Risk Factor Analysis on the Predictors of the Transsphenoidal Pituitary Surgery on Macroadenomas: A Multivariate Logistic Regression Analysis

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This study was conducted to evaluate the independent and strongest predictor of the transsphenoidal surgery on pituitary macoadenomas.

A prospective study was designed and 51 patients with pituitary macroadenoma were included in this study who underwent transsphenoidal surgery from January 2011 to February 2012.The preoperative volume was calculated in the contrast enhanced Magnetic Resonance Imaging. The parasellar and suprasellar extension of the tumor was also classified by Knosp classification and Modified Hardys classification. The postoperative residual tumor was compared with respect to the preoperative tumor volume, parasellar extension and suprasellar extension.

The median preoperative volume was more in case of residual tumor (P value<0.01) Univariate logistic regression analysis revealed that preoperative volume, Knosp (grade II, III and IV) for parasellar extension and Modified Hardys (B and C) for suprasellar extension were associated with residual tumor.However Multiple logistic regression analysis revealed that Knosp classification(II,III,IV) for parasellar extension proved to be the strongest predictor with odds ratio of 8.89(P value0.02), followed by preoperative tumor volume (>6.63ml) with odds ratio of 5.42(P value 0.04).Hardys classification B and C with suprasellar extension did not prove to be the independent predictor with odds ratio of 1.052(P value 0.95).

The parasellar extension of the tumor with cavernous sinus invasion is the strongest and independent predictor for the residual tumor in transsphenoidal pituitary surgery due to difficulty in surgical approach followed by preoperative tumor volume as second independent predictor.

Key Words: macroadenomas, residual tumor, risk factor, transsphenoidal pituitary surgery

Pituitary adenomas are benign neoplasm that represent 10-15% of the intracranial tumors.[4,9] The epidemiological studies have demonstrated that nearly 20% of the general population harbor pituitary adenoma.[11] Pituitary macradenomas are more than 1 cm in diameter and they can be either functional or non functional tumors. Beside hormonal imbalances, they can also present with mass effect which includes cranial nerve defect secondary to cavernous sinus invasion or visual deficits due to compression of optic apparatus. Patients can also suffer from hypopituitarism secondary to compression of the normal functioning pituitary gland.[3]

Surgical therapy remains the primary treatment of choice in case of pituitary macroadenomas except for medically treatable prolactinomas. In 1907 Herman Schloffer performed the first successful transsphenoidal resection of pituitary tumor via a transfacial approach.[30] With the introduction of radiofluoroscopic intra-operative control and microsurgery by Guiot and Hardy in 1914, transsphenoidal pituitary surgery gained world-wide recognition [10,31] and became the preferred surgical approach for most pituitary tumors.[19] Now transsphenoidal surgery is adopted in more than 90% of pituitary tumor surgeries. Recent advances with regards to endoscopic transsphenoidal techniques represent the latest development in surgery of sella.[1]

Pituitary macroadenomas can frequently extend from the sella to the suprasellar regions from the diaphragm sella. Similarly they can also extend to parasellar regions and invade the cavernous sinus due to the absence of the bony interface in the lateral limits of pituitary fossa.[16] These extensions of the tumor result in difficulty in the total resection of the tumor. Beside the suprasellar and parasellar extension of the tumor, the volume of the tumor in itself can also influence the outcome of the transsphenoidal surgery and also provides the three dimensional status of the tumor.[2,8]

The three main morphological tumor feature have been regularly included in various classification system viz, suprasellar extension, parasellar extension with invasion of cavernous sinus and irregular shape.In this present study we have also classified the tumor according to modified Hardys classification for the suprasellar expansion and Knosp classification for the parasellar expansion respectively. We have also evaluated the preoperative MRI and calculated the preoperative volume. Then we have attempted to compare the preoperative volume of the tumor along with the suprasellar and parasellar extension of the tumor and their impact on the residual tumor.

Materials and Methods

This prospective study was conducted in the Department of neurosurgery in the first affiliated hospital of Xi'an Jiaotong University. A total of 51 patients with pituitary macroadenoma were included in this study who underwent transsphenoidal surgery from January 2011 to February 2012.The parameters like patient's age, sex, complaint, hormonal status, visual symptoms were recorded. The preoperative volume of the tumor was calculated in the gadolinium enhanced contrast MRI scan (with 1.5 Tesla SIGNA EXCITE GEHC MRI scanner) and all the patients were sent for postoperative contrast MRI scans within 4-7 days postoperatively and the presence of residual tumor was noted.

