

# Strategy for Management of Giant Invasive Pituitary Adenoma

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**Objective :** Giant invasive pituitary adenoma looks histologically benign, but these tumors have an aggressive clinical course. The authors review 10 cases and discuss the results obtained and the strategy to use for the management of giant invasive pituitary adenoma.

**Methods :** Out of a series of 155 pituitary adenomas treated surgically between 1994 and 2002, ten patients with giant invasive pituitary adenoma were selected and their clinical problems, radiologic findings, extent and invasiveness, hormonal and histologic findings and surgical results were analyzed retrospectively.

**Results :** There were 4 male and 6 female patients, with an average age of 47 years and an average follow-up period of 42 months. The average size of tumor was 50.7mm. These tumors revealed severe invasions into surrounding structures. 8 patients underwent transsphenoidal approach(TSA) operations, 1 patient with transcranial operation and 1 patient with combined TSA and transcranial operation. In all cases, subtotal resection was performed. The histologic findings were 2 prolactinomas and 8 hormonal non-function adenomas. The therapies administered after surgical removal consisted of conventional fractionated radiotherapy (2 patients), treatment with dopamine agonists to control hyperprolactinemia (2 patients), and treatment with hormone replacement (2 patients).

**Conclusion :** Giant invasive pituitary adenomas are characterized by different forms of expansion and invasiveness and variable clinical problems. Because of their aggressive expansion and invasiveness, there are many different strategies which can be considered for their management. The authors obtain good results by choosing conservative surgical removal and multidisciplinary treatments with serial radiological and hormonal follow-up.

**KEY WORDS :** Giant invasive pituitary adenoma · Transsphenoidal surgery · Tumor invasion.

## Introduction

Pituitary adenomas are considered to be benign tumors; however, they may infiltrate the dura, cavernous sinus, or the bone of the sella turcica or clivus. Invasive pituitary adenomas were described as early as the 1940s and were defined as adenomas that extended beyond their capsules and invaded contiguous structures<sup>6,7</sup>.

The radiological classification of pituitary adenomas proposed by Jules Hardy in the 1970s distinguished between enclosed and invasive adenomas<sup>5</sup>. The ability of pituitary adenomas to infiltrate the dura may be reflected in their tendency to persist or recur after transsphenoidal excision. This may influence the cure rate for endocrinologically active tumors and the rate of recurrence for clinically nonfunctioning adenomas<sup>13,14</sup>.

The authors reviewed 10 cases of giant invasive pituitary adenoma and discussed the results obtained and the strategy to use for its management.

## Materials and Methods

Between 1994 and 2002, 155 patients underwent transsphenoidal and transcranial pituitary surgery performed by a single surgeon at the University of Yeungnam. Of these 155 patients, ten patients were diagnosed with giant invasive pituitary adenoma and their clinical problems, radiologic findings, extent and invasiveness, hormonal and histologic findings and surgical results were analyzed retrospectively (Table 1).

The preoperative magnetic resonance(MR) images were reviewed and the maximum size (in millimeters) of the pituitary tumors was used to classify them. Based on the size of the pituitary tumors the patients were classified into four groups : 1) microadenomas ( $\leq 10\text{mm}$ ); 2) macroadenomas ( $>10\text{mm}$  to  $\leq 20\text{mm}$ ); 3) macro-plus adenomas ( $>20\text{mm}$  to  $\leq 30\text{mm}$ ); 4) giant adenomas ( $>40\text{mm}$ ).

