Endoscopic Transsphenoidal Surgery for Acromegaly: Remission Using Modern Criteria, Complications, and Predictors of Outcome

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Context: Despite the growing application of endoscopic transsphenoidal surgery (ETSS), outcomes for GH adenomas are not clearly defined.

Objective: We reviewed our experience with ETSS with specific interest in remission rates using the 2010 consensus criteria, predictors of remission, and associated complications.

Design and Setting: This was a retrospective single institution study.

Patients, Interventions, and Outcome Measures: Sixty acromegalic patients who underwent ETSS were identified. Remission was defined as a normal IGF-I and either a suppressed GH less than 0.4 ng/ml during an oral glucose tolerance test or a random GH less than 1.0 ng/ml.

Results: Remission was achieved in all 14 microadenomas and 28 of 46 macroadenomas (61%). Tumor size, age, gender, and history of prior surgery were not predictive on multivariant analysis. In hospital postoperative morning GH levels less than 2.5 ng/ml provided the best prediction of remission ($P < 0.001$). Preoperative variables predictive of remission included Knosp score ($P = 0.017$), IGF-I ($P = 0.030$), and GH ($P = 0.042$) levels. New endocrinopathy consisted of diabetes insipidus in 5%, adrenal insufficiency in 5.4%, and new hypogonadism in 29% of men and 17% of women. However, 41% of hypogonadal men had normal postoperative testosterone levels and 83% of amenorrheic women regained menses. The most common complaints after surgery were sinonasal (36 of 60, 60%) resolving in all but two.

Conclusions: ETSS for GH adenomas is associated with high rates of remission and a low incidence of new endocrinopathy. Despite the panoramic views offered by the endoscope, invasive tumors continue to have lower rates of remission. **(*J Clin Endocrinol Metab* 96: 2732–2740, 2011)**

Left untreated, patients with acromegaly have a 10-yr reduction in life expectancy compared with healthy subjects (1). Although the standardized mortality ratio is 1.72, life expectancy merges with that of the matched general population if GH secretion can be controlled (1, 2). Although various GH levels have previously been used to define remission, the standard definition from the 2000 consensus guidelines has been a normal IGF-I and a nadir GH less than 1 ng/ml during oral glucose tolerance testing (OGTT) (3). Numerous centers have published their surgical results using these criteria (4–12).

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Abbreviations: CI, Confidence interval; CSF, cerebrospinal fluid; CV, coefficient of variation; DI, diabetes insipidus; MRI, magnetic resonance imaging; OGTT, oral glucose tolerance testing; OR, odds ratio.

With the advent of more sensitive GH assays, it has been recognized that these previous criteria can be associated with a persistent risk of recurrence (13, 14). Given the increased sensitivity of GH assays, in 2010 more stringent criteria for remission were proposed (14). In addition to a normal IGF-I level, this consensus group proposed lowering the acceptable GH to less than 0.4 ng/ml during OGTT and the acceptable random GH to less than 1.0 ng/ml.

Various strategies have been used to maximize the chances of surgical remission, including intraoperative magnetic resonance imaging (MRI) and presurgical suppressive medical therapy (9). In addition, endoscopic techniques have been increasingly adopted (5, 12, 15–17). Despite the growing adoption of these techniques, no large series have detailed the surgical and endocrinological complications associated with the technique, the predictors of remission, or the remission rates according to the 2010 guidelines.

Patients and Methods

Inclusion criteria for the retrospective study included all patients undergoing endoscopic transsphenoidal surgery for acromegaly. From August 2004 to December 2009, 62 patients with acromegaly who underwent endoscopic pituitary tumor resection were identified. Two patients who were lost to follow-up were excluded, leaving 60 patients. With approval from our institutional review board, the medical records and imaging studies were reviewed.

All patients underwent neurological and endocrinological evaluations before and after surgery. Those patients with visual signs or symptoms also underwent ophthalmological examinations. Tumors were categorized as microadenomas or macroadenomas and for evidence of cavernous sinus invasion according to the Knosp classification based on coronal T1-weighted contrasted imaging (Fig. 1) (18). Macroadenomas were subcategorized based on size into three groups: greater than 10–20 mm (mesoadenoma), greater than 20–30 mm, and greater than 30 mm.

