond the intercarotid line. Grade II means that the tumor crossed beyond the intercarotid line but does not cross beyond the lateral tangent of intra- and supra-cavernous ICA. Grade III means that the tumor has crossed beyond the lateral tangent of intra- and supra-cavernous ICA. Grade IV means that there was total encasement of the intra-cavernous ICA by the tumor.

Modified Hardy's classification is based upon suprasellar extension of the tumor.[9] Grade 0 means that the tumor remains intrasellar. Grade A means that the tumor is expanding into the suprasellar cistern. Grade B means that the anterior recess of the third ventricle is obliterated. Grade C means that the floor of third ventricle is grossly displaced.

Statistical analysis

Nominal and categorical data were expressed as frequency, and numerical data were expressed as mean ± standard error (SE). Statistical analysis was performed with the software SPSS (version 13.0; SPSS Inc., Chicago, IL, USA). Data were compared by χ^2 test or one-way analysis of variance (ANOVA) and Student-Newman-Keuls post hoc test. Differences in values were considered significant if $P<0.05$.

RESULTS

Baseline characteristics

There were total 48 patients with the mean age of 43.7 years ranging from 16 years to 73 years. There were 30 [illegible] (62.5%) and 18 male patients (37.5%) with female: male ratio of 1.67:1. The mean preoperative volume was (6.8±0.8) ml and the mean postoperative volume was (0.8±0.1) ml.

There were 10 (20.8%) cases of microadenoma and 38 (79.2%) cases of macroadenoma. Regarding functional status of the tumor there were 21 (43.75%) cases of functional adenoma and 27 (56.25%) cases of non functional adenoma. Among the functional tumors, 10 cases were microadenoma and 11 cases were macroadenoma whereas in non functional tumors, all were macroadenomas. In functional tumors, 8 cases were prolactinoma, 6 were growth hormone (GH) secreting tumors and 5 were adrenocorticotropic hormone (ACTH) secreting tumors. The rest 2 were mixed hormone secreting tumors. The commonest symptoms of patients with functional adenoma were pertaining to their respective hormonal excess with amenorrhea-galactorrhea, acromegaly, and Cushing's syndrome. In cases of nonfunctional macroadenomas, they most frequently presented with headache followed by bitemporal hemianopia, and monocular blindness. One patient presented with features of pituitary apoplexy.

The frequency analysis of nominal and categorical data showed that baseline characteristics, including gender, functional status, preoperative volume, and modified Hardy's classification, were comparable (Table 1). However, it was seen that macroadenoma cases greatly outnumber microadenoma and Knosp grade 0 was more in number.

The parasellar extension of the tumor with Knosp classification and the suprasellar extension of the tumor with modified Hardy's classification were also noted with

Table 1. Baseline characteristics analysis

Parameters	*n*
Gender*	
Male	18
Female	30
Size of tumor	
Microadenoma	10
Macroadenoma	38
Functional status*	
Functional tumor	21
Non functional tumor	27
Preoperative volume*	
Group 1 (<4 cm^3)	19
Group 2 (4–8 cm^3)	15
Group 3 (>8 cm^3)	14
Knosp's classification	
Grade 0	24
Grade I	8
Grade II	5
Grade III	7
Grade IV	4
Modified Hardy's classification*	
Grade 0	17
Grade A	13
Grade B	9
Grade C	9

*χ^2 test, $P>0.05$.

respect to different preoperative subgroups of volume (Table 2). It was observed that in group 3, 11 out of 14 cases (79%) belonged to Knosp grades III and IV and 13 of 14 cases (93%) belonged to Hardy's grades B and C with *P* value less than 0.01.

Table 2. Numbers of parasellar extension (Knosp classification) and suprasellar extension (modified Hardy's classification) in different subgroups of preoperative volume (*n*)

Classifications	Group 1 (<4 cm^3)	Group 2 (4–8 cm^3)	Group 3 (>8 cm^3)	Total
Knosp's classification*				
0	17	7	0	24
I	2	6	0	8
II	0	2	3	5
III	0	0	7	7
IV	0	0	4	4
Total	19	15	14	48
Modified Hardy's classification†				
0	14	3	0	17
A	3	9	1	13
B	1	3	5	9
C	1	0	8	9
Total	19	15	14	48

*χ^2 test, $P<0.01$, grades 0, I and II as a combined group vs. grades III and IV as a combined group. †χ^2 test, $P<0.01$, grades 0 and A as a combined group vs. grades B and C as a combined group.