Pituitary tumor volume was calculated by using the formula (0.5* pituitary tumor length * pituitary tumor height* Pituitary tumor width).[20,23,27] Pituitary tumor height and pituitary tumor length were taken in sagittal MR image and Pituitary tumor width was taken in Coronal MRI. In our study we used contrast MR Imaging to calculate the preoperative volume as MR imaging with dynamic enhanced study is accepted as the most sensitive imaging method for the evaluation of the pituitary adenoma.[12]

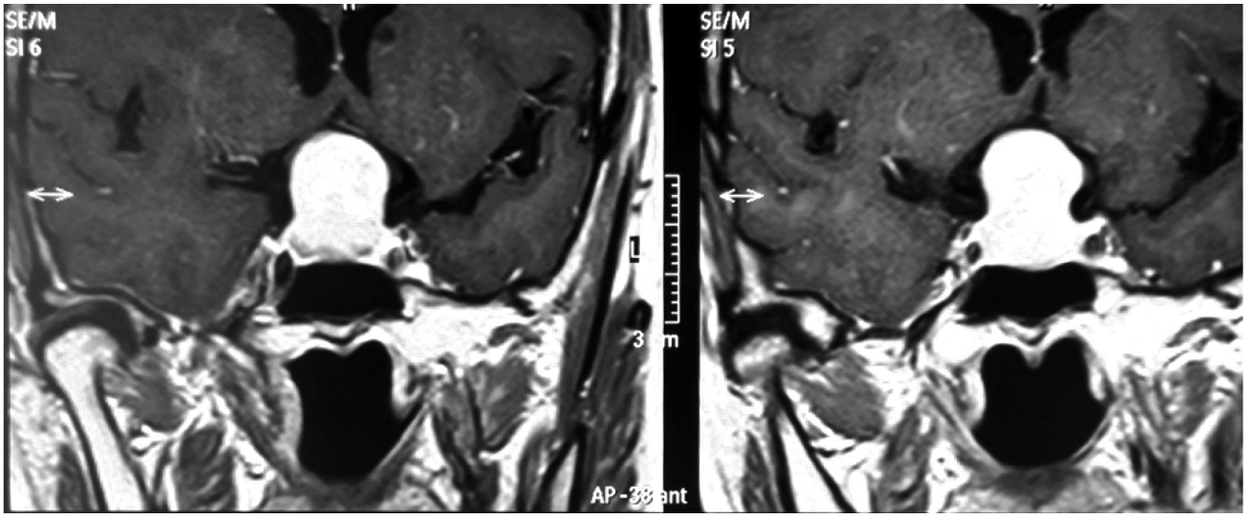

Figure 1: Preoperative contrast enhanced MRI, coronal image with preoperative tumor volume of 7.95 ml with Knosp II(on the left) and Hardys B class

