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Endoscopic endonasal approach for growth hormone secreting pituitary adenomas: outcomes in 53 patients using 2010 consensus criteria for remission

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Abstract We report the outcomes of the endoscopic endonasal approach (EEA) for resection of growth hormone secreting pituitary adenomas using 2010 consensus criteria. We also assess outcomes with additional medical therapy and radiosurgery (RS) for patients not achieving remission with EEA alone. A retrospective review of 53 patients who had follow up endocrinologic data at least 3 months post-surgery was performed among patients who were treated by EEA between 1998 and 2012. Data were analyzed for remission using GH and IGF-I levels based on 2010 consensus criteria. We also analyzed the outcomes using 2000 consensus criteria for ease in comparison to prior studies of outcomes of surgery for acromegaly. In this series of mostly large (88.2 % macroadenomas), invasive (46.9 % Hardy–Wilson C, D, E) adenomas, there were 27 patients (50.9 %) who achieved remission after EEA only. For patients who had no remission with EEA alone, RS and/or medical therapy were used and 37 patients (69.8 %) achieved remission overall. Statistical analysis showed larger tumor size, Hardy Stages C, D, E and Knosp Scores 3, 4 to be predictive against remission for EEA only and EEA with other modalities. The volume of residual tumor after EEA was not found to be predictive of remission with additional therapies. We used stringent consensus criteria from 2010 in a series which included a high proportion of invasive GH secreting adenomas to show that EEA alone or combined with other modalities results in comparable remission rates to earlier studies which used less strict criteria, while retaining low complication rates.

Keywords Endoscopic endonasal · Acromegaly · Transsphenoidal · Transnasal · Pituitary adenoma

Abbreviations

EEA	Endoscopic endonasal approach
RS	Radiosurgery
GH	Growth hormone
IGF-I	Insulin growth factor-I
GHRH	Growth hormone releasing hormone
CSF	Cerebrospinal fluid
ICA	Internal carotid artery
DI	Diabetes insipidus
CN	Cranial nerve

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Introduction

Acromegaly is a disease manifested by progressive bone and cartilage growth which leads to dysmorphic craniofacial features and extremity changes, as well as cardiovascular, metabolic, and respiratory complications. Elevated growth hormone (GH) and insulin-like growth factor-I (IGF-I) levels lead to various systemic complications such as hypertension, cardiomyopathy, sleep apnea, arthritis, and diabetes, contributing to the higher mortality of these patients for all causes compared to the general population [1]. In greater than 95 % of the cases, acromegaly results from GH overproduction by a benign pituitary adenoma, and in only a small minority of cases, from ectopic growth hormone releasing hormone (GHRH) production [2].

The first line therapy for acromegaly has been surgical resection assuming the availability of an experienced pituitary surgical team [3, 4]. Surgical resection alone leads to disease control in 90 % of microadenoma cases and 40–60 % of macroadenoma cases [5, 6]. Growth hormone secreting pituitary adenomas with cavernous sinus or extrasellar invasion have been described to have low rates of disease control [7]. In such cases, medical management with somatostatin analogues, GH receptor antagonist, or dopamine agonist is often used following surgical resection [8]. Radiosurgery is also helpful in patients who have aggressive adenomas that are resistant to medical management, with remission rates ranging from 42 to 60 % [9]. The focus for acromegaly treatment has been to decrease GH and IGF levels by surgical resection alone or in combination with RS and medical therapy.

Previously, surgical resection of GH secreting pituitary adenomas involved microsurgical, transsphenoidal approaches [10–14]. However, endoscopic endonasal resection of these tumors has been shown to result in equivalent efficacy and safety [15, 16] while reducing time in the operating room and the hospital [17–19]. Recent studies have reported the outcomes of endoscopic transsphenoidal surgery for the treatment of GH secreting pituitary adenomas, with biochemical control rates ranging from 46 to 85 % [7, 20–22]. Currently, there are only two endoscopic studies reporting remission rates using the 2010 consensus criteria for remission of acromegaly [4, 23]. In this study, we report 53 cases with GH secreting pituitary adenoma that underwent endoscopic endonasal approach (EEA) from 1998 to 2012. We also review the outcomes of previous studies using the microsurgical as well as the endoscopic approach and compare the remission rates with respect to invasiveness and size of the tumor.