Assessment of remission was performed at initial follow-up 2 months after surgery. GH and IGF-I were measured by a two-site enzyme-labeled chemiluminescent immunometric assays [Nichols Advantage system (Nichols Institute Diagnostics, San Clemente, CA) before January 2006, Siemens Immulite thereafter; Siemens (Healthcare Diagnostics, Deerfield, IL)]. The day-to-day coefficient of variation (CV) of the Nichols assays was less than 10%. The CV of the Siemens GH assay was 3–6% at concentrations of 6–25 ng/ml and 10% at concentrations of 0.4 ng/ml. The CV of the IGF-I assay was 3–7% at concentrations of 70–500 ng/ml. External quality assurance was provided through programs of the U.K. National External Quality Assessment Service for IGF-I and the College of American Pathologists for GH and IGF-I. Patients were considered in biochemical remission if their IGF-I level was normal and either their GH nadir was less than 0.4 ng/ml during an OGTT or their random GH was less than 1.0 ng/ml (14). If a patient's OGTT was normal but the IGF-I level remained elevated at first follow-up 2 months after surgery, the IGF-I level was drawn again 6 months later because IGF-I levels can continue to decrease over several months. If this level was normal, the patient was considered in remission. If discordance between the IGF-I and OGTT remained beyond this time, the patient was considered to have failed to attain remission.

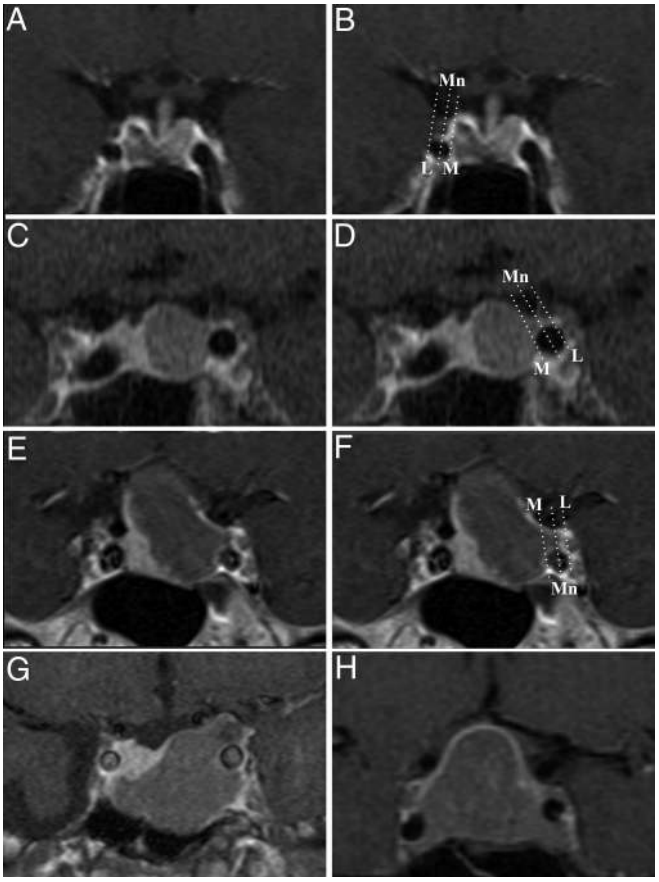

FIG. 1. Knosp classification of tumors. All images are preoperative T1-weighted contrasted coronal images. A and B, Knosp grade 0 tumor. Same patient without (A) and with (B) Knosp *lines* drawn on the carotid tangents. Note that all tumor is medial to the medial carotid tangent. C and D, Knosp grade 1 tumor. Same patient without (C) and with (D) *lines* drawn on carotid tangents. Note that tumor crosses the medial tangent but does not cross the median tangent. E and F, Same patient without (E) and with (F) *lines* drawn on carotid tangents. Note that tumor crosses the median tangent but does not cross the lateral carotid tangent. G, Knosp grade 3 tumor. Tumor crosses the lateral carotid tangent. H, Knosp grade 4 tumor. Tumor encircles the carotid artery. M, Medial carotid tangent; Mn, median carotid tangent; L, lateral carotid tangent.