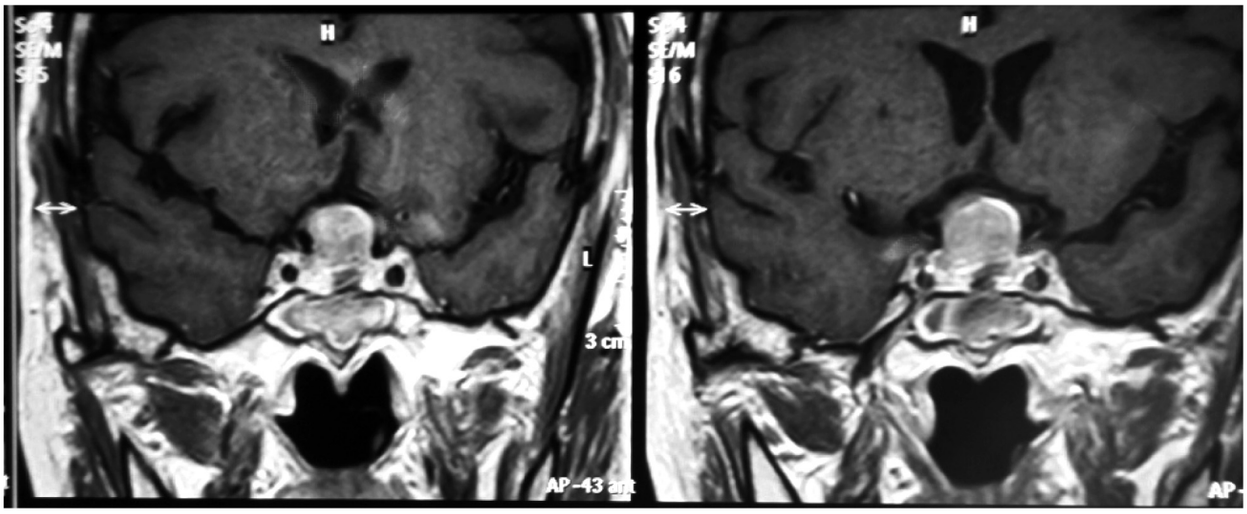

Figure 2: Postoperative contrast-enhanced MRI, coronal image of same patient with residual tumor more in left parasellar region.

Similarly, enhanced MRI imaging 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 the nodular and the combined enhancement must be a residual tumor as the normal gland did not fully expand in the early postoperative period.[25]

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 of Parasellar Extension of the Tumor[17]

It was based on the coronal section of the MRI scans with internal carotid artery (ICA) serving as the radiological landmark. It consists of five grades.

Grade 0 : The adenoma did not encroach the cavernous sinus space; not crossing the medial aspect of intra and supracavernous ICA.
Grade 1 : The tumor crossed the medial tangent but does not extend beyond the intercarotid line.
Grade 2 : The tumor crossed beyond the intercarotid line but does not cross beyond the lateral tangent of intra and supra cavernous ICA.
Grade 3 : The tumor crossed beyond the lateral tangent of intra and supracavernous ICA
Grade 4 : There was total encasement of the intracavernous carotid by the tumor.

Modified Hardys Classification of Suprasellar Extension of the Tumor[28]

Grade 0 : None
Grade A : Expanding into the suprasellar cistern
Grade B : Anterior recess of the third ventricle obliterated
Grade C : Floor of third ventricle grossly displaced

Statistical Analysis

Descriptive analysis of numerical data was performed using the frequency distribution and percentage. Nominal and categorical variables were expressed as frequency and P value within groups was calculated by chi square test. The Mann-Whitney U test was used to compare the continuous variable between preoperative volume and residual tumor. Chi square test was used to compare the categorical variables between parasellar and suprasellar extension with residual tumor. Univariate logistic regression analysis was done to test the effect of preoperative tumor volume, suprasellar and parasellar extension of the tumor. This test was followed by multivariate logistic regression analysis to determine the independent predictors of the residual tumor. P value less than 0.05 was considered significant. The statistical analysis were performed with statistical software (version 13.0; SPSS,Inc.,Chicago,IL).

Distribution of Variables

There were total 51 patients with the mean age of 43.7 years with minimum age of 16 years to maximum age of 73 years. There were 29 female patients (56.8%) and 22 male patients (43.13%) with female: male ratio of 1.31. The mean preoperative volume was 8.9 ml with standard deviation of 5.93 ml and median value was 6.63ml. There were 15(29.4%) cases of functional adenoma and 36(70.6%) cases of non functional adenoma. Among the functional tumors, 9 cases were Growth Hormone (GH) secreting tumors, 5 cases were prolactinoma and 1 case was Adrenocorticotropic Hormone (ACTH) secreting

		Number	P value
Sex	Male	22	0.32
	Female	29	
Functional status	Functional tumor	15	0.003
	Non functional tumor	36	
Knosp classification	0	18	0.08
	I	9	
	II	7	
	III	10	
	IV	7	
Modified Hardys classification	0	10	0.76
	A	15	
	B	14	
	C	12	

Table 1: Frequency analysis of Nominal and Categorical variables

		Residual		
		No	Yes	Total
Knosp Classification	0	15	3	18
	I	8	1	9
	II	3	4	7
	III	2	8	10
	IV	0	7	7
Total		28	23	51

*P value <0.01 (Chi square test)

Table 2: Table showing number of residual tumor in different subgroups of Knosp Classification

		Residual		
		No	Yes	Total
Modified Hardys Classification	0	7	3	10
	A	12	3	15
	B	7	7	14
	C	2	10	12
Total		28	23	51