Table 1 Patient population data

Characteristic	n (%)	Mean	Range
Age (year)		43.7	14–67
Gender (M/F)	30 (56.6 %)/23 (43.4 %)		
Tumor size (mm)		19.4	7.6–55.6
Recurrent tumors	7 (13.2 %)		
Hospital stay (days)		3.6	1–15
Operating time (h:min)		3:42	1:28–8:10
Follow up time (years)		2.5	0.24–10.73

Number of subjects, mean values, and range are displayed. A few cases had high values: a hospital stay of 15 days was due to multiple cerebrospinal fluid (CSF) leaks in one patient

Subjects and methods

Patient demographics

Data were collected by retrospective review of medical records of all patients with GH-secreting pituitary adenomas treated by EEA at the University of Pittsburgh Medical Center from November 1998 to February 2012. The data collection for this study was approved by the Institutional Review Board (IRB) of the University of Pittsburgh (IRB: PRO12020326). Among the 60 patients operated by EEA within this time period, 53 patients had sufficient data with regard to postoperative GH and IGF-I. The GH and IGF-I values assessed at greater than 3 months postoperatively were used for evaluation of remission. There were 7 additional patients who did not have adequate GH and IGF-I data and therefore could not be evaluated for remission. These patients were excluded from the analysis. The patient characteristic data is listed in (Table 1). None of the patients in our series were pretreated with somatostatin analogs.

Endocrine analysis

Patients underwent pre- and postoperative evaluation of GH and IGF-I levels. For patients from outside hospitals and patients operated before 2004, hormonal values were not accessible by electronic records. They were included as part of this study based on medical records of previous diagnosis of acromegaly. Disease control was determined by the following criteria from 2010 consensus guidelines [23]: IGF-I value within normal range for age and gender and GH value <0.4 ng/mL after glucose load or a random GH value <1.0 ng/mL. For patients on Pegvisomant therapy at the time of measurement, only IGF-I value was used as a criteria for remission [24]. For patients on Octreotide or Cabergoline, IGF-I and random GH values were used to assess for remission [25]. For quantification of serum GH, a two-site enzyme-linked immunosorbent assay (ELISA) was used from 1998 to present. This assay has a lower limit

of detection for GH of 0.05 ng/mL, and assay linearity is from 0.05 to 40.0 ng/mL.

Radiologic analysis

The size and tumor extension as well as degree of resection was assessed by evaluating T1 or T2 -weighted MR images of the patients pre- and postoperatively or past radiology reports. Postoperative imaging was performed at least 3 months following surgery. Tumor sizes were recorded as microadenomas if they were <1 cm in diameter and macroadenomas if 1 cm or greater in diameter on a coronal image. Since radiographic images prior to 2005 were unavailable in the electronic medical record, tumor size categorization information was retrieved from radiology report only. An independent radiologist who was blinded to surgical outcomes evaluated MRIs to categorize tumors according to Hardy–Wilson Classification (Table 2) [26] and Knosp Score [27].

Surgical technique

Patients were operated by a team of an otolaryngologist and a neurosurgeon using a binarial approach. For larger pituitary adenomas, nasoseptal flap reconstruction [28, 29] was performed in cases after 2007. As previously described [30], sphenoid ostia were visualized and sella was exposed. In cases where the cavernous sinus was thought to be invaded and occupied by tumor (Knosp Scores 3, 4), a more lateral exposure was achieved by carefully and completely exposing the anterior wall of the cavernous sinus up to the lateral aspect of the parasellar internal carotid artery (ICA); the paraclinoidal segment of the ICA was also exposed to allow greater access to the cavernous sinus.

