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Outcomes of Transsphenoidal Surgery in Growth Hormone-Secreting Pituitary Adenomas

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Abstract

Growth hormone (GH)-secreting pituitary adenomas (PA) make up 15 to 20% of total amount of hormonally active adenomas. In addition to acromegaly and gigantism, these tumors cause deep metabolic disturbances. Its systemic impact leads to increased mortality ratio of 1.32 compared with general population. Surgical removal remains the priority treatment option in controlling acromegaly and provides endocrinologic remission in up to 72% patients. A total of 92 patients were included in the study. All surgeries were performed via microscopic transsphenoidal approach (TSA) by the senior author in our institution between December 2009 and October 2019. Only patients who were followed-up with 75 g oral glucose tolerance tests (OGTTs), GH, and insulin-like growth factor I (IFG-I) measurements preoperatively, 1 week, and every 6 months postoperatively were analyzed. Based on standard preoperative 1.5-T MR imaging with contrast enhancement, the adenomas were identified and distributed according to the size and KNOSP classification. The efficacy depends on KNOSP grade, which is directly correlated with invasiveness to cavernous sinus (CS). Grades 3 and 4 are unfavorable factors influencing prognosis. Excluding grade 0 adenomas, as the surgery was not difficult with the excellent outcomes, we reached 75% (36 out of 48) remission in grade 1 to 2 groups. In contrast, only 17% (2 out of 12) had successful outcomes after surgery alone. In conclusion, the study demonstrates the efficiency of TS surgery in patients with confirmed GH-secreting PA.

Keywords
- pituitary adenoma
- acromegaly
- transsphenoidal approach

Introduction

Growth hormone (GH)-secreting pituitary adenomas (PA) make up 15 to 20% of total amount of hormonally active adenomas.[1] They can purely secret GH or cosecrete prolactin (PRL) in up to 40%.[2,3] In addition to acromegaly and gigantism, these tumors cause deep metabolic disturbances. Its systemic impact leads to increased mortality ratio of 1.32 compared with the general population.[4] It is worth mentioning the fact that the high level of insulin-like growth factor-1 (IGF-1) in acromegaly is related to an increased risk of some cancers.[5,6] The mean diagnostic delay is 7 years due to insidious symptoms.[7]

Surgical removal remains the priority treatment option in controlling acromegaly and provides endocrinologic remission in up to 72% patients.[1,8] Size has an inverse relationship with success rate: 87% for micro- and 66% for macroadenomas.[9] Cavernous sinus (CS) invasion seems to be the most important factor for remission.[10,11] Medical and radiation therapy provide remission rates ranging from 42% to 60%, but takes more time for results, and have long-term multisystem comorbidities.[2,9,10] Conservative approach may be used if the patient is not a surgery candidate or when the resection fails to provide biochemical remission. Continuous administration of drugs has a higher cost, and its withdrawal leads to relapse

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of symptoms.[12] Radiation therapy takes 2 to 3 years to reach the effect and can lead to hypopituitarism in 85% of patients.[13,14]

The lack of data related to prognostic parameters for patients with acromegaly attracts attention to this issue. Thus, the aim of this study was to demonstrate the results of GH-secreting PA surgical treatment that might assist in strategy decisions and subsequently better outcomes.

Methods

Patient Population

By analyzing the medical records, males and females, aged >18 years, with histologically and clinically verified GH-secreting PA were retrospectively included in the study. All surgeries were performed via microscopic transsphenoidal approach (TSA) with endoscopic assistance by the senior author in our institution between December 2009 and October 2019. Only patients who were followed-up with 75 g oral glucose tolerance tests (OGTTs), GH, and IFG-I measurements preoperatively, 1 week, and every 6 months postoperatively were analyzed. In addition, all patients underwent a complete clinical, neurological, and ophthalmological examination. The diagnosis was established based on the results of clinical picture, laboratory parameters, and MRI data. Consent was obtained by all participants in this study. Expert Commission of the Clinical Hospital "Feofaniya" of the State Administration of Affairs issued approval Quality Management System Certificate UA126Q01 19 076 01.

Radiologic Evaluation

Based on standard preoperative 1.5-T MR imaging with contrast enhancement, the adenomas were identified and distributed according to the size and KNOSP classification. Tumors with the maximal diameter of greater than or equal to 10 mm were defined as macroadenomas, while microadenomas were those with maximal diameter of less than 10 mm. According to KNOSP classification, grades were distinguished from each other by a medial tangent, the intercarotid line (through the cross-sectional centers), and a lateral tangent on the intra- and supracavernous internal carotid arteries. Grade 0 represented the tumor medial to medial tangent and grade 4 corresponded to the total encasement of the intracavernous carotid artery.[15,16] We excluded adenomas with suprasellar and antesellar nodes, isolated expansion beyond the medial line and tumor-induced hydrocephaly, as these cases required either transcranial approach or complex several-staged treatment.

Postoperative MRI was performed within 3 months and 1 year after surgery to evaluate the extent of resection.[17] Gross total resection (GTR) was defined as complete tumor removal confirmed by the surgeon intraoperatively and no evidence of residual tumor on postoperative MRI within 3 months and a year after the procedure. Subtotal resection (STR) was defined as the presence of residual tumor left by the surgeon intraoperatively or proven on images.