*P value<0.05(Chi square test)

Table 3: Table showing number of residual tumor in different subgroups of modified Hardys Classification

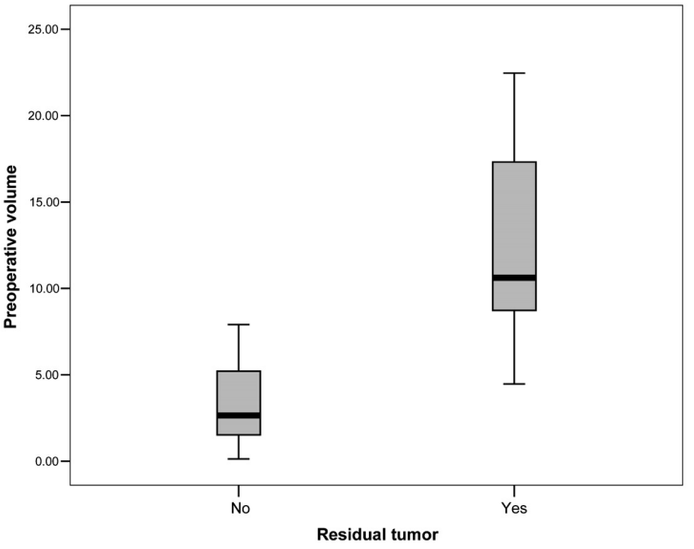

Figure 3: Box plot showing difference in the median preoperative volume in residual tumor.

		No residual	Residual	Odds ratio	P value	95% Confidence interval for odds ratio
Preoperative volume	<6.6 ml >6.6 ml	20 8	3 20	Ref 12	0.01*	2.84-50.58
Knosp Classification	0,1 2,3,4	23 5	4 19	Ref 24.375	<0.01*	4.5-130
Modified Hardys Classification	0,A B,C	19 9	6 17	Ref 5.91	0.04*	1.761-20.37

*P value significant

Table 4: Univariate analysis of Preoperative volume, Knosp classification and Modified Hardys classification

	Odds ratio	P value	95% confidence interval for odds ratio
Knosp classification	8.889	0.02*	1.275-61.96
Preoperative volume	5.426	0.04*	1.1-43.35
Modified Hardys	1.052	0.95	0.176-6.285

*P value significant

Table 5: Multivariate logistic regression analysis

tumors. The commonest symptoms of the patients were pertaining to their respective hormonal excess with acromegaly, amenorrhea-galactorrhea and Cushings disease respectively. The commonest symptoms of nonfunctional macroadenoma were headache followed by bitemporal hemianopia, and monocular blindness. One patient presented with features of pituitary apoplexy.

The frequency analysis of nominal and categorical data **(Table 1)** showed that significant differences in number of cases amongst subgroups exist only in functional status of the tumor. The nonfunctional tumor greatly outnumbered the functional tumor. However there is no significant difference in the subgroup in the Knosp classification and modified Hardys classification.

Postoperative Outcomes Based on Volume, Suprasellar Extension and Parasellar Extension

Complete excision of the tumor was achieved in 28 cases (55%) and residual tumor was present in 45% of the cases. There was difference in median of the preoperative volume in these two groups. In case of residual tumor group the median preoperative volume was 14.4 ml whereas it was 5ml where there was no residual tumor postoperatively. The difference was statistically significant (P value<0.01) on Mann Whitney test. Graph 1 shows the box plot with the difference in the preoperative volume in two surgical outcomes.

Similarly the postoperative outcome was also compared on the basis of Knosp and modified Hardys classification.**(Table2 and Table 3)**. It was observed that residual tumor was more with higher level of classification of Knosp (P value <0.01). The tumor which had crossed beyond the intercarotid line that is (grade II) and above had more risk of having the residual tumor. Furthermore the residual tumor was more in case of Hardys B and C (P value<0.05). That means the tumour which had expanded beyond suprasellar cistern were more likely to have residual tumor. **Figure 1 and 2** show the case of pituitary macroadenoma with residual tumor.