Table 2 Hardy classification modified by Wilson (Hardy–Wilson) [26]

Hardy classification-modified by Wilson
Stage 0: no suprasellar extension
Stage A: extension to suprasellar cistern
Stage B: recesses of third ventricle obliterated
Stage C: third ventricle grossly displaced
Stage D: intracranial
Stage E: into/beneath cavernous sinus
Grade I: sella normal; tumor <10 mm
Grade II: sella enlarged; tumor ≥10 mm
Grade III: local perforation of sellar floor
Grade IV: diffuse sellar floor destruction

Each case in the current study was evaluated using the Hardy–Wilson Classifications. Degree of suprasellar and parasellar extension was described as Stages A–E, and degree of sellar floor erosion was described as Grades I–IV

Table 3 Statistical Analysis of categorical (a) and continuous (b) variables for patients treated by *EEA only*

	N	# remission (2010 criteria)	% remission from total (2010 criteria)	*p* value
(a)				
Macro/micro				
Macro	45	21	46.67	
Micro	6	5	83.33	0.191
Hardy–Wilson Stage				
A, B	26	17	65.38	
C, D, E	23	8	34.78	0.033
Hardy–Wilson Grade				
I, II	19	12	63.16	
III, IV	30	13	43.33	0.176
Knosp Score				
0, 1, 2	35	23	65.71	
3, 4	14	2	14.29	0.001

	No remission (2010 criteria)	Remission (2010 criteria)	*p* value
(b)			
Age			
Mean	43.88	42.52	
SD	17.84	11.16	
Median	47.00	44.00	0.795
Tumor size (cm)			
Mean	2.11	1.58	
SD	0.59	0.67	
Median	2.07	1.33	0.045
Tumor volume (mL)			
Mean	3.53	2.25	
SD	2.60	3.40	
Median	3.49	1.03	0.077

Parameters shown associated with remission were analyzed using the 2010 criteria

Statistical analysis

Data were analyzed using 9.3.1 SAS software. Chi-square or Fisher's exact tests were used for comparison of categorical variables whereas Student's *T* tests were used for continuous variables. Remission rates were compared between degrees of invasiveness, tumor size, tumor volume, and age (Table 3). Due to the skewness of the data, comparisons of tumor size and tumor volume were based on log-transformed data. When *p* values were ≤0.05, the differences were considered statistically significant.

Results

Radiographically, of the 53 patients in this study, 42 (79.2 %) received gross total resection, 11 (20.8 %) received near total resection (90–99 % resection). No patient had subtotal resection.

The data was analyzed by looking at the remission rates for the cases treated by 3 different modalities and 4 possible combinations: 1. EEA only, 2. EEA and RS, 3. EEA and medical treatment (Pegvisomant, Octreotide, or Cabergoline), 4. EEA, RS, and medical treatment. Using 2010 criteria, 27 patients achieved remission with only EEA (50.9 %). Three of 7 cases treated by EEA followed by RS achieved remission, and 3 of 5 cases treated by EEA and medical therapy were in remission. Four of 5 cases treated by EEA, RS, and medical treatment achieved remission. With all modalities combined, the remission rate was 69.8 % using 2010 criteria. Outcomes were not different when recurrent tumors were excluded.

Of the 53 cases in this series, data for both endocrinologic outcome and tumor size was available for 51 cases. Macroadenoma was present in 45 of these cases (88.2 %), and microadenoma was present in only 6 cases (11.7 %). Among the macroadenoma cases, 21 cases achieved remission by EEA only (46.7 %), and among the microadenoma cases, 5 cases achieved remission by EEA only (83.3 %) with 2010 criteria.

A comparison of remission rates for microadenomas versus macroadenomas showed no statistically significant difference for patients treated by EEA and other modalities (Supplementary Table 1). However, patients who achieved remission had smaller tumor volume compared to patients who did not achieve remission (3.87 vs. 5.37 mL, $p \leq 0.05$). Tumor diameter on a coronal image also showed smaller size for patients achieving remission (1.74 vs. 2.35 cm, $p \leq 0.01$).

