Endoscopic endonasal transsphenoidal surgery for growth hormone–secreting pituitary adenomas

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Object. The aim of this study was to determine the preoperative predictors of the extent of resection and endocrinological remission following endonasal endoscopic removal of growth hormone (GH)-secreting pituitary adenomas.

Methods. The authors analyzed a prospectively collected database of 24 consecutive acromegalic patients who underwent endoscopic endonasal transsphenoidal surgery. The extent of resection was evaluated on postoperative contrast-enhanced MR imaging. Endocrinological remission was defined as normal insulin-like growth factor I (IGF-I) serum levels and either a nadir GH level of < 0.4 ng/ml after an oral glucose load or a basal GH serum level < 1 ng/ml.

Results. The majority of acromegalic patients (83%) had macroadenomas > 1 cm in maximum diameter. Gross-total resection was achieved in 17 (71%) of 24 patients. Notably, endoscopic transsphenoidal surgery allowed complete resection of all lesions without cavernous sinus invasion, regardless of the suprasellar extent. Biochemical remission was achieved in 11 (46%) of 24 patients. A smaller tumor volume and a postoperative reduction in GH serum levels were associated with a higher rate of biochemical cure (p < 0.05). During a 23-month follow-up period 5 patients (21%) underwent Gamma Knife treatment of any residual disease to further reduce excess GH production. Twenty patients (83%) reported significant relief of their symptoms, while 3 (13%) considered their symptoms stable. Two patients (8%) with large macroadenomas experienced postoperative panhypopituitarism, and 2 patients (8%) suffered from CSF leaks, which were treated with lumbar CSF diversion.

Conclusions. A purely endoscopic endonasal transsphenoidal adenoma resection leads to a high rate of gross-total tumor resection and endocrinological remission in acromegalic patients, even those harboring macroadenomas with wide suprasellar extension. Extended approaches and angled endoscopes are useful tools for increasing the extent of resection. *(DOI: 10.3171/2010.7.FOCUS10173)*

Key Words • endoscopy • acromegaly • growth hormone • insulin-like growth factor I • minimally invasive procedure • transsphenoidal surgery • skull base

Acromegaly is most commonly caused by GH-secreting pituitary adenomas. This rare but very serious condition carries at least twice the mortality rate compared with that in the general population.[3,26,28,34] Excessive secretion of GH causes cardiovascular disease, musculoskeletal deformity, diabetes mellitus, and an increased incidence of malignancies. Cardiovascular and cerebrovascular accidents are common causes of death in acromegalic patients. Importantly, the normalization of GH levels alleviates symptoms and reduces mortality rates to those in the general population. Thus, a definition of cured acromegaly involves the normalization of excessive GH secretion as determined by circulating IGF-I and nadir GH of < 0.4 ng/ml after an oral glucose load.[12,13,23] Although somatostatin analogs and the GH receptor antagonist pegvisomant are increasingly prescribed as adjuvant or even primary therapy, resection remains the first-line treatment. In patients with intrasellar microadenomas, microsurgical removal alone provides biochemical control with the normalization of IGF-I in 75%–95% of patients; control rates decrease to 40%–68% of patients with macroadenomas.[21,25,33] Resection can be performed either alone or in combination with the administration of medical treatment as wells as radiotherapy.[22]

Abbreviations used in this paper: GH = growth hormone; GKS = Gamma Knife surgery; GTR = gross-total resection; IGF-I = insulin-like growth factor I; STR = subtotal resection.

In the current study we describe our experience with a purely endoscopic endonasal transsphenoidal approach in 24 patients with GH-secreting pituitary adenomas. Our aim was to analyze predictors of biochemical and clinical outcomes after the endoscopic resection of such lesions.

Methods

Patient Demographics

We reviewed a prospectively collected database of all endoscopic endonasal surgeries for GH-secreting pituitary adenomas performed at Weill Cornell Medical College, New York–Presbyterian Hospital, Geisinger Neurosciences Institute, and Temple University School of Medicine between February 2004 and May 2010 as a collaboration between the Departments of Neurosurgery and Otolaryngology. Patients selected for this study all underwent surgery during which an endoscopic endonasal transsphenoidal approach was used. In 3 patients an extended transsphenoidal approach with removal of the tuberculum sellae and planum sphenoidal was performed.[18] All patients underwent preoperative MR imaging. All tumors were analyzed using contrast-enhanced MR images on postoperative Day 1, at 3 months after surgery, and then at a yearly interval. Tumor volume was approximated by an ellipsoid model by using the product of the maximal anteroposterior, lateral, and rostrocaudal radii.[2,17,36] Invasion of the cavernous sinus was diagnosed according to the following criteria: three-fourths or more encasement of the internal carotid artery, obliteration of the carotid sulcus venous compartment, or crossing of the lateral intercarotid line by the tumor.[6] For each surgery, the pathology, duration of surgery, estimated blood loss, type of exposure, use of intraoperative fluorescein and lumbar drainage, technique of closure, and complications were recorded. The institutional review board at both institutions approved the study.