Patients' residual pituitary function was assessed during their hospitalization and at their initial 2-month follow-up. During the hospitalization, patients were monitored for diabetes insipidus (DI) using a strict monitoring of fluid input and output, serum sodium levels, and urinary specific gravity measurements. Patients who received desmopressin before or after discharge were considered to have DI. During the hospitalization steroid replacement was withheld from patients without preoperative evidence of hypoadrenalism and morning cortisol levels were drawn daily. Patients with cortisol levels less than 8 μg/dl were considered to have central hypoadrenalism and were replaced

with hydrocortisone. Patients were instructed to withhold their corticosteroid replacement 2 d before their first clinic follow-up 2 months after surgery.

Routine screening of pituitary function was performed during this first postoperative visit, and the results at this time period was used to assess our endocrine outcomes. Central hypoadrenalism was assessed using random serum cortisol measurements and inquiry regarding symptoms of adrenal insufficiency. Stimulation testing was not routinely performed. Central hypothyroidism was screened for using free T_4 measurements. Gonadal function was assessed in women of child-bearing age based on the resumption of menses. In male patients, testosterone levels were used to assess gonadal function. Patients were also questioned regarding symptoms of DI.

Surgical approach

All patients underwent a purely endoscopic transsphenoidal approach, which included a binarial three-hand technique with wide anterior sphenoidotomy and partial posterior septectomy without middle turbinectomy (19). Frameless stereotactic image guidance was used in 15 operations (25%) including all 10 recurrent tumors. A lumbar drain was not used postoperatively.

Statistical analysis

Data are presented as mean and range for continuous variables and as frequency for categorical variables. Statistical analyses of categorical variables were carried out using χ^2 and Fisher's exact tests as appropriate. Statistics of means were carried out using the unpaired Student *t* test, both with and without equal variance (Levene's test) as necessary and Wilcoxon rank sum tests when variables were not normally distributed. ANOVA followed by Bonferroni *post hoc* testing was used to assess means among three or more groups. Odds ratios and 95% confidence intervals were calculated using univariate logistic regression analysis. Clinical covariates predicting remission with a univariate $P < 0.10$ were included in the multivariable logistic regression analysis. $P \leq 0.05$ was considered statistically significant.

Results

Study population and clinical presentation

Of the 60 patients, 27 were women and 33 men, with a mean age of 48 yr (range 14–73 yr) (Table 1). Ten patients had undergone 11 prior microscopic transsphenoidal operations (six at outside facilities and four at our institution) and one patient had undergone prior γ-knife radiosurgery. No patient had received fractionated radiation therapy. One patient was receiving medical therapy [Sandostatin long acting release, 30 mg per month (Novartis Pharmaceuticals Corporation, East Hanover, NJ)] at the time of their transsphenoidal surgery, which was discontinued after surgery.

Seven of 60 patients (11.7%) reported visual deficits. The mean preoperative IGF-I was 728 ng/ml (±272, range 256-1600 ng/ml) and the mean preoperative random GH was 23 ng/ml (±38, range 0.76–200 ng/ml). DI was present preoperatively in one patient who had undergone previous surgery. Twenty-eight patients had at least one deficit in anterior pituitary function. Fifteen patients were receiving thyroid replacement and one had hyperthyroidism secondary to a mixed GH/TSH adenoma. Two had adrenal insufficiency and two others were taking corticosteroid preparations to treat other medical conditions (recent sinusitis and polymyositis). Among the 13 female patients whose gonadal function was considered evaluable (age <50 yr, no previous hysterectomy, and not receiving oral contraceptive agents), six were hypogonadal. Among the 33 male patients, 17 of 32 (53%) were found to have low free testosterone levels (one male patient did not undergo preoperative biochemical screening for hypogonadism).

