



# Combined Treatment of Invasive Giant Prolactinomas\*

Chonjiang Yu, Zhebao Wu, and Jian Gong

Beijing Neurosurgical Institute, Beijing 10050, P.R. China

**Abstract.** The management of invasive giant prolactinomas (IGP) has been an area of some controversy. The relative roles of transsphenoidal surgery, craniotomy, radiation therapy and dopamine agonist based medical therapy are gradually becoming clarified.

We report the results of management of 30 patients with IGP. Surgery was the initial therapy in 18 patients and was nearly always followed by adjunctive treatment with radiotherapy and/or bromocriptine. A second group of 12 patients had initial therapy with bromocriptine; 6 had subsequent radiotherapy and only 1 had transsphenoidal surgery.

Outcomes with regard to relief of mass effect, visual improvement, pituitary function and complications of therapy were superior in the bromocriptine treated patients.

**Key Words.** prolactinoma, pituitary adenoma, bromocriptine, transsphenoidal surgery

Invasive giant prolactinomas (IGPs) are defined as tumors larger than 4 cm in diameter with a prolactin level higher than 200 ng/ml, and mass effect. The incidence of the tumors is not high and they constitute 2% of all pituitary neoplasms in our database. Because these giant tumors are always invasive, surgery alone is not satisfactory, and they still remain a difficult problem for neurosurgery. We report 30 cases of IGPs that underwent combined treatment and discuss the outcome and the nuances of management.

## Patients and Methods

Among the 30 patients (26 male and 4 female), the age at diagnosis ranged from 17 to 52 (mean age 39), and the course of the disease ranged from 1 month to 10 years (mean 3.5 yr). The clinical manifestations included: visual deterioration (19); amenorrhea (4/4); 16 with headache; 11 with loss of axillary and pubic hair; 2 with hemoptysis; 2 cases with respiratory obstruction; 2 facial numbness and pain, 1 with oculomotor nerve palsy; and 1 with coma; 13 of the 26 men presented with sexual dysfunction or hyposexuality. Imaging and endocrine examination showed: the tumor diameter ranged from 40 to 100 mm (mean 58 mm); in 24 cases the tumor invaded the cavernous sinus bilaterally, and in 6 cases unilaterally. Preoperatively, in all cases the PRL level was higher than 200 ng/ml; in 10 cases, the PRL level was higher than 4000 ng/ml.

## Treatment

The patients were divided into two groups according to different treatment strategies: Group A (surgery group, 18 cases): patients initially underwent surgery and were then given radiotherapy and/or medication (bromocriptine). Group B (medication group, 12 cases): patients initially underwent medical (bromocriptine) treatment, and some also had radiotherapy (6 cases); surgery was employed when necessary (one case). Specifically, for Group A (Surgery Group) treatment included: 10 cases of unilateral subfrontal craniotomy approach, 1 case of right frontal craniotomy interhemispheric approach, 5 cases of trans nasal-transsphenoidal approach, 1 case of craniotomy with a pterional craniotomy, and 1 case of frontotemporal zygomatic craniotomy. In group A, 13 of 18 cases had complete follow-up; of these, 2 were given medication (bromocriptine), 4 cases were given radiotherapy, and 7 cases had medication combined with radiotherapy. In Group B (medication group): the patients had medication (bromocriptine), 6 of them combined with radiotherapy; and 1 case had transsphenoidal surgery to remove residual tumor after medication combined with radiotherapy.

## Results

1. Short-term effects of surgery: For Group A, the tumor was sub-totally removed in all cases, and partially decompressed in 11 cases. Complications of surgery are given in Table 1. In all cases the PRL level was higher than 200 ng/ml post-operatively.
2. Results of long-term follow up: For the two groups combined, 1 patient died and 4 were lost to follow-up. The duration of follow-up in the remaining 25 patients ranged from 3 to 63 months (mean 31.7 months). The follow-up data of the two groups are given in Table 2.