Table 3. Postoperative volumes in different groups of preoperative volume

Preoperative tumor volume (cm^3)	Patients (*n*)	Preoperative volume (cm^3)	Postoperative volume (cm^3)
Group 1 (<4)	19	2.1±0.3	0.1±0.1
Group 2 (4–8)	15	6.1±0.3*	0.3±0.1
Group 3 (>8)	14	12.1±1.1*†	2.2±0.1*†

Data are expressed as mean ± SE. One-way ANOVA and Student-Newman-Keuls test. *$P<0.01$, vs. group 1. †$P<0.01$, vs. group 2.

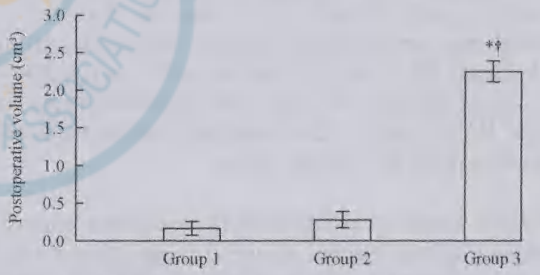

Figure 1. Postoperative volumes in different groups of preoperative volume. Data are expressed as mean ± SE and are compared by one-way ANOVA and Student-Newman-Keuls test (n=14–19). *$P<0.05$, vs. group 1 (preoperative volume <4 cm^3). †$P<0.05$, vs. group 2 (preoperative volume between 4 and 8 cm^3).

Postoperative outcomes based on volume

Postoperative volume comparison data are shown in Table 3. The *P* value between all groups was found to be statistically significant ($P<0.01$). The 95% confidence interval for mean postoperative volume overlapped between group 1 and group 2 but it did not overlap in group 3. There was no significant difference between preoperative group 1 and group 2, but there were significant differences in group 3 with respect to group 1 and group 2 ($P<0.01$). So, it is more likely that the preoperative volume more than 8 cm^3 have residual tumor (Figure 1).

There was residual tumor in 19 (39%) of the cases. Figure 2 shows a case of pituitary macroadenoma in group 3 preoperatively (Figure 2, Panels A and B) and with residual tumor postoperatively (Figure 2, Panels C and D). The entire cases of residual tumor occurred in macroadenomas with none in microadenoma. All cases in group 3 and 5 cases in group 2 had residual tumor whereas none of the cases in group 1 had residual tumor. Hormonal correction was achieved in almost all cases except one case of Cushing's disease where ACTH level was still high postoperatively. Regarding visual recovery status, 80% of patients had visual improvements.

DISCUSSION

Pituitary adenomas are benign neoplasm that represent 10%–15% of the intracranial tumors.[10] The epidemiological studies have demonstrated that nearly 20% of the general population harbor pituitary adenoma.[11] The transsphenoidal microsurgery has been proven to be the most commonly used procedure because of its safety and effectiveness. Though it is the preferred choice for pituitary adenoma, the gross total excision of the tumor becomes difficult in many cases. The factors