TABLE 1. Patient characteristics

Variable	n = 60 (%)
Male	33 (55)
Age	48 ± 13.3
Knosp grade	
0	27 (44.3)
1	14 (23.3)
2	4 (6.6)
3	7 (11.5)
4	8 (13.1)
Prior surgery	10 (16.7)
Visual deficits	7 (11.7)
Tumor size (mm)	
0–9	14 (23)
10–19	24 (40)
20–29	16 (27)
30–40	4 (<1)
>40	2 (<1)

Imaging features

Macroadenomas were more common than microadenomas (46 *vs.* 14, respectively) (Table 1). Although most tumors were smaller than 30 mm, six were larger. Fifteen tumors were Knosp grade 3 or 4. Among the 14 patients with microadenomas, six had standard pituitary protocol MRI that were interpreted as showing no definitive adenoma. However, on spoiled gradient recalled sequences, adenomas were identified in all patients.

Surgical outcomes and remission

The average length of stay was 2.32 d (range 2–7 d). The mean follow-up was 21.84 months (median 19.27 months, range 2–68 months). Biochemical remission was achieved in 42 of 60 patients (69.7%) including in all 14 patients with microadenomas and 60.9% with macroadenomas (Table 2). Remission was based on both IGF-I levels and OGTT in 29 patients and IGF-I levels and random GH levels (<1 ng/ml) in 13 patients. Three patients had reduced but still elevated IGF-I levels at

TABLE 2. Biochemical remission

Variable	Total number	Surgical remission (%)
Tumor size		
Microadenoma (1 cm)	14	100
Macroadenoma (≥1 cm)	46	60.9
Mesoadenoma (1–2 cm)	24	75
>2 cm	22	45.5
Knosp grade		
0–2	45	82.2
3–4	15	33.3
3	7	42.9
4	8	25
Age (yr)		
<35	12	41.7
35–65	39	74.4
>65	9	88.9
Preoperative GH (ng/ml)		
<4.5	17	100
4.5–30	27	74.1
>30	11	18.2
Preop IGF-I (ng/ml)		
<625	21	100
625–825	17	76.5
>825	19	31.6
Postoperative GH (ng/ml)[a]		
<2.5	48	86.7
≥2.5	9	0

[a] Morning GH level drawn on postoperative d 1 and 2. Three patients were excluded from analysis: two did not have immediate postoperative GH measurements and one was on medical therapy at the time of surgery.

initial follow-up at 2 months and were subsequently found to have normalized IGF-I levels 6 months later. OGTT was not repeated at this time point but all three had random GH levels less than 1 ng/ml.

Among the 18 patients who failed to attain remission, seven patients had discordant results. Of these, five patients had normal IGF-I levels but failed to suppress GH levels during OGTT, whereas two patients had elevated IGF-I levels but appropriately suppressed during OGTT. Eleven of the 18 patients who failed surgical remission were treated with stereotactic radiosurgery (10 γ-knife, one cyberknife) and medical therapy. All had persistent elevations in both IGF-I and GH levels. Patients with discordant IGF-I and OGTT results are being followed up expectantly.

History of prior transsphenoidal surgery, age, and sex were not found to be predictive of remission (Table 3). Seventy percent of patients (7 of 10) with previous surgery attained remission; all three of the surgical failures in this group occurred in Knosp grade 3 or 4 tumors. All seven patients with preoperative visual deficits experienced improvement and no patient experienced a new visual deficit.

Effect of tumor size and cavernous invasion on remission

Patients achieving remission had significantly smaller tumors compared with those who failed to attain remission (mean diameter 15.1 *vs.* 24.6 mm) ($P < 0.001$) (Table 3). Among the 46 macroadenomas, remission was attained in 18 of 24 tumors measuring between 10 and 20 mm (75%), eight of 16 tumors between 20 and 30 mm (50%), and two of six tumors larger than 30 mm (33.3%). Tumors greater than 20 mm had a significantly lower rate of remission compared with smaller tumors ($P = 0.01$).

Using the Knosp classification of preoperative MRI to determine cavernous sinus invasion, Knosp grade 0–2 tumors were associated with a significantly higher rates of remission (37 of 45, 82.2%) compared with Knosp grade 3–4 tumors (five of 15, 33.33%) ($P < 0.001$). Although the patients achieving remission with Knosp grade 3 tumors had no evidence of residual tumor on postoperative imaging, both patients with Knosp grade 4 tumors who attained remission had clear evidence of residual tumor on postoperative MRI (Fig. 2). Nevertheless, based on the consensus criteria, these patients were still considered to be in remission.