Categorization of invasiveness and remission rates

Hardy–Wilson classification was used to indicate the degree of suprasellar and parasellar extension as well as sellar floor erosion. Data on preoperative tumor invasiveness or endocrinologic outcome of 4 patients were not found for analysis, so only 49 patients' data were used for this analysis. For suprasellar and parasellar extension, 20 patients (40.8 %) were Stage A, 6 (12.2 %) were Stage B, 12 (24.5 %) were Stage C, 8 (16.3 %) were Stage D, and 3 (6.1 %) were Stage E. For sellar floor destruction, 8 patients (16.3 %) were Grade I, 11 (22.4 %) were Grade II, 11 (22.4 %) were Grade III, and 19 (38.8 %) were Grade IV. When Knosp Classification was used to categorize cavernous sinus invasion, 15 patients (30.6 %) were Grade 0, 8 (16.3 %) were Grade 1, 12 (24.5 %) were Grade 2, 9 (18.4 %) were Grade 3 and 5 (10.2 %) were Grade 4.

Since involvement of the suprasellar area and cavernous sinus increases the difficulty of tumor resection, remission rates of invasive tumors with Hardy–Wilson Stages C, D, E or Knosp Grades 3, 4 were compared to Hardy–Wilson Stages A, B or Knosp Grades 0, 1, 2, respectively (Fig. 1). When evaluating results of EEA only using 2010 criteria, Hardy–Wilson Stages A, B resulted in 65.4 % remission and Hardy–Wilson Stages C, D, E resulted in 34.8 % remission ($p = 0.033$), whereas Knosp 0, 1, 2 resulted in 65.7 % remission and Knosp 3, 4 resulted in 14.3 % remission ($p = 0.001$) (Table 3). The results of treatment with all modalities roughly mirror these outcomes. By 2010 criteria, Hardy–Wilson Stages A, B resulted in 84.6 % remission and Hardy–Wilson Stages C, D, E resulted in 47.8 % remission ($p = 0.006$), whereas Knosp 0, 1, 2 resulted in 80 % remission and Knosp 3, 4 resulted in 35.7 % remission ($p = 0.006$) (Supplementary Table 1).

Further analysis of Knosp 4 cases treated by EEA only showed no differences in remission rates compared to Knosp 3 cases (0 vs. 22 %, $p > 0.1$), likely due to sample size. When overall remission rates treated by all modalities were compared between Knosp 4 and Knosp 3 cases, no differences were found.

Among the patients that had residual tumor after EEA, patients who achieved remission with additional therapeutic