Surgical Technique

Following the induction of general anesthesia, antibiotics, glucocorticoids, and intrathecal fluorescein are given.[27] BrainLAB neuronavigation is routinely used. A detailed description of the procedure has already been published.[18,31] Briefly, after topical exposure of the nasal mucosa to cocaine and injection of the mucosa of the middle turbinates with a mixture of lidocaine 1% and epinephrine (1:100,000), the sphenoid ostia are bilaterally identified and the bony opening is enlarged. The posterior third of the nasal septum adjacent to the vomeric bone and maxillary crest is resected with a tissue shaver. The anterior wall of the sella is opened using a high-speed drill and curettes. In more recent cases with large macroadenomas, a nasoseptal flap may be harvested at the start of the case. For the resection of microadenomas, an attempt is made to remove the tumor en bloc. For macroadenomas, the lesion is first internally decompressed by removing the inferior portion of the tumor followed by the lateral portions to prevent the suprasellar arachnoid from herniating down into the sella and obstructing the view. The suprasellar component is resected last. Exposure of this region may require an extended approach including removal of the tuberculum sellae and planum sphenoidale. Tumor is dissected off the medial wall of the cavernous sinus. Angled endoscopes are used to enter the cavernous sinus and remove tumor that can easily be dissected from this area. Closure is performed in a multilayer fashion.[20]

Endocrinological Evaluation

Basal fasting levels of GH and IGF-I were measured in the serum of patients preoperatively, postoperatively, and at the time of the last follow-up. Biochemical remission was evaluated according to IGF-I serum levels combined with an oral glucose tolerance test in 10 patients. A glucose tolerance test was considered normal if serum GH levels were suppressed to < 0.4 ng/ml following a 75-g oral glucose load. In the remaining 14 patients, biochemical remission was evaluated by IGF-I levels combined with basal GH levels. Random basal GH serum levels of ≤ 1 ng/ml were considered normal. Insulin-like growth factor I was always evaluated according to age-related diagrams. Our goal is to attempt an oral glucose test to determine cure in all patients, but this test is not always possible in patients referred from outside endocrinologists who may not comply or follow up reliably at our institution.

Statistical Evaluation

Continuous variables are displayed as the means ± SD and the range. Categorical values are shown as percentages. Associations between the effect of tumor size, invasion of the cavernous sinus, extension into the suprasellar cistern, or preoperative GH serum levels on endocrinological remission and the extent of resection were calculated using a chi-square test for categorical variables and the Pearson correlation coefficient for continuous variables. Postoperative GH serum levels were compared using a Mann-Whitney U-test. Outcome predictors were determined with binary logistic regression modeling. A p value < 0.05 was considered significant.

Results

Patient Characteristics

Twenty-four patients who underwent purely endoscopic transsphenoidal resection of GH-secreting pituitary adenomas were included in the series. The cohort consisted of 13 males and 11 females with a mean age of 50.7 ± 14.7 years (range 22–75 years; Table 1). Approximately half of these patients presented with increases in ring and shoe size as well as the typical coarse acromegalic facial features. Fewer patients sought medical attention for bone and joint pain or amenorrhea. The majority of lesions were macroadenomas defined by a maximum diameter > 1 cm. However, presenting symptoms were attributable to excess hormonal production in all but 1 patient, who presented with diplopia caused by tumor invasion of the cavernous sinus. None of the patients demonstrated impairment on preoperative visual field testing. Assessment of preoperative contrast-enhanced MR imaging revealed a cavernous sinus invaded by tumor in 10 patients.