The extension of the pituitary mass on the MR images was

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**Table 1.** The clinical features and surgical outcomes of giant invasive pituitary adenomas

| Case No | Age /sex | Chief complains                       | Size (mm) | Invasion type | Surgical method  | Surgical resection | Histology      | Followup periods (Months) | Adjuvant therapy                                 | Longterm outcome                |
|---------|----------|---------------------------------------|-----------|---------------|------------------|--------------------|----------------|---------------------------|--|---------------------------------|
| 1       | 20/F     | headache                              | 95        | diffuse       | TSA+transcranial | subtotal           | nonfunctioning | 0                         | –  | death                           |
| 2       | 65/F     | bitemporal hemianopsia                | 44        | diffuse       | TSA              | subtotal           | nonfunctioning | 72                        | radiation  | size increased                  |
| 3       | 54/M     | total blindness<br>panhypopituitarism | 48        | cavernous     | TSA              | subtotal           | nonfunctioning | 28                        | hormone replace<br>dopamine agonist              | asymptomatic residual tumor     |
| 4       | 16/F     | Amenorrhea<br>headache                | 45        | diffuse       | transcranial     | subtotal           | prolactinoma   | 60                        | –  | asymptomatic residual tumor     |
| 5       | 35/M     | bitemporal hemianopsia                | 44        | cavernous     | TSA              | subtotal           | nonfunctioning | 20                        | –  | asymptomatic residual tumor     |
| 6       | 72/F     | bitemporal hemianopsia                | 48        | sphenoid      | TSA              | subtotal           | nonfunctioning | 27                        | –  | asymptomatic residual tumor     |
| 7       | 65/F     | bitemporal hemianopsia ptosis         | 45        | diffuse       | TSA              | subtotal           | nonfunctioning | 15                        | –  | asymptomatic residual tumor     |
| 8       | 34/F     | bitemporal hemianopsia                | 45        | cavernous     | TSA              | subtotal           | prolactinoma   | 101                       | radiation<br>dopamine agonist<br>hormone replace | size increased                  |
| 9       | 61/M     | stupor d/t hydrocephalus              | 48        | diffuse       | TSA              | subtotal           | nonfunctioning | 10                        | –  | asymptomatic residual tumor     |
| 10      | 51/M     | bitemporal hemianopsia<br>headache    | 45        | diffuse       | TSA              | subtotal           | nonfunctioning | 42                        | –  | size increased but asymptomatic |

TSA : transsphenoidal approach

classified as follows : 1) intrasella extension (pituitary adenoma remains within the confines of the sella turcica); 2) suprasellar extension(extension of the pituitary adenoma beyond the diaphragm sellae in the direction of the optic chiasm); 3) parasellar extension into the cavernous sinus (loss of the medial dural wall of the cavernous sinus on MR imaging and extension of pituitary adenoma tissue into the cavernous sinus, with partial or complete encasement of the carotid artery); 4) parasellar extension into the temporal lobe(the same as 3 but, in addition, there is loss of the lateral dural wall of the cavernous sinus and extension of pituitary adenoma tissue into the medial aspect of the temporal lobe); 5) extension into the sphenoid sinus (loss of the sellar floor on MR imaging and visible extension of pituitary adenoma tissue into the sphenoid sinus); and 6) diffuse extension (the extreme form of infiltration in several different directions)<sup>2,5).</sup>

The follow-up period was defined as the time elapsed between the date of surgery and the last available date of follow up.

## Results

In the group of patients who underwent primary pituitary surgery, 4 men and 6 women were treated for giant

invasive pituitary adenoma (10/155). Their mean age was 47 years.

The most common clinical problems were visual symptoms. There were 6 cases of bitemporal hemianopsia, 1 case of ptosis, 1 case of total blindness. 3 patients complained of headache and the other problems reported were amenorrhea, panhypopituitarism, and sudden deterioration of consciousness due to acute hydrocephalus (Table 1).

The maximum diameter of the tumor ranged from 42 to 95 mm (mean 50.7mm). Severe invasion into the cavernous sinus was observed in 3 patients, and invasion into the sphenoid sinus was observed in 1 patient. The diffuse form involving multidirectional invasion was found in 6 patients. The hormonal and pathologic study revealed prolactinoma (20%) and non-functioning adenoma (80%).