Effect of GH and IGF-I levels on remission

Preoperative IGF-I levels, random preoperative GH levels, and postoperative morning GH levels all were sig-

TABLE 3. Univariate predictors of remission

Variable	Remission (n = 42)	No remission (n = 18)	Significance *P* value
Male	23 (69.7%)	10 (30.3%)	0.955
Age (yr)	50.4	44	0.0941
Prior surgery	7 (70%)	3 (30%)	1.000
Knosp grade			
0–2	37 of 45 (82.2%)	8 of 45 (17.8%)	<0.001
3–4	5 of 15 (33.3%)	10 of 15 (66.7%)	
Preoperative GH (ng/ml)	9.9	51.7	<0.001
Preoperative IGF (ng/ml)	631	952.6	<0.001
Postoperative GH (<2.5 ng/ml)[a]	39 of 39 (100%)	10 of 18 (55.6%)	<0.001
Tumor size	15.1	24.6	<0.001

[a] Three patients were excluded from analysis: two did not have immediate postoperative GH measurements and one was on medical therapy at the time of surgery.

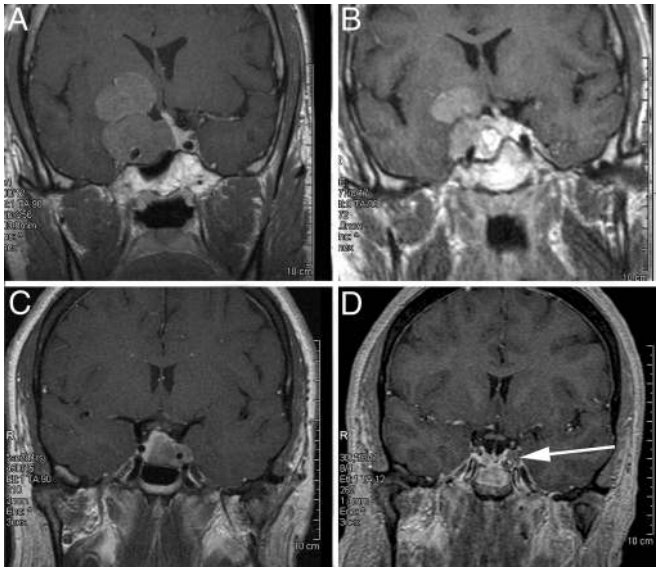

FIG. 2. Biochemical remission in spite of residual tumor. A, Preoperative T1-weighted contrasted coronal image of a patient with a Knosp 4 tumor. B, Postoperative T1-weighted contrasted coronal image of the same patient with clear residual tumor. C, Preoperative T1-weighted contrasted coronal image of a patient with a Knosp 4 tumor. D, Postoperative T1-weighted contrasted coronal image of the same patient revealing residual hypointense tumor (indicated by the *arrow*). Both patients attained biochemical remission according to the 2010 consensus criteria.

nificant predictors of remission (Tables 2 and 3). Preoperative IGF-I levels less than 625 ng/ml were associated with a 100% rate of remission, compared with a 31.6% with IGF-I levels above 825 ng/ml ($P < 0.001$). Similarly, preoperative GH levels less than 4.5 ng/ml were associated with a 100% rate of remission, whereas a level greater than 30 ng/ml was associated with remission rates of only 18.2% ($P < 0.001$). Morning GH levels during the first 2 postoperative days of less than 2.5 ng/ml were the best prediction of remission ($P < 0.001$) with a positive predictive value of 100% and a negative predictive value of 87%.

Multivariant analysis

In multivariant analysis preoperative variables predictive of remission included Knosp grade [odds ratio (OR) 2.22, 95% confidence interval (CI) 1.15–4.26, $P = 0.017$)], preoperative IGF-I levels (OR 1.005, 95% CI 1.0005–1.009, $P = 0.03$), and preoperative growth hormone levels (OR 1.04, 95% CI 1.001–1.008, $P = 0.042$).