## Discussion

The diagnostic standard for IGPs [1] includes: (1) tumor diameter >4 cm; (2) serum PRL >1000 ng/ml;

\*Report of 30 cases

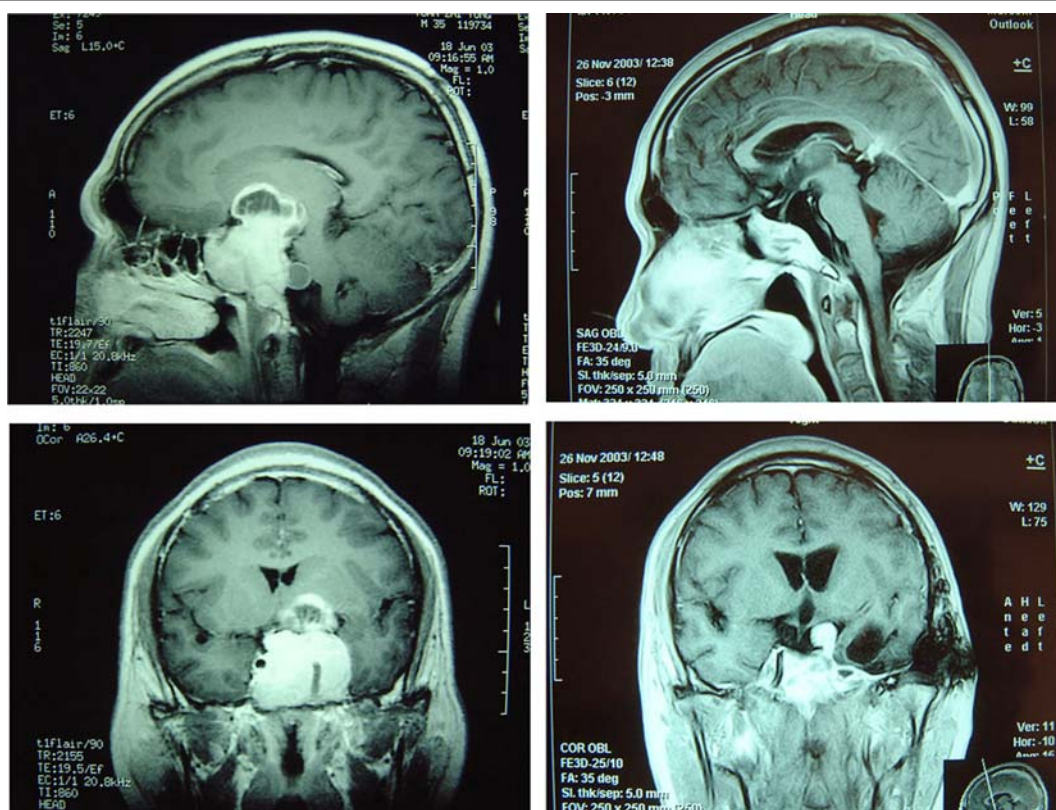
Address correspondence to: Jian Gong, MD, PhD., Department of Neurosurgery, Box 800212 HSC, University of Virginia, Charlottesville, VA 22908-0212, USA.

**Table 1.** Surgical complications in 18 cases of IGPs

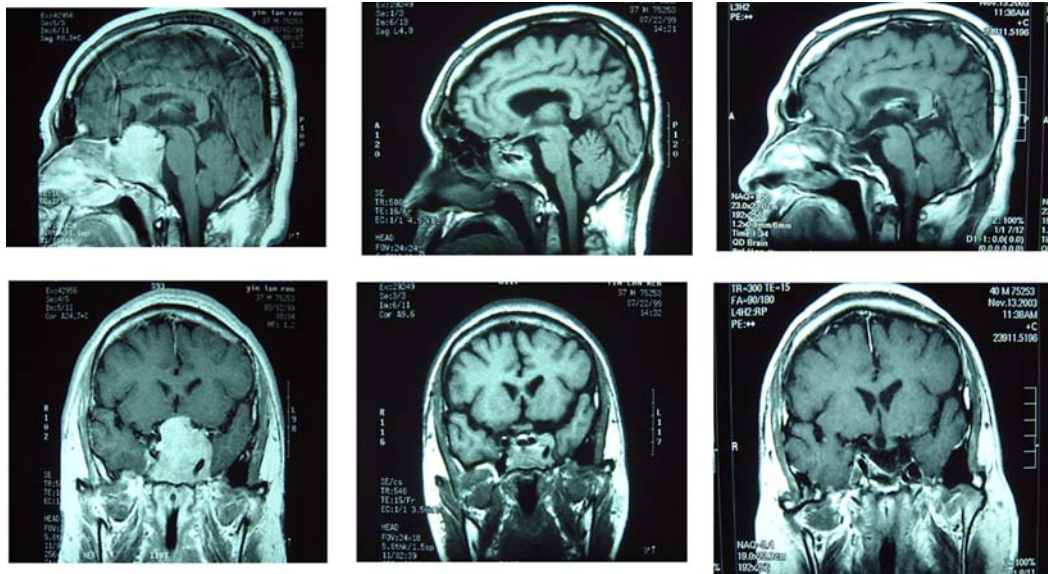
Complications (n=18)	Cases	Incidence (%)
Diabetes insipidus	11	61
Visual deterioration	7	39
Electrolyte disturbance	6	33
Mental symptoms	4	22
Cranial nerve palsy		
III	3	17
V	1	6
VI	2	11
CSF leak	2	11
Hemiplegia	2	11
Hyperglycemia, ketoacidosis	2	11
Epilepsy	1	6
Aphasia	1	6
Epidural hematoma	1	6
Anosmia	1	6
Nasal deformity	1	6
Death	1	6