Endocrinologic Evaluation

Elevated IGF-1 confirmed a diagnosis of acromegaly. In cases of equivocal IGF-1 levels, an OGTT was performed, and lack of GH suppression to < 1 µg /L was diagnostic.[18] Efficacy of surgery defines disease control by mean fasting random serum GH level < 2.5 µg /L or normalization of age- and gender-matched IGF-1 after the procedure.

All patients underwent combined pituitary function tests before surgery to estimate anterior pituitary.

Statistical Analysis

Statistical analyses were conducted using SPSS statistics version 23. The quantitative data was tested for normality. The mean of numeric variable between the two groups were compared with independent-samples two-tailed *t*-tests. The distributions of categorical variables between the two groups were compared using Chi-squared test.

Results

A total of 92 patients were included in the study. The median duration of symptoms until the treatment was 4 years. Acral enlargement (86%) and macroglossia (31%) were the prominent features. Carpal tunnel syndrome and arterial hypertension were associated in 18% and 61%, respectively. Patients'

Table 1 Clinical characteristics and surgical outcomes of GH-secreting pituitary adenomas

	KNOSP classification									
	Grade 0		Grade 1		Grade 2		Grade 3		Grade 4	
Number of patients	33 (36%)		27 (29%)		21 (23%)		7 (8%)		5 (4%)	
Median GH level at diagnosis in ng/mL	26.4		25.3		27.9		31.6		30.5	
Median IGF-1 level at diagnosis in ng/mL	553.5		646.5		752.7		569.4		617	
Microadenoma	32 (97%)		2 (7%)		0		0		0	
Macroadenoma	1 (3%)		25 (93%)		21 (100%)		7 (100%)		5 (100%)	
Remission	33 (100%)		23 (85%)		13 (62%)		2 (28%)		0	
Radicality of resection	GTR 33 (100%)	STR 0	GTR 24 (89%)	STR 3 (11%)	GTR 13 (62%)	STR 8 (38%)	GTR 3 (43%)	STR 4 (57%)	GTR 0	STR 5 (100%)

Abbreviations: GH, growth hormone; GTR, gross total resection; IGF-1, insulin-like growth factor 1; STR, subtotal resection.

main characteristics and distribution are shown in ►**Table 1**. The mean tumor volume was 4.8 cm^3 and the most common KNOSP grade was 0 (36%). Grade 1 and 2 groups consisted of approximately identical number of patients. Less common were grade 3 and 4 with 8% and 4%, respectively. Microadenomas consisted 97% of grade 0 tumors. In contrast, grade 1 included only 7% of adenomas less than 1 cm in diameter. From grade 2 to grade 4, all tumors were macro. The GTR as well as remission were reached in 100% in the first group. In 24 out of 27 patients with KNOSP grade 1, the GTR and remission were achieved in all but one case. Surgery was 100% effective in grade 3 group. A minority of procedures were successful in grade 3 adenomas (3 out of 7). Neither operation led to acromegaly control in KNOSP group 4. Mean follow-up time was 19 months ($p = 0.125$) after surgery. Patients without GTR and biochemical remission were sent for radiotherapy. If the remission was not reached in 3 months, further tactics were defined by endocrinologist. Cerebrospinal fluid (CSF) rhinorrhea in four patients was resolved after surgical repair. Ten patients had transient diabetes insipidus. We had no other complications. Median GH level at diagnosis was 28.3 ng/mL ($p = 0.134$); median IGF-1 level at diagnosis was 627 ng/mL ($p = 0.276$); median patients age was 42 years ($p = 0.238$).

Discussion

According to previous investigations, the overall remission after TS surgery is 42 to 72%. Surgical removal remains the first-line treatment.[6,7,19] The efficacy depends on KNOSP grade, which is directly correlated with invasiveness to CS. Grades 3 and 4 are unfavorable factors influencing prognosis.[20] Excluding grade 0 adenomas, as the surgery was not difficult with the excellent outcomes, we reached 75% (36 out of 48) remission in grade 1 to 2 groups. In contrast, only 17% (2 out of 12) had successful outcomes after surgery alone. However, the population in these groups was relatively small. Some surgeons practice debulking TS surgery in combination with medications and radiosurgery. They believe that aggressive excision risks overlap the benefits.[21-23] In contrast, our surgeries on adenomas with CS invasions were effective and without marked complications.

Surgical technique could be improved by precise analysis of MRI and understanding the intraoperative relations, especially infundibulum and normal hypophysis location. As the removal of invasive tumors is often associated with CSF leak, as a rule, we use patient's fat application, followed by anterior wall of sphenoid sinus reimplantation. Our study also confirms that postoperative IGF-1 is the predictor for uncontrolled disease. We found it crucial for definition of appropriate treatment strategy in complex with intraoperative findings and postoperative MRI. We had two cases where the resection was estimated as gross total, but hormonal levels were not satisfactory.

Conclusion

In conclusion, the study demonstrates the efficiency of TS surgery in patients with confirmed GH-secreting PA. The experienced surgeon and adequate preparation could provide the safe resection that leads to remission or, at least, minimization of adenoma's influence with subsequent improvement of the success of adjuvant therapy.

Funding
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Conflict of Interest
None declared.

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