Endoscopic resection of GH-secreting pituitary adenomas

TABLE 1: Summary of characteristics in 24 patients with acromegaly*

Characteristic	No. (%)
sex	
M	13 (54.2)
F	11 (45.8)
mean age (yrs)	50.7 ± 14.7
previous op	
yes	4 (16.7)
no	20 (83.3)
presenting symptoms	
increased ring & shoe size	11 (45.8)
bone & joint pain	4 (16.7)
amenorrhea	2 (8.4)
max tumor diameter	
microadenoma (<1 cm)	4 (16.7)
macroadenoma (>1 cm)	19 (83.3)
invasion of the CS	
yes	10 (41.7)
no	14 (58.3)
suprasellar tumor extension	
yes	7 (29.2)
no	17 (70.8)
GTR	
yes	17 (70.8)
no	7 (29.2)
mean FU (mos)	23.2 ± 25.4

* CS = cavernous sinus; FU = follow-up.

TABLE 2: Summary of operative details in 24 patients with acromegaly

Parameter	No. (%)
mean op time (min)	181.6 ± 57.3
mean estimated blood loss (ml)	153.1 ± 206.4
extended approach	
yes	3 (12.5)
no	21 (87.5)
intrathecal fluorescein	
yes	18 (75.0)
no	6 (25.0)
intraop CSF leak	
yes	13 (54.2)
no	11 (45.8)
closure of skull base defect	
fat	13 (54.2)
vomer	10 (41.6)
fascia lata	2 (8.3)
DuraSeal	24 (100.0)
lumbar drain	
yes	3 (12.5)
no	21 (87.5)
mean hospital stay (days)	3.6 ± 1.8

The tumor extended into the suprasellar cistern in 7 patients. The average duration of the follow-up period from resection to laboratory testing was 23 months (range 1–74 months).

Surgical Results

Purely endoscopic transsphenoidal surgeries lasted an average of 182 minutes (range 104–326 minutes). The estimated blood loss was 153 ml (range 30–800 ml). An extended transsphenoidal approach was performed in 3 patients with suprasellar tumor expansion and invasion of the cavernous sinus. In more than two-thirds of the cases, intrathecal fluorescein was given to label the CSF, which is an institutional protocol at Weill Cornell Medical College. Intraoperative CSF leaks were encountered in approximately one-half of the patients (Table 2). In 83% of the cases with intraoperative CSF leaks, abdominal fat was harvested for the enforcement of a multilayer closure. Twenty-five percent of these patients also underwent spinal CSF drainage for 3 days to facilitate watertight closure of the skull base defect. Postoperative MR imaging revealed that GTR was achieved in 71% of the cases. Two factors were associated with STR; greater tumor volume and cavernous sinus invasion were linked to a higher rate of residual tumor (p < 0.01 and p < 0.001, respectively; Fig.

1). Gross-total tumor resection was achieved in all patients who did not have invasion of the cavernous sinus and in 3 of the 10 patients who did have cavernous sinus invasion. Thus, residual tumor was identified in the cavernous sinus of 7 patients. In 1 of these patients residual tumor was also found in the frontal lobe, and in another patient tumor was left in the suprasellar cistern. Note, however, that tumor expansion into the suprasellar cistern was not correlated with a higher rate of STR. Only tumor volume was a significant predictor for GTR, according to a logistic regression model (p < 0.05). Five patients who underwent STR and had poor control of their GH serum levels underwent GKS. One of these patients achieved biochemical remission following adjuvant medical therapy. Another 2 patients had near complete restoration of GH and IGF-I levels and did not require medical treatment. However, 2 of these 5 patients who underwent GKS continued to have poor control of excess GH secretion despite adjuvant medical therapy.