Of the 10 giant invasive pituitary patients, 8 patients underwent transsphenoidal approach (TSA) operations, 1 patients underwent a transcranial operation and 1 patient underwent a combined TSA and transcranial operation. In all cases subtotal removal of the tumors mass was performed. One patient with diffuse form invasive adenoma died after the TSA and transcranial tumor removal operations, due to acute hydrocephalus. There were two cases of transient

diabetes insipidus and one case of transient hyponatremia after surgical treatment. The follow-up period for the nine surviving patients ranged from 14 months to 9 years after surgical treatment, with a mean follow-up of 42 months. The two patients with prolactinoma had preoperative serum prolactin levels of 386ng/ml, and 318ng/ml, and postoperative prolactin levels of 280ng/ml and 216ng/ml, respectively. Preoperatively, one patient was less responsive to dopamine agonist therapy whereas the other patients showed a progressive mass effect. These patients with prolactinoma showed an uncontrolled serum prolactin level during the follow-up periods and have been treated with a dopamine agonist combined with endocrinological follow-up. Those patients with nonsymptomatic residual lesions were observed clinically and radiologically. During the period of observation, the residual tumor grew in size in 3 cases. The two of them showed symptomatic conditions and underwent radiation treatments. There were radiologically demonstrated reductions in the tumor size and symptoms were improved after radiation treatment. One patient with panhypopituitarism and one patient with prolactinoma were treated with hormonal replacement. In all cases except for the patient with preoperative blindness, the visual symptoms were improved.

## Illustrative Case

A 65-year-old woman presented with a history of headaches and progressive visual defect. The clinical evaluation revealed a bitemporal hemianopsia. MRI of the brain (Fig. 1A) showed an invasive pituitary tumor with diffuse form invasiveness. Subtotal tumor removal was performed using a transsphenoidal approach. The results of hormonal and histological workup were consistent with a nonfunctioning pituitary adenoma. The visual symptom was much improved after surgery. After follow-up 12 months, the patient complained of visual defect again and the follow-up MRI showed increased tumor mass. Radiation therapy was administered. The visual symptom was improved and the follow-up MRI, 32 months after surgery, showed no increase of tumor mass (Fig. 1B).

## Discussion

Early reports on invasive pituitary adenomas have focused primarily on their gross extrasellar expansion and the radiological features of invasiveness, that is, sellar enlargement, suprasellar extension and erosion of the sellar bone or clivus. Based on the findings of plain x-ray films, grossly invasive macroadenomas and giant adenomas occur with a frequency

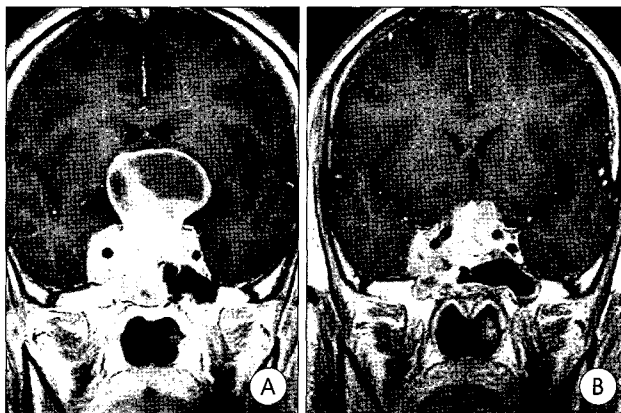


Fig. 1. A : diffuse form invasive giant pituitary adenoma. B : postoperative 32 months follow-up coronal T1-weighted magnetic resonance image.

of approximately 10%<sup>2)</sup>. The development of sophisticated imaging technology (computerized tomography scanning and MR imaging) and biochemical hormone assays has resulted in higher rates of detection of invasive pituitary adenomas<sup>12)</sup>.