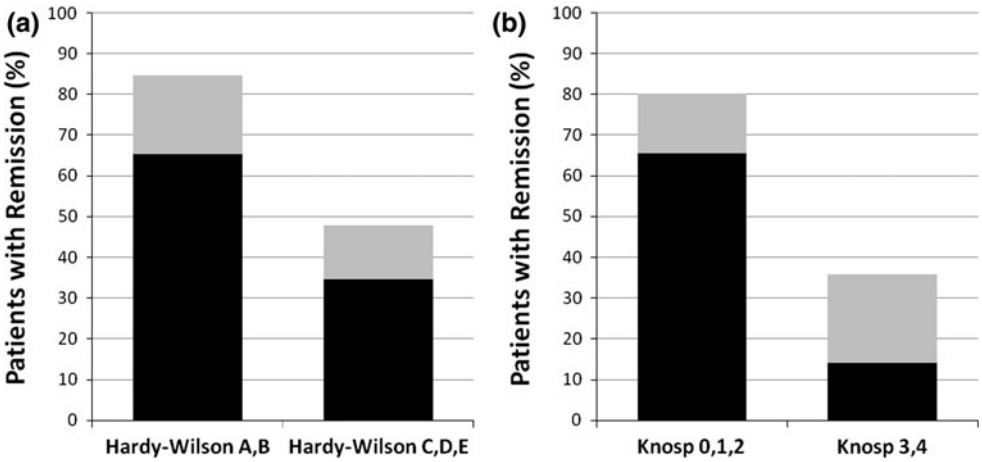

Fig. 1 Remission rates of Invasive adenomas. Invasive adenomas were defined as those with Hardy–Wilson Stages C, D, E (**a**) or Knosp Scores 3, 4 (**b**). *Black bars* represent remission rates with *EEA only*, and *gray bars* represent remission rates achieved with additional modalities such as RS and medical therapy

modalities did not have tumor volumes significantly different from patients who did not (0.32 ± 0.12 mL and 0.28 ± 0.11 mL, respectively, $p > 0.1$). There were also no differences in remission rates between tumors less than 0.25 mL and tumors greater than 0.25 mL (50 % remission vs. 40 % remission, $p > 0.1$). Percentage tumor volume resection was also not different between cases with remission (94.5 %) compared to cases with no remission (95.3 %), $p > 0.1$. Among the patients who received RS postoperatively, the mean time lag between surgery and RS was 24.9 months. Post RS, the mean time to reach hormonal remission was 23.5 months. There were 10 patients treated by Gamma Knife surgery and 2 treated by Cyberknife. The mean time elapsed after RS until last follow up was 5.0 years. Among the patients treated with medical therapy, there were 7 on somatostatin analogs, 2 on Pegvisomant, and 1 on Cabergoline.

Some patients in the series had discordant IGF-I and GH results: normal IGF-I but elevated GH above 1 ng/mL. When using only normal IGF-I value as a criteria for remission, there were 32 patients in remission at the latest follow up (60.4 %). With all treatment modalities combined, there were 44 patients with remission (83.0 %). Mean GH for the 7 patients with normal IGF-I and elevated GH was 1.56 ng/mL (range: 1.07–2.14 ng/mL).

Postoperative complications

Postoperatively, there were 6 patients with new hormonal deficits in one or more axes, and 2 additional patients developed deficits following RS. Three patients (5.7 %) developed panhypopituitarism, 2 patients (3.8 %) developed hypothyroidism and adrenal insufficiency, 2 patients (3.8 %) developed GH deficiency, 2 patients (3.8 %) developed permanent diabetes insipidus (DI), and 2 of 30 males (6.7 %) developed hypogonadism. Five patients (9.4 %) developed transient DI. A transient cranial nerve (CN) VI palsy developed in 1 patient (1.9 %), and a transient CN III palsy developed in another patient (1.9 %). One patient developed corneal keratopathy due to decreased sensation of the left eye, but this resolved in 3 months. There were 2 patients (3.8 %) with CSF leaks. A total of 2 patients (3.8 %) developed meningitis, one of which had CSF leak and another without CSF leak (meningitis due to infection from lumbar drain). Both cases resolved with no neurological deficits.

Discussion

Definition of biochemical remission

The 2000 consensus guidelines for endocrinologic remission in acromegaly are defined as IGF-I level in age and sex-adjusted normal range and random GH value <2.5 ng/mL [1, 4] or GH value <1 ng/mL during an oral glucose tolerance test [4]. With the recent development of highly sensitive and specific GH assays, even lower threshold values for random GH of 1.0 ng/mL and oral glucose tolerance test GH value of 0.4 ng/mL have been suggested [4, 23]. The actual cutoff value for GH and IGF-I that defines biochemical remission is controversial due to the heterogeneity among assays at different laboratories. Differences in antibodies used for assays, calibration methods, serum fluctuations of hormones, age, and sex account for the variability.

Monitoring GH values to assess disease control is complicated by medical therapy given at the time of the assay. For patients treated by somatostatin analog or dopamine agonist, GH level monitoring after oral glucose load is deemed unreliable for assessment of biochemical control [25]. Also, patients treated with GH receptor antagonist Pegvisomant show increase in serum GH levels despite disease control [31]. Following the findings in these reports, only IGF-I values were used as criteria for patients receiving Pegvisomant therapy and IGF-I and random GH measurements were used as criteria for patients receiving Octreotide or Cabergoline therapy.