Endocrinological Outcome

Preoperative serum GH levels of 31 ng/ml (range 1–150 ng/ml) decreased to 4 ng/ml (range 0–36 ng/ml) postoperatively. Insulin-like growth factor I levels of 806 ng/ml prior to surgery (range 15–1321 ng/ml) decreased to 462 ng/ml (range 6–937 ng/ml) postoperatively (Table 3). At 23 months after resection, 11 patients (46%) had a biochemical cure. Considering only patients with macroadenomas (maximum diameter > 1 cm), the rate of endocrinological remission decreased to 42%. A smaller tumor volume was associated with a higher rate of biochemical cure by endoscopic transsphenoidal surgery (p
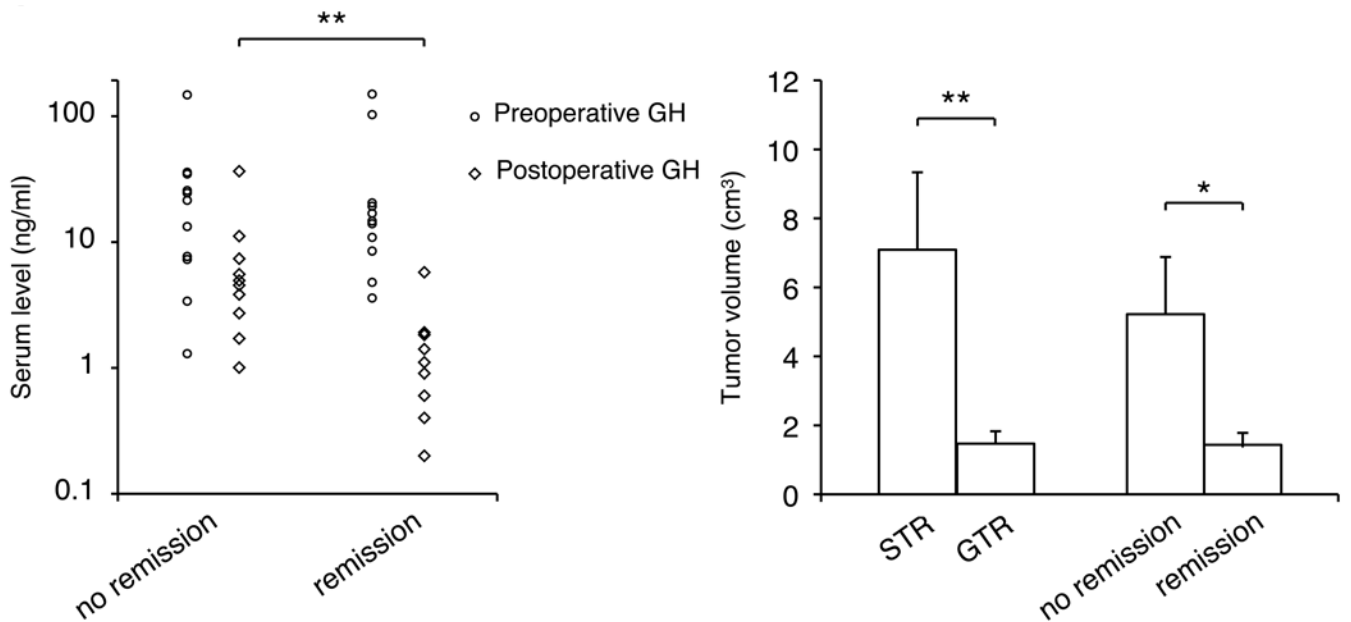
FIG. 1. Graphs showing the association between GH levels or tumor size and endocrinological remission. Comparison of pre- and postoperative GH serum levels in patients with and without endocrinological remission (left). *Horizontal line* indicates the median. Lesions associated with GTR and endocrinological remission are significantly smaller than lesions for which no GTR or remission was achieved (right). Values are shown as the means. *Error bars* represent the SEM. *p < 0.05 and **p < 0.01.

< 0.05; Fig. 1). While preoperative GH serum levels did not differ significantly between patients who demonstrated an endocrinological remission and those who did not, postoperative GH serum levels were significantly lower in patients who had a remission (p < 0.01). Thus, postoperative GH serum level was a significant predictor of endocrinological remission in a logistic regression model (p < 0.05). Of 11 patients in biochemical remission, 9 were cured by resection alone. One patient achieved endocrinological remission by a combination of resection, GKS, and adjuvant medical therapy, and 1 patient by resection and adjuvant medical therapy (Table 3). Seven of the 13 patients who did not achieve endocrinological remission required medical therapy for elevated GH serum levels. The other 6 patients had GH levels close to normal so that their endocrinologist selected conservative treatment with serial GH and IGF-I serum level checks.

Clinical Outcome and Complications

Twenty-three months after resection, 25% of the patients believed that their initial presenting symptoms had normalized and another 58% experienced significant improvement in their condition (Table 4). The remaining patients felt no change in their symptoms, and 1 patient with severe bone and joint paint believed that he had gotten worse following surgery.

Two patients who had an intact hypothalamic-pituitary axis prior to the procedure demonstrated panhypopituitarism following resection of their adenoma. Notably, the lesions in both of these cases were macroadenomas. Cerebrospinal fluid rhinorrhea developed in 2 patients after the resection of a GH-secreting macroadenoma. Both CSF leaks were successfully treated with 3–4 days of lumbar CSF drainage. Two patients suffered from sinusitis following the procedure and were treated with oral antibiotics. Transient diplopia was noticed by a patient who underwent resection of a recurrent pituitary macroadenoma with invasion of the cavernous sinus. Immediately after the procedure the patient demonstrated cranial nerve VI paresis ipsilateral to the side of invasion.