A microadenoma may grow, seated within the anterior lobe. Once it breaks through the normal pituitary tissue, it may potentially infiltrate neighboring structures. It is important to distinguish tumor extension from invasion; invasion implies destructive infiltration of adjacent tissue, whereas extension implies directional tumor growth with compression of underlying tissue<sup>1,7-9)</sup>. Often, invasive adenomas exhibit both qualities. Adenomas may invade in any of a number of directions. Superiorly, they infiltrate and permeate the diaphragm sellae to gain access to the suprasellar cistern. Inferiorly, they may penetrate the sellar floor and invade the sphenoid sinus. Tumors that show lateral invasion permeate and penetrate the dural wall of the cavernous sinus. Posterior invasion causes destruction of the clivus. The cells of invasive adenomas may surround the nerve in the cavernous sinus and obliterate the venous structures that compose the sinus. Occasionally they invade the nerve trunks and may be found in the adventitia of carotid artery<sup>2,11)</sup>.

There was a clear progression of the frequency of microscopic evidence of dural invasion with increasing tumor size : 24% ( $\leq 10$ mm), 35% ( $>10$  to  $\leq 20$ mm), 55% ( $>20$  to  $\leq 40$ mm), 70% ( $>40$ mm), respectively, in patients undergoing primary transsphenoidal surgery<sup>2)</sup>. Selman et al. also demonstrated a positive correlation between dural invasion and tumor size<sup>13)</sup>. The clinically nonfunctioning adenomas that were investigated were rarely restricted to the sella turcica and very frequently showed a large sized mass and invasive patterns. In the present study, we found that 8 cases (80%) were endocrinologically nonfunctioning adenomas. On average, these adenomas are the largest tumors, they occur mainly in older patients, and

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the clinical signs develop because of their mass effect and rather than from a hypersecretory endocrinopathy. Therefore, the relationship between adenoma type and invasiveness may be a reflection of tumor size.

In another study, A. Goel et al. reported on a selected series of 118 cases of giant pituitary adenomas (defined as measuring more than 4cm in one of their largest dimensions), which were surgically treated during a period of 7 years and that included only hormonally inactive tumors. They introduced a new classification that included Grade I in which the tumors were confined under the diaphragma sellae, Grade II in which there was evidence of transgression into the cavernous sinus, Grade III in which the superior wall of the cavernous sinus was elevated and there was extension of this elevation into the surrounding structures, and Grade IV in which all of the surrounding structures were transgressed and there was penetration into the subarachnoid space of the brain with encasement of the arteries of the Circle of Willis<sup>4</sup>). With this grading system, Grade II may be described as "giant locally invasive", Grades III and IV as "giant infiltrative aggressive", and these three groups were included in the classification of "giant invasive pituitary adenomas" in the present study. In this way, in the above study, 64 of the 118 cases (54%) were classified as giant invasive pituitary adenomas, and the total removal of the tumor mass was accomplished in only 4 cases, while 60 cases involved subtotal removal. In the present study, all cases involved subtotal removal. Within the mean 42 months follow-up period, one patient died, three patients showed residual tumor growth and three patient had endocrinological adjuvant therapies. The prognosis after presentation with a giant invasive pituitary tumor appear to be poor<sup>3,6,10</sup>). In one study the rate of recurrence of radiologically identified invasive nonsecreting adenomas (33%) was significantly higher than that of enclosed adenomas (15%)<sup>3</sup>). In another long-term follow-up study, 60 out of 83 patients with suprasellar extension of their pituitary adenomas were alive after 12 years, whereas only 3 out of 19 patients with huge invasive tumors were still alive<sup>6</sup>). The growth rate, growth potential, pattern of the clinical course, and management strategy of giant invasive pituitary adenomas

have not yet been clearly described in the literature, and will have to be analyzed on the basis of larger series with longer follow-up periods.

## Conclusion

Although based on our short experience, we consider that the transsphenoidal approach is best choice for safe surgical resection, symptomatic relief and cytoreduction prior to the radiation of giant invasive pituitary adenomas, and multidisciplinary treatments should be applied during long-term follow-up periods.

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