Endocrine outcomes

Among the 59 patients without preoperative DI, five (8.5%) experienced new postoperative DI, which persisted beyond 2 months in three (5%) (Table 4). None of the 44 patients who were euthyroid preoperatively experienced new hypothyroidism. Of the 56 patients not on corticosteroids preoperatively, 10 patients (17.9%) were discharged on hydrocortisone; however, only three (5.4%) required steroid replacement beyond 2 months.

New hypogonadism occurred in 28.6% male patients (four of 14). However, 41% of male patients with preoperative hypogonadism (seven of 17) experienced normalization of their testosterone levels after surgery (Table 4). Of the 13 women younger than 50 yr who had not experienced menopause or hysterectomy, six (46%) were amenorrheic before surgery. Five of these six women (83%) regained regular menses after surgery. One woman who was younger than 50 yr at the time of surgery became hypogonadal for an incidence of new female hypogonadism of 17%. This patient had undergone her third transsphenoidal surgery and did attain surgical remission. Patients who achieved remission were not more likely to experience either a new endocrinopathy ($P = 0.415$) or gain of pituitary function ($P = 0.478$) compared with those who failed to attain remission.

Perioperative complications

The most common complaints at first follow-up were sinonasal (36 of 60, 60%) including nasal congestion in 25 (42%), alteration in taste or smell in 18 (30%), self-reported sinusitis in 18 (30%), and epistaxis in four patients (6.7%). All but two patients ultimately experienced resolution of their sinonasal symptoms. It should be noted that a high percentage of patients reported sinonasal complaints preoperatively (40 of 60, 67%). Even so, preoperative sinonasal

TABLE 4. Endocrine outcomes

Abnormality	Preoperative deficit	New deficit	Gain of function
DI	1.67% (1/60)	5.08% (3/59)	None
Adrenal insufficiency	3.45% (2/58)[a]	5.36% (3/56)	50% (1/2)
Hypothyroidism	25.42% (15/59)[b]	None	None
Hypogonadism (male)	53.13% (17/32)[c]	28.57% (4/14)[c]	41.18% (7/17)
Hypogonadism (female)	46.15% (6/13)[d]	16.67% (1/6)[d]	83.33% (5/6)

[a] Two patients excluded who were on corticosteroids for other medical issues (acute sinusitis, polymyositis).

[b] One patient was excluded who presented with a GH/TSH tumor and resultant hyperthyroidism.

[c] One male was not tested prior to surgery, and one male was not tested after surgery.

[d] Fourteen women were excluded secondary to oral contraceptives, hysterectomy, or menopause. One patient did not have follow-up data regarding menses.

complaints did not appear to predict postoperative sinonasal complications. Of the 40 patients who endorsed preoperative sinonasal issues, 57.5% reported sinonasal issues at first follow-up compared with 65% of those who did not report preoperative sinonasal problems.

Excluding patients with sinonasal complaints, major and minor postoperative complications occurred in 12 of the 60 patients (20%). There were nine patients who experienced minor complications. One patient's sellar graft extruded spontaneously and another required removal for sinusitis related to the graft. One patient experienced a fat graft site infection that required antibiotic treatment. Symptomatic hyponatremia occurred in six patients (10%) and was successfully treated with fluid restriction in all. Major complications occurred in three patients (5%). Of the 18 patients who experienced an intraoperative cerebrospinal fluid (CSF) leak, one patient (5.5%) experienced postoperative rhinorrhea requiring a return to the operating room. One patient experienced a carotid injury with pseudoaneurysm treated by Onyx (ev3, Plymouth, MN) embolization, and one patient experienced postoperative meningitis treated with iv antibiotics.

Discussion

In this study we found that the endoscopic approach affords a high rate of remission in patients with GH adenomas. Although subjective sinonasal complaints were common in the early postoperative period, these complaints were self-limited in the overwhelming majority. Major morbidity was rare, as was new central hypothyroidism and hypoadrenalism. Gain of pituitary function (typically gonadal) occurred in over 40% of men and 83% of evaluable women. Additionally, Knosp grade, random GH levels, and IGF-I levels were the most significant preoperative predictors of remission. Postoperative d 1 or 2 morning GH levels less than 2.5 ng/ml were the best predictor of remission.