Discussion

Resection is currently the first-line treatment for GH-secreting adenomas. While endocrinological remission leads to symptom relief and the restoration of normal life expectancy, some patients are not cured by surgical treatment alone. Analysis of the determinants of a failed endoscopic transsphenoidal technique may assist in appropriate patient selection and further refinement of the procedure.

During the last few decades, the criteria for endocrinological remission have been constantly revised.[12,13] In early series, GH levels < 5 ng/ml were used to define biochemical remission.[1,29] Using these criteria, Abosch et al.[1] report that 76% of 254 patients had endocrinological remission after transsphenoidal pituitary resection. Similarly, Ross and Wilson[29] found GH levels < 5 ng/ml in 79% of 165 patients at the 76-month follow-up. However, basal GH levels are an unreliable marker for endocrinological remission given the pulsatile nature of GH secretion and the changes in serum levels with sleep, age, and nutritional status of a patient.[14] For that reason, subsequent studies included an assessment of the absolute nadir in levels of GH after an oral glucose load. Using a nadir level < 2 ng/ml, Fahlbusch et al.[8] reported a 57% rate of endocrinological remission after transsphenoidal surgery. More recent studies have used stricter criteria such as a

TABLE 3: Treatment characteristics and endocrinological outcome of 24 patients with GH-secreting pituitary adenomas*

Case No.	Age (yrs) & Sex	Preop GH	Preop IGF-I	Postop GH	Postop IGF-I	GKS	Adjuvant Medical Therapy	Last FU GH	Last FU IGF-I	OGTT†	Endocrin Cure	FU (mos)
1	48, F	13.3	624	4.5	261	yes	none	1.7	274	NA	no	10
2	56, M	NA	15.4	3.8	6.4	yes	none	4.8	267	NA	no	47
3	55, M	7.7	NA	1.0	422	no	none	NA	NA	NA	no	44
4	37, F	NA	773	5.7	506	yes	bromocriptine, cabergoline, Sandostatin	0.9	180	NA	yes	61
5	48, M	4.8	940	0.2	530	no	none	0.1	118	NA	yes	74
6	35, F	1.3	411	1.7	288	no	none	1.7	120	NA	no	13
7	60, M	35.9	567	2.7	313	no	none	2.7	313	NA	no	53
8	58, M	103	757	0.9	190	no	none	0.9	165	NA	yes	66
9	65, M	8.5	902	1.1	635	no	none	0.8	191	normal	yes	21
10	66, F	10.9	534	1.4	85	no	none	0.017	87	NA	yes	24
11	65, F	3.6	836	0.4	547	no	none	0.056	148	NA	yes	31
12	39, M	19.3	855	0.2	597	no	none	0.1	135	NA	yes	4
13	69, M	24.6	895	4.9	478	no	Sandostatin	2.2	200	NA	no	69
14	65, F	14.7	1012	1.8	526	no	cabergoline	0.98	260	normal	yes	6
15	60, M	16.9	NA	1.9	539	no	none	1.9	289	abnormal	no	5
16	44, M	7.3	1251	1.0	602	yes	octreotide	0.3	394	normal	no	4
17	26, F	148	1022	11	841	yes	octreotide	3.4	655	abnormal	no	5
18	22, F	25.7	660	36	756	no	octreotide	18	884	NA	no	1
19	56, F	150	626	0.4	87	no	none	0.7	145	NA	yes	1
20	58, M	20.5	896	0.6	407	no	none	7.0	198	normal	yes	3
21	40, M	34.8	1297	7.3	937	no	Sandostatin	3.1	290	abnormal	no	2
22	75, M	14	1241	1.1	494	no	none	0.9	140	normal	yes	5
23	26, F	21.5	1321	2.7	900	no	Sandostatin	3.9	799	abnormal	no	3
24	44, F	3.4	296	5.5	147	no	Sandostatin	3.4	193	abnormal	no	4
average		31.4	806.0	4.1	462.0			2.7	286.8			23.2
SD		43.4	330.0	7.3	255.5			3.9	216.6			25.4

* All serum hormone levels are expressed in ng/ml. Abbreviations: Endocrin = Endocrinological; NA = not applicable; OGTT = oral glucose tolerance test.