Univariate analysis was performed on these three parameters to know about their respective odds ratio **(Table 4)**.The preoperative volume was classified into two groups with less than 6.63 ml and more than 6.63 ml according to the median value of the cases. Similarly, in case of Knosp classification 0 and I subgroup was taken as the reference group and in case of Modified Hardys classification 0 and A subgroup was taken as the reference group. It was observed that there was 12 times more risk of having the residual if the preoperative volume was more than 6.6 ml(P value=0.01). If the tumor belonged to Knosp grade II,III or IV, then the likelihood of residual tumor was 24 times higher than those of Group 0 and Group I(P valu<0.01). In case of Hardys B and C groups the the likelihood of residual tumour was 5.9 times more than Hardy 0 and A subgroups (P value=0.04).This univariate analysis concluded that all these three parameters could be considered as the risk factor for the residual tumor.

Furthermore we wanted to see the strongest predictor among these three parameters for which we preformed multivariate logistic regression analysis **(Table 5)**. This revealed that Knosp classification(II,III,IV) for parasellar extension proved to be the strongest predictor with odds ratio of 8.89(P value0.02), followed by preoperative tumor volume(>6.63ml) with odds ratio of 5.42(P value 0.04).Hardys classification B and C with suprasellar extension did not prove to be the independent strong predictor with odds ratio of 1.052(P value 0.95).

Discussion

The transsphenoidal microsurgery has been proven to be the most commonly used procedure for pituitary adenoma because of its safety and effectiveness. Though the transsphenoidal surgery is the preferred choice for pituitary adenoma, the gross total excision of the tumour becomes difficult in many cases. The factors determining complete excision are cavernous sinus invasion or parasellar extension, suprasellar extension and consistency of the tumor.[6, 26]

In this study we found that parasellar extension of the tumor with Knosp II, III and IV was strongest predictor for the residual tumor. Min Su Kim et al and Joaquim et al have revealed that cavernous sinus invasion with Knosp grade III or IV is more likely to have more residual tumor due to the difficulty in the surgical approach.[16,22] Knosp et al have noted that the grade of parasellar extension was directly related to the tumor size and have stated that the critical area where invasion of cavernous sinus space becomes very likely and can prove surgically, is represented in Group II,with tumor between the intercarotid and the lateral tangent line.[17] Many other authors have also considered cavernous sinus invasion or parasellar extension as a result for an incomplete excision.[6,7,24,26] However J .Ensenat et al have revealed that pituitary macroadenomas can be safely resected with low morbidity and mortality despite tumor extension to the cavernous sinus.[13]

The second strongest predictor of residual tumor in this study was tumor volume. The tumor volume gives the 3-dimensional assessment of tumors; hence this can also prove to be a strong predictor for the outcome of surgery. Amit Kumar Jain et al have revealed that the preoperative tumor volume of more than 5 ml was associated with a 90.90% probability of the residual tumor.[2] Christoph et al have proposed that 10 ml of preoperative volume is a modern definition of giant adenoma and is associated with higher likelihood of subtotal resection and postoperative morbidity.[5]

Similarly tumors with more pronounced suprasellar extension of the tumor i.e. Hardys B and C also have higher incidence of subsequent enlargement.[29] In this study, suprasellar extension of tumor was one of the risk factors of residual tumor in case of univariate study but it did not prove itself to be the independent risk factor in multivariate study. J. Honeggar et al have reported that suprasellar extension was the most significant independent predictor of surgical success and with increasing suprasellar expansion the likelihood of radical removal decreased and they also correlated the dumbbell shape of the tumor with the suprasellar extension of the tumor.[14] However they did not study about the relationship with the cavernous sinus invasion.

Regarding the morphometric parametes, parasellar extensions are more difficult to handle. It is believed that in case of nonfunctioning tumor small parasellar residual mass is acceptable but it should be removed in case of functional adenoma for the hormonal cure.[2,22] However the concept of adjunctive gamma knife therapy in residual tumor has been also evolving and is considered to be a safe and effective method of tumor control.[15,18,21]

Conclusions

The parasellar extension of the tumor with cavernous sinus invasion is the strongest predictor for the residual tumor in transsphenoidal pituitary surgery due to difficulty in surgical approach. As the tumor volume gives the 3-dimensional assessment of tumors; hence this can also prove to be a strong predictor for the outcome of surgery. Though this study does not reveal the suprasellar extension of the tumor as an independent risk factor, a larger prospective study is recommended.

Conflict of Interest

The authors declare that there is no conflict of interest.

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