The design of this study does not allow a definitive comparison of the endoscopic and microscopic transsphenoidal approaches (Table 5). Using the more stringent 2010 criteria for remission, the overall rate of remission in our series was 70%. No previous microsurgical studies have assessed outcomes using the 2010 criteria; only one endoscopic series has (17). Using the 2000 consensus guidelines, series of microsurgical resection have reported overall remission rates of 42–72% (7, 9, 10, 20–22). Remission rates vary greatly, depending on patient selection as well as the respective proportions of macroadenomas and invasive tumors. For microadenomas, microsurgical series report remission in 67–95% of patients. Macroadenomas are reported to achieve remission in 47–68%. Trepp *et al.* (22) further subdivided macroadenomas into

TABLE 5. Biochemical remission: modern surgical series

Author/year	n	Size micro/macro	Remission		
			Overall	Microadenoma	Macroadenoma
Microscopic series					
Kim *et al.* (41), 2009[a]	42	12/30	64%	67%	60%
Ludecke and Abe (9), 2006[a]	147	21/126	72%	95%	68%
Trepp *et al.* (22), 2005[a]	69	5/64	42%	80%	39%
Nomikos *et al.* (10), 2005[a]	506	142/364	57%	75%	50%
Esposito *et al.* (20), 2004[a]	67	13/54	57%	77%	52%
De *et al.* (7), 2003[a]	90	29/61	63%	79%	56%
Beauregard *et al.* (4), 2003[a]	103	22/81	52%	82%	47%
Kaltsas *et al.* (42), 2001[a]	67	17/42	34%	59%	26%
Shimon *et al.* (11), 2001[a]	88	44/44	74%	84%	64%
Kreutzer *et al.* (37), 2001[a]	57	19/38	70%		
Endoscopic series					
Hofstetter *et al.* (17), 2010[b]	24	4/20	38%		
Gondim *et al.* (24), 2010[a]	67	14/53	75%	86%	72%
Campbell *et al.* (5), 2010[a]	26	4/22	58%	75%	55%
Tabaee *et al.* (16), 2009[a]	6		83%		
Yano *et al.* (12), 2009[a]	31		71%		
Dehdashti *et al.* (8), 2008[a]	34	8/26	71%	83%	65%
Frank *et al.* (23), 2006	83	24/59	70%	83%	65%
Kabil *et al.* (25), 2005	48	13/35	85%	100%	80%
Rudnik *et al.* (26), 2005	12	4/8	83%		
Cappabianca *et al.* (15), 2002[a]	36	6/30	64%	83%	60%
Cappabianca *et al.* (6), 2002[a]	23	3/20	57%	67%	55%
Current series[b]	60	14/46	70%	100%	61%

Micro, Microadenoma; Macro, macroadenoma.

[a] Used 2000 consensus criteria (normal IGF-I, OGTT <1 ng/ml).

[b] Used 2010 consensus criteria (normal IGF-I, OGTT <0.4 or random GH <1 ng/ml).

mesoadenomas (1–2 cm) and adenomas greater than 2 cm. The authors found remission rates to be significantly lower in patients with tumors greater than 2 cm (27%) when compared with mesoadenomas (65%). In our series, remission was attained in 75% of mesoadenomas and a similar decrease in remission rate was seen in those tumors greater than 2 cm (45.5%).

Several series of GH adenomas treated with the endoscopic approach have been reported using the 2000 consensus criteria for remission (5, 6, 8, 12, 15–17, 23–26). Remission rates for microadenomas range from 67 to 100% and from 55 to 80% for macroadenomas. Only one previous study reported remission based on the recent 2010 consensus criteria for remission. Hofstetter *et al.* (17) reported on 24 patients and found an overall remission rate of 38%. This series, however, did not stratify remission rates for microadenomas *vs.* macroadenomas (17).