(3) clinical symptoms induced by hyperprolactinemia or mass effect. In our data, the patients whose PRL levels were higher than 200 ng/ml and conformed to the other two criteria were also considered to be IGPs, and constituted 2% of all the pituitary adenomas treated in our department at Beijing Tiantan Hospital during the most recent eight years. Males constituted the majority of this group, with a male/female ratio 6.5:1, which can probably be attributed to ignorance of the importance of sexual dysfunction, and the subsequently delayed diagnosis (Figs. 1–4) [2].

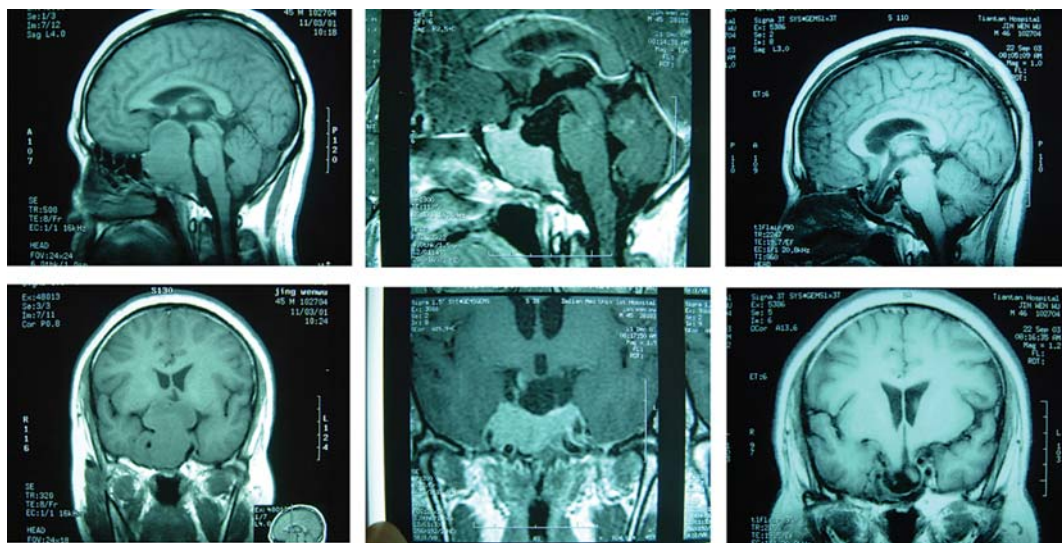
Because of the size and extent of the tumor, vision in many of the patients was impaired or lost. Most patients had surgery recommended to decompress the visual pathways. However, the IGPs are so large that they often invade the cavernous sinus (in our data, the incidence was 100%), protrude upward into the third ventricle, downward into the sphenoid sinus and clivus and may even extend into the anterior and middle cranial fossae and the interpeduncular fossa, so, total



**Fig. 1.** Male, 34 years of age, admitted with left upper toothache for 3 years, visual deterioration for 1 year, diplopia for 3 months. Vision: L: 0.3, R: 1.5. PRL :>6000 ng/ml. MR image before surgery (Figure A, B) shows tumor invades inferiorly into sphenoid sinus and clivus, superiorly into the third ventricle, laterally into the cavernous sinus and encloses the internal carotid artery, posteriorly into interpeduncular fossa. Left fronto-temporal craniotomy with resection of the tumor. The patient received radiotherapy 1 month after surgery; 4 months later had repeat MR imaging (C, D) PRL: 252 ng/ml. The patient was maintained on bromocriptine 2.5 mg, tid.