† Test is considered normal if serum GH is lower than 0.4 ng/ml following a 75-g oral glucose load.

nadir level < 1 ng/ml.[3,19,25] But a nadir level < 1 ng/ml would miss the diagnosis of acromegaly in up to 25% of patients.[7,11] Given the widespread availability of ultrasensitive GH assays, a recent consensus statement proposed a nadir level < 0.4 ng/ml as the criterion for an endocrinological cure.[13] An additional criterion for endocrinological cure also includes an assessment of IGF-I serum levels, which reflects integrated 24-hour GH secretion and remains relatively constant over the day. Normalization of IGF-I levels has been demonstrated following the successful treatment of acromegaly.[5,15,30] Consequently, normal IGF-I levels and a nadir level < 1 ng/ml of GH after a glucose load were proposed by a consensus statement in 2000 as criteria for an acromegaly cure.[12] The application of these criteria yielded endocrinological remission rates of 57%–67% after microsurgical transsphenoidal approaches.[3,19,25] When considering only pituitary macroadenomas (diameter > 1 cm), Nomikos et al.[25] reported an endocrinological remission in 51% of patients, and Beauregard et al.[3] documented remission in 47%. Using more stringent criteria for endocrinological remission as proposed by a consensus statement from 2010,[13] we report a 46% endocrinological remission rate in our patients with GH-secreting pituitary adenomas.

In the current series a purely endoscopic transsphenoidal technique was used. In accordance with microscopic transsphenoidal series, we found that tumor volume was a predictor of resectability and an endocrinological cure.[3,25] Using a purely endoscopic technique, we found residual suprasellar tumor in only 1 of 7 patients with suprasellar tumor extension. In contrast, tumor was left in 7 of 10 patients with invasion of the cavernous sinus. This finding contrasts with that in a study by Bohinski and colleagues,[4] who investigated the extent of macroadenoma resection via a microsurgical technique by using intraoperative MR imaging. In that series, residual tumor was

TABLE 4: Clinical outcomes and complications in 24 patients with acromegaly

Parameter	No. (%)
adjuvant medical treatment	
yes	9 (37.5)
no	15 (62.5)
GKS	
yes	5 (20.8)
no	19 (79.2)
endocrinological remission	
yes	11 (54.2)
no	13 (45.8)
clinical outcome	
asymptomatic	6 (25.0)
improved	14 (58.3)
stable	3 (12.5)
worse	1 (4.2)
complication	
panhypopituitarism	2 (8.4)
CSF leak	2 (8.4)
sinusitis	2 (8.4)
diplopia	1 (4.2)

detected both in the suprasellar cistern and adjacent to the cavernous sinus in 66% of all cases. A similar rate of residual tumor was reported by Nimsky and colleagues.[24] In their series, intraoperative MR imaging detected residual disease in 41.5% of all macroadenomas treated with a microsurgical transsphenoidal technique. The superiority of the endoscopic technique for visualizing the pathology in the suprasellar cistern was very recently demonstrated by Theodosopoulos et al.,[35] who performed intraoperative MR imaging after purely endoscopic transsphenoidal tumor resections. In a series of 27 patients, these authors were able to detect tumor remnants in the suprasellar cistern in 2 of 5 cases utilizing the endoscopic technique. These results are similar to those of Schwartz et al.,[32] who found residual tumor with intraoperative MR imaging in only 20% of patients after endoscopic surgery. The endoscopic technique offers the advantage of a wider field of view, better illumination, and the possibility of looking around corners using angled scopes. The ability to visualize and resect lesions in the suprasellar cistern was corroborated in the current series. However, tumor invasion of the cavernous sinus remains associated with a high rate of STR and poor disease control. Nevertheless, more aggressive surgery within the cavernous sinus by using endoscopic techniques has been shown to lead to a higher rate of endocrinological cure.[9,10,16]

While the current series demonstrates a high rate of endocrinological remission after endoscopic macroadenoma resection, additional larger studies using the most recent criteria for endocrinological cure are needed to corroborate our findings. Larger studies may also allow for subgroup analysis with regard to various tumor sizes and grades. Our results may be skewed by the adjuvant radiation and/or medical therapy that more than one-third of our patients received, but this limitation is inherent to the retrospective nature of our study. Mounting a controlled study of the separate use of resection, radiation, or medical therapy would be barely feasible.

Conclusions

In summary, an endoscopic transsphenoidal approach for the resection of GH-secreting pituitary adenomas leads to endocrinological remission in 46% of patients. Procedure-associated morbidity is low and three-fourths of our patients experienced improvement of their clinical symptoms. While the endoscopic technique greatly facilitates the resectability of lesions in the suprasellar cistern, resection of a tumor in the cavernous sinus remains a challenge.

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