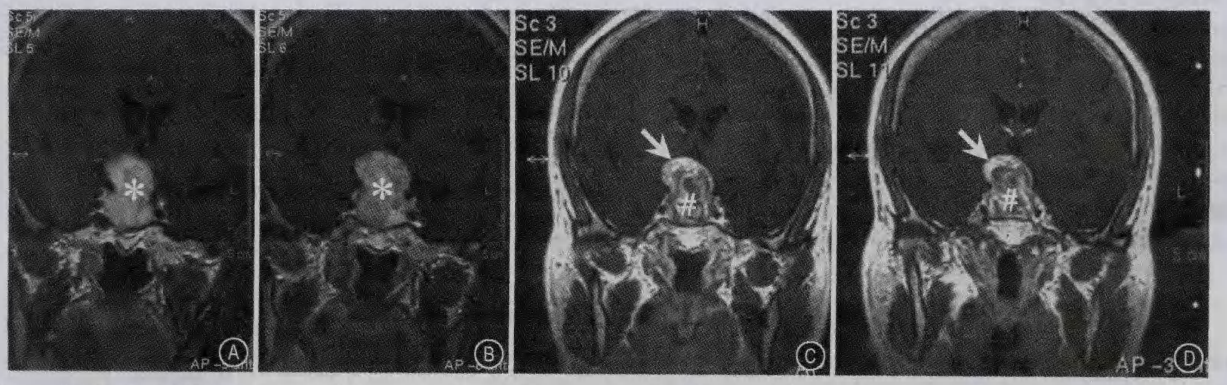

Figure 2. Contrast MRI of a case with tumor volume of more than 8 cm^3 with Knosp grade III and Hardy's grade C. **A** and **B:** Preoperative contrast MRI coronal images. Asterisk symbol (*) shows pituitary macroadenoma. **C** and **D:** Postoperative contrast MRI coronal images. Arrow shows residual tumor in suprasellar region. Pound symbol (#) shows postoperative clots with gelatin sponges.

determining complete excision are cavernous sinus invasion or parasellar extension, suprasellar extension and consistency of the tumor.[12] Kim et al[13] and Vieira et al[2] have revealed that cavernous sinus invasion with Knosp grade III or IV is more likely to have residual tumor due to the difficulty in the surgical approach. Knosp et al[8] have noted that the grade of parasellar extension was directly related to the tumor size. Many other authors have also considered cavernous sinus invasion or parasellar extension as a result for an incomplete excision.[14] However Ensenat et al[15] have revealed that pituitary macroadenomas can be safely resected with low morbidity and mortality despite tumor extension to the cavernous sinus. Similarly tumors with more pronounced suprasellar extension of the tumor, i.e. Hardy's grades B and C also have higher incidence of subsequent enlargement.[16] However Zhang et al[17] stated that microsurgical technique is safe in suprasellar extension except in fibrous and dumbbell tumors. Another predictor is the irregular and asymmetrical tumor shape which also hampers the complete excision of the tumor.[18] There are not many studies regarding the comparison of the preoperative tumor volume as an independent predictor. Tumor volumetry of pituitary adenoma has been done in many studies especially to calculate the volume shrinkage after postoperative radiation therapy and there are different methods of volume calculation as illustrated in various studies.[19,20] The formula for the calculation of the pituitary tumor volume that is (0.5 × pituitary tumor width × length × height) has been well accepted for the calculation of pituitary volume and it provides fairly adequate calculation of tumor volume except in the largest tumors.[6] It is a known fact that tumor volume will take into consideration of the suprasellar and parasellar extensions. Nowadays the concept of tumor volume is becoming more popular to determine the residual tumor.[3] The same study also revealed that the preoperative tumor volume of more than 5 ml was associated with 90.90% probability of the residual tumor.[3] Christoph et al have proposed that 10 cm^3 of preoperative volume is a modern definition of giant adenoma and is associated with higher likelihood of subtotal resection and postoperative morbidity.[21] Our study has shown that preoperative tumor volume in group 3 (more than 8 cm^3) had higher risk of residual tumor than group 1 and group 2. The parasellar and suprasellar extension of the tumor with respect to the tumor volume also showed that 11 of 14 cases (79%) with tumor volume more than 8 cm^3 belonged to Knosp grade III or IV and 13 of 14 cases (93%) were Hardy's B and C grades. This means that about 79% of the tumor with more than 8 cm^3 tumor volume can have cavernous sinus invasion and about 93% of these tumors may expand beyond the suprasellar cistern. This also signifies that increased tumor volume can be a predictor for higher grades of classification, hence more risk of pituitary residual tumors. Though our study lacked long term follow-up, it has been reported that there is tumor re-growth in 12%–46% of these patients after transsphenoidal surgery.[22-24] Even though the risk of tumor re-growth in patient with residual tumor is controversial; its treatment is highly advocated.

The tumor volume gives the three dimensional assessment of tumors, hence this can prove to be a strong predictor for the outcome of surgery. This study reveals that tumor volume of more than 8 cm^3 has greater risk of having postoperative residual tumor. These groups of tumor belong to higher grades of Knosp and Modified Hardy's classification and hence can have parasellar or suprasellar extensions.

Acknowledgement: The author would like to thank Prof. DANG Shao-nong from Department of Epidemiology and Biostatistics of Medical School of Xi'an Jiaotong University for reviewing statistical analysis of data.

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(Received February 9, 2012)
Edited by JI Yuan-yuan