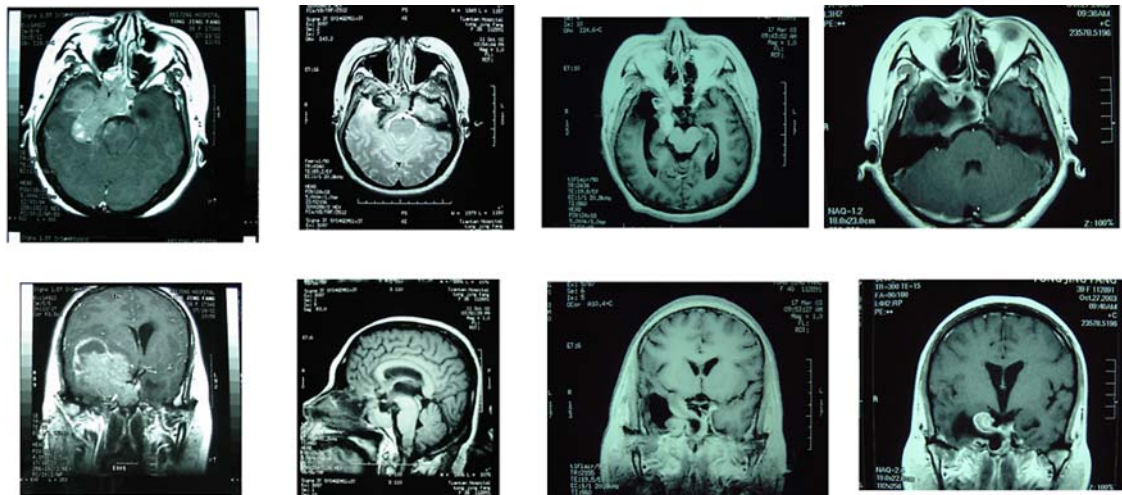
**Fig. 2.** Male, 37 years of age, admitted for visual deterioration of both eyes for one and a half years, vision: L: 0.8, R: 1.5. PRL: >200 ng/ml. MR image before surgery (A, B) Right frontal craniotomy for resection of the tumor. The patient received radiotherapy 2 months after surgery and continued bromocriptine treatment for 4 months after surgery, repeat MR imaging (C, D). 55 months later, repeat MR imaging (E, F) with PRL: 19 ng/ml.



**Fig. 3.** Male, 45 years of age, admitted sexual dysfunction accompanied by visual deterioration for 4 years. Vision on presentation: L 0.7, R hand movements, bi-temporal hemianopia, PRL: >280 ng/ml. MR images (A, B). The patient was given bromocriptine 2.5 mg tid. After 8 months, repeated MR imaging (C, D) showed that tumor volume decreased dramatically; PRL was 1431.4 ng/ml. The patient continued bromocriptine 2.5 mg tid. Repeat MR imaging 2 years later, 2003 (E) showed that the tumor had disappeared; PRL: 30 ng/ml, corrected vision of both eyes: 1.0, the patient was maintained on bromocriptine 2.5 mg qd.

resection is impossible and the incidence of complications of surgery is high (see Table 1). The incidence of postoperative diabetes insipidus was 66% and 1 patient died (6%). With the development of microsurgery, the incidence of complications of surgery decreased, but it has been reported [3,4] that the mortality rate still ranges from 5.2%~31.2%.

Bromocriptine, which is the most commonly used D-2-receptor agonist in our clinic, can normalize the serum prolactin level and decrease the volume of the tumor in 75~92% of the patients with prolactinomas [5-14]. The primary mechanism is the selective activation of the D-2-receptor on the cell membrane of prolactin cells, thus inhibiting the expression of the PRLm-



**Fig. 4.** Female, 37 years of age, admitted amenorrhea for 6 years, paroxysmal pain of the right face for 3 years, worsening for 2 months on June 11th, 2001. Vision on presentation: R 0.4, L 0.6, bi-temporal hemianopia, PRL: >8000 ng/ml. MR images showed that the tumor volume measurement was  $75 \times 50 \times 40$  mm, the tumor invaded the right temporal lobe and completely invaded the right cavernous sinus (4A, B). Because the patient had adverse reactions to bromocriptine, she was given radiotherapy. Two months after radiotherapy the right temporal component of the tumor clearly decreased, with a decrease in overall tumor volume of 79% (4C, D), but vision in both eyes deteriorated dramatically and the patient was advised to take bromocriptine 2.5 mg, tid. Repeat MR imaging 2 years later showed that tumor volume decreased by 95% (Fig. 4E, F), vision in each eye was 0.02, PRL: 523 ng/ml. Repeat MR imaging 7 months later showed further decrease of tumor volume (4G, H), vision in each eye was 0.04, PRL: 226 ng/ml. She was maintained on bromocriptine 2.5 mg, tid.