A recent 2010 consensus statement on acromegaly remission criteria advocates use of the lower threshold values for basal and post glucose load GH levels when compared to the 2000 consensus criteria. These 2000 remission criteria were revised to reflect the use of more sensitive two- sites immunoassays when compared to the older, less sensitive radioimmunoassays used before 1998. The adoption of the more stringent 2010 criteria for remission as a treatment goal likely should lead to even lower long term morbidity associated with acromegaly [23]. In light of this more recent consensus, it is important that any new study evaluate the results of treatment of acromegaly using the 2010 guidelines.

Tumor classification

Larger tumor size and invasion to the neighboring structures increase the difficulty and morbidity of the surgery, as critical neurovascular structures such as the ICA and cranial nerves in the cavernous sinus are intimately associated or involved. As described in the results section, the proportion of the cases with invasive adenoma in our series was high (Table 4). There were 24.5 % of cases classified as Hardy–Wilson Stage C, 16.3 % of cases classified as Stage D, and 6.1 % classified as Stage E. The degree of sellar floor erosion was also high, with 22.4 % for Grade III and 38.8 % for Grade IV.

The proportion of macroadenomas in this series was also higher than in other reports. Macroadenoma was present in

Table 4 Comparison of results of previous studies compared to the current study

Report	Definition of invasiveness	% cases with invasive tumors	Total remission rate (%)	Follow up time (months)	Surgery	Definition of remission
Beauregard et al. [38]	Hardy–Wilson III, IV	28.2	59	12	Microsurgery	Normal IGF-I and either GH < 2.5 ng/mL or OGTT GH < 1 ng/mL
Kim et al. [39]	Knosp 3, 4	23.8	64	49.4	Microsurgery	Normal IGF-I, GH < 5 ng/mL, and OGTT GH < 1 ng/mL
Gittoes et al. [37]	Suprasellar or Lateral extension	37.9	64	N/A	Microsurgery	GH < 5 ng/mL or OGTT GH < 2 ng/mL
Ross et al. [11]	Hardy–Wilson B–E	21.6	79.4	76	Microsurgery	GH < 5 ng/mL
	Hardy–Wilson III, IV	31.2				
Gondim et al. [20]	Hardy C, D	32.8	74.6	24	Endoscopic	Normal IGF-I and OGTT GH < 1 ng/mL
	Hardy III, IV	17.9				
Hofstetter et al. [21]	Cavernous Sinus Invasion	41.7	46	23	Endoscopic	Normal IGF-I and either GH < 1 ng/mL or OGTT GH < 0.4 ng/mL
Jane et al. [47]	Knosp 3, 4	25	70	2	Endoscopic	Normal IGF-I and either GH < 1.0 ng/mL or OGTT GH < 0.4 ng/mL
Current Study (2010 criteria)	Hardy–Wilson C, D, E	46.9	50.9	30	Endoscopic	Normal IGF-I and either GH < 1.0 ng/mL or OGTT GH < 0.4 ng/mL
	Hardy–Wilson III, IV	61.2				
	Knosp 3, 4	28.5				

Invasive tumors using the Hardy–Wilson, Hardy, Knosp, or other classifications are reported

88.2 % of cases, and microadenoma was present in only 11.7 % of cases. In comparison, other studies on transphenoidal approach for acromegaly had macroadenomas in 79.1 % [20], 84.6 % [7], and 83 % [21] of the cases. Larger and invasive tumors have been reported to have lower remission rates and higher complication rates [32–36]. Although there was a high proportion of cases with macroadenoma and high rate of invasion of suprasellar and parasellar areas, the remission rate of our study is comparable to that reported by others even with more stringent criteria for remission (Table 4). These results suggest the effectiveness of the expanded endoscopic approach to these challenging parasellar and suprasellar regions.