RNA gene and the metabolism of prolactin cells, which leads to decreased synthesis and secretion of PRL and decreased tumor volume. Comparing the extent of tu-

**Table 2.** Comparison of the two groups: treatment results

	Group A (surgery group) N = 18	Group B (medication group) N = 12
Extent of removal		
Total	0	1 <sup>a</sup>
Subtotal	18	–
Biopsy	11	–
Mean Follow up (months)	42.5	23
Tumor total disappearance on MRI	6/18	4/12
Tumor volume reduction rate	76.5%	91.3%
PRL (ng/ml)		
<25	4/18	2/12
25–200	3/18	6/12
>200	6/18	4/12
Visual function		
Improvement	2/18	6/12
No change	8/18	5/12
Worse	3/18	1/12

<sup>a</sup>1 case had transsphenoidal surgery and residual tumor disappeared after medication combined with radiotherapy.

mor volume decrease after treatment in Groups A and B, in the 42.5 months of follow-up in Group A, mean tumor volume decreased 76.5%, while in the 23 months of follow-up in Group B, mean tumor volume decreased 91.3%. This difference was not statistically significant.

In the combined data the tumor disappeared on MRI in 6 cases in Group A (mean post-treatment time, 42.5 months), and in 4 cases in Group B (mean post-treatment time, 27.8 months), not a significant difference.

Tumor volume decrease or disappearance on imaging reflects relief of mass effect. To obtain a biological remission, however, it is necessary to protect normal pituitary function and to achieve a normal PRL level. Gokalp [4] stated that the normalization rate for PRL of IGPs treated by surgery is 0. Roux [15] stated that surgery can normalize the PRL level in only 0–5% of IGP patients. Our data from Group A revealed that the PRL levels of all 18 patients were higher than 200 ng/ml after operation, which confirmed that surgery alone cannot control the PRL level effectively. In group B, treated by bromocriptine therapy, in only 4 cases was the post-treatment serum prolactin higher than 200 ng/ml. That is, pharmacotherapy (bromocriptine) was the only effective treatment for controlling the serum PRL level. [8–14]. Sieck [9] reported 24 cases of IGPs, with bromocriptine as the only treatment. The mean percentage decrease in prolactin level was 89% in two days, and 95% in 6 weeks, with 16 of their cases

achieving a normal level. Grebe [7] reported 4 cases of IGPs, in which 3 cases were treated with bromocriptine and their prolactin levels returned to normal in 2 to 24 months, the remaining case was close to a normal level after 36 months.

Our data revealed that there were 2 patients with visual improvement in the 13 cases of Group A (15%), and 6 such cases in Group B (50%), a statistically significant difference. Medication was superior to surgery in producing visual improvement. One possible reason could be that blood supply to the optic nerve and optic chiasm can be impaired during surgical manipulation. The tumor volume decreases gradually with medical treatment, preventing acute injury to the optic nerve and optic chiasm. Another possible reason could be associated with radiotherapy; 11 cases (85%) in Group A and 7 cases (58%) in Group B received radiotherapy. Many authors [1,2,7,8–14] confirm that visual symptoms of patients with giant prolactinomas can be relieved after several days to several weeks of bromocriptine treatment.

For most patients medication can reduce tumor volume and control PRL level effectively in a relatively short period of time. Shrivatava [1] reported 10 cases of male giant prolactinomas, and stated that 90% of the cases could be controlled by medicine alone, and only 10% needed early surgery. Acquati [16] presented a retrospective analysis of 132 cases of giant prolactinomas receiving combined treatment, and he concluded that medication was the preferred choice; surgery was considered when the patient could not tolerate pharmacotherapy or had bromocriptine resistance. Comprehensive analysis of our data reveals them to be in accordance with other authors; that is, even for invasive giant prolactinomas, medication is still a better choice. Early surgery was appropriate for the following patients: those whose vision deteriorated very rapidly; patients who experienced tumor apoplexy with severe clinical symptoms; and patients who could not tolerate pharmacotherapy or had pharmacological resistance; and patients who developed cerebrospinal fluid leakage after medical therapy and needed repair [1,3,4,16–18].

In conclusion, on one hand, the “cure” of IGPs requires disappearance of the tumor on imaging, preserving normal pituitary function and decreasing PRL to a normal level. On the other hand, it requires a high quality of life for the patient with as much benefit as possible from safe treatment. Therefore, medication is the superior initial choice to reduce tumor volume, and to control PRL level effectively. Even if there is residual tumor, the tumor may be altered from “invasive” to “non-invasive”, so that there is an opportunity to treat the tumor remnant by minimally-invasive surgery or by stereotactic radiosurgery, lessening the risks of surgery and reducing the overall cost of treatment.

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