Remission rates and comparison to previous studies

Direct comparison of our current study to previous microsurgical studies for GH-secreting pituitary adenomas is difficult due to the different criteria used to define biochemical remission in these studies [10–12, 37–39]. Several studies used GH levels <5 ng/mL as the criteria for remission, with reported remission rates of 76 % [10], 79.4 % [11], and 81.3 % [12] which cannot be directly compared to our remission rate of 50.9 % by 2010 criteria.

Reports on endoscopic resection of GH secreting pituitary adenomas demonstrated disease control in 58–75 % [7, 20, 40–42] of the cases using the less stringent 2000 criteria, which also cannot be directly compared to our remission rate. We also analyzed our data using 2000 criteria for remission and obtained a remission by EEA alone of 62.3 % and remission with EEA plus additional therapies of 84.9 % in our series. Because the GH assay used in our series was the more sensitive two-sites assay, we reanalyzed the data using 2010 criteria and obtained a remission rate roughly 10 % lower than if 2000 criteria were applied.

Previous reports have also analyzed cases with discordance between IGF-I and GH values in as high as 40 % of patients [43–46]. Based on metabolic profile, elevated IGF-I rather than elevated GH was shown to indicate active disease [44]. Thus, we reanalyzed the data when IGF-I value is used as a criteria. Among the cases with normal IGF-I, only patients with elevated GH by oral glucose tolerance test (OGTT) were considered to be truly not in remission. Using this criteria among patients treated by EEA only, there was a higher rate of remission (60.4 % by EEA only and 83 % by all modalities combined). Among the 7 patients with normal IGF-I but elevated GH, 4 were Knosp 3, 4 cases. The remission rates were low in Knosp 3, 4 cases (14.3 %, Table 3), based on IGF-I and random GH measurement. Although elevated GH after OGTT would have truly ruled out remission, these patients did not receive OGTT within 1 year of latest follow up.

Currently, there are only two reported endoscopic studies using the 2010 criteria for remission. These studies demonstrated disease control in 46 % [21] and 70 % [47] of the cases. Proportion of macroadenomas in these studies were 83 % and 76 %, respectively, whereas we reported a higher proportion of 88.2 %. Using the same criteria as these studies, our results show a comparable remission rate of 50.9 %. In the second study [47], GH and IGF-I values were assessed at 2 months after surgery, and if IGF-I values were elevated at 2 months, they were repeated at 6 months follow up. Patients with normal IGF-I at 6 months were considered in remission. Our series assessed GH and IGF-I values at 3 months or after and reviewed data from a longer mean follow up of 30 months. We used the minimum time of 3 months since it was previously shown that postoperative IGF-I levels fluctuate and only stabilize at 3 months [48]. Although this previous study [47] shows thorough assessment of remission, we provided longer follow up which is preferred for ascertaining the success of surgery.

Endoscopic endonasal techniques provide significantly greater access to the cavernous sinus by allowing direct exposure as well as access lateral to the ICA even out to the middle fossa [49–51]. The limitation for these higher grade Hardy–Wilson and Knosp tumors may not be technical or access-related, but rather related to the nature of the tumors (invasive to surrounding structures and therefore more likely to recur). In addition, the excessive morbidity that results when accessing the lateral cavernous sinus where the cranial nerves reside should lead surgeons to avoid this specific region. This surgical philosophy combined with RS and medical therapy can lead to very effective overall control of invasive tumors, even with the strictest critera, with low morbidity. This current study supports the efficacy of this treatment concept.

Surgical and medical treatment

We assessed the relationship between residual tumor volume after EEA and remission rate achieved with additional therapeutic modalities. No significant difference was found in residual tumor volume between the patients who achieved remission and patients without remission with use of additional therapies. It should be noted that there were a small numbers of cases (n = 5 in remission, n = 6 in no remission group) as well as small volumes of the residual tumor contributing to proportionately large measurement error. However, one possible interpretation of this data is that presence of postoperative invasive residual tumor does not necessarily predict lack of remission. Therefore, surgical resection followed by long term medical therapy or RS, rather than aggressive repeat surgery should be recommended for patients with residual invasive tumor.

Although intrasellar microadenomas result in high rate of complete resection and biochemical control ranging 75–95 % [13, 14, 34, 36, 38, 42], complete removal of the tumor is difficult for invasive adenomas. For these cases, some reports have questioned whether surgery should still be a primary treatment modality given the limited success for biochemical control in invasive macroadenomas [8, 52]. However, recent studies have shown that surgical debulking may increase the chance of biochemical control with somatostantin analogs in patients not amenable to gross total resection [53–55]. These studies support the important role of surgery even in patients with low prospect of surgical cure. In addition, macroadenomas that are invasive to cavernous sinus are oftentimes compressing the optic chiasm. Although somatostatin receptor ligands reduce tumor mass, most studies define 10–25 % reduction in tumor volume as a significant shrinkage [56] with a few studies showing mean volume reduction in 40–50 % range [57, 58]. This degree of volume reduction may not be sufficient decompression compared to surgical resection which provides immediate decompression.

These previously mentioned studies show additive reductions in GH levels by both somatostatin analogs and surgical debulking, and relying on primary medical therapy may not significantly reduce the risk of visual deficit from optic nerve compression. In these invasive cases, resection combined with medical therapy will result in higher chance of remission. However, in cases of high expression of SST2 receptors where medical therapy has shown excellent response [59] or in patients with surgical contraindications, medical therapy should be pursued as a primary approach. Newer studies also show the effectiveness of Pegvisomant for normalization of IGF-I levels, and when used in addition to somatostatin analogs, combined treatment regimen catered to each case may provide the best biochemical control of acromegaly [60].

The remission rate of all modalities combined was 69.8 % in our series. There were 16 patients at last follow up who were not in remission by 2010 criteria. Reasons for lack of remission in these patients were as follows: 2 patients could not tolerate medical management (gastrointestinal distress, symptomatic cholestasis); 1 patient had to withdraw medical treatment due to pregnancy; 2 patients started medical management with insufficient time at last follow up to achieve an adequate response; 8 patients were not treated with additional therapy because they were asymptomatic with normal IGF-1 and only mild GH elevation (1–2.5 ng/ml). There were 3 additional patients that had insufficient data in the electronic medical records as to why they were not managed by further medical treatment, RS, or repeat surgery. Thus, considering these factors, the remission rate with multiple modalities would likely be higher if medical management had been used more

aggressively in these patients and if a longer period of follow up was available.

As residual tumor tissue increases the risk of recurrence and reduces the chance of biochemical control, maximal resection without surgical complication is ideal. However, we do acknowledge that resection of tumor invasive to cavernous sinus may post risks such as ICA injury, optic nerve injury, and cranial nerve palsies. Along with these risks, high control rates are achieved only with an experienced skull base team which conducts at least 50 pituitary operations yearly [5, 37, 61]. Thus, extensive resection into cavernous sinus for invasive tumor is not generally recommended.

By using 2010 criteria, data on 53 cases of GH secreting pituitary adenoma were compared to data from previous studies. The authors in this series performed extended endoscopic resection, which includes carotid artery exposure and exploration of the cavernous sinus. Although the carotid artery and cavernous sinus are accessible in experienced hands with low complications, this does not appear to diminish the need for multimodality treatment with this functional tumor. The data in this series demonstrate that despite extensive surgical resection, chances of cure for invasive tumors are not remarkably higher. This is a reflection of the biology of this challenging tumor with its tendency for recurrence and therefore cavernous sinus dissection should be applied only in carefully selected cases with limited invasion. This case series demonstrates the importance of multimodality therapy for invasive GH secreting pituitary adenomas, by combination of surgery, radiosurgery, and medical treatment.

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