A number of studies have investigated the preoperative factors predictive of outcome. Multiple studies both before and after the 2000 consensus agreement for remission reported lower rates of remission for larger and more invasive tumors (5, 11, 12, 17, 24, 27–32). In an endoscopic series by Yano *et al.* (12), endocrine remission was achieved in 76.9% tumors of Knosp grades 0–2 (20 of 26) and 40% of patients with Knosp grade 3–4 tumors (two of five). In our series, 82.2% of noninvasive tumors (Knosp grade 0–2) achieved remission compared with 33% of patients with Knosp grade 3 and 4 tumors. It is expected that a significant proportion of the Knosp grade 3 and 4 patients will experience recurrence. Indeed, two patients with Knosp grade 4 tumors who attained biochemical remission in our series had clear evidence of residual tumor on postoperative MRI (Fig. 2). It is possible that some tumors are inefficient in hormone secretion, allowing for biochemical normalization despite tumor residual. This has previously been reported by Nishioka and Haraoka (33) and calls into question the lack of imaging criteria in characterizing remission using even the most current consensus guidelines (3, 14).

Tumor size predicted remission in our series, but size was not a final predictor in multivariate analysis. Indeed, this failure to find size as an independent predictor has been noted in several older studies (27, 28) before the 2000 consensus guidelines for remission criteria and in a recent endoscopic series by Gondim *et al.* (24) using the 2000 guidelines. This may be due to the fact the Knosp grade, or degree of cavernous sinus invasion, is a more significant predictor of outcome than size (5, 12, 17).

Many authors, primarily before the modern consensus era, have reported that preoperative GH levels were predictive of remission (27, 29, 30, 32, 34). Various preoperative GH levels have been found to be predictive. In our series, preoperative GH levels less than 4.5 ng/ml were associated with a 100% rate of remission, whereas a level greater than 30 ng/ml was associated with remission in 18.2%. Previous studies have noted that immediate postoperative GH concentrations during the hospital stay are predictive of biochemical remission at follow-up (17, 30, 34, 35). In our series GH less than 2.5 ng/ml provided the most accurate prediction of remission.

The potential advantages of the endoscope center on the panoramic view of the operative field. Unlike the microscope, which is limited by line of sight, the endoscope more readily provides visualization of the suprasellar compartment and cavernous sinus walls. Despite these apparent advantages, the endoscopic rate of remission and its visual and endocrine outcomes are not definitively superior to previously published microscopic series. The endoscopic view does not change the biology of invasive tumors. It is therefore not surprising that the same predictors of remission described in previous microscopic series were found to be predictive in this series. Although some macroadenomas may be more completely removed using the endoscope, tumors that are a challenge with the microscope remain so with the endoscopic technique.

Major complications occurred in three patients (5%) including one postoperative CSF leak, one pseudoaneurysm, and one incident of meningitis; postoperative CSF leaks have previously been reported in 0–7% of cases (7, 9, 27, 36, 37). In our series, our rate of postoperative CSF leak was 5.6% (one of 18) if one includes only those who experienced an intraoperative CSF leak. Although pseudoaneurysm has not previously been reported in acromegalic series, intraoperative carotid injury has, albeit rarely (4, 9). Postoperative meningitis has previously been reported with an incidence of 1–3% (7, 27, 31, 38, 39). Stroke, cranial nerve deficits, and deaths were not experienced in our series (7, 17, 30). The rate of major morbidity with the endoscope appears comparable with microscopic series.

Although Kreutzer *et al.* (37) previously reported a low incidence of septal perforations and sinusitis, specific sinonasal complications have not previously been elucidated in the literature. Sinonasal complaints were experienced by 60% of our patients during the early postoperative period. It is unclear whether these high incidences relate to our endoscopic approach, our specific postoperative care, or our routine practice to specifically inquire regarding these parameters at follow-up. A recent series by Hofstetter *et al.* (17) reported sinusitis requiring antibiotic therapy in 8.3% of their patients. Furthermore, in our series, self-limited postoperative epistaxis was reported in 6.7%. A similar rate of postoperative epistaxis

was reported by Gondim *et al.* (24) from their endoscopic series. Although we believe the endoscopic approach places the posterior nasal branch of the sphenopalatine artery at greater risk than does a transseptal approach, prior microscopic series have also reported on the occurrence of postoperative epistaxis with rates of 2.7% (9). It should be noted that in our series, 67% of our acromegalic patients reported sinonasal complaints preoperatively, and only two patients continued to report sinonasal complaints beyond 2 months postoperatively.

Previous studies have indicated a wide range in the rate of new anterior pituitary deficits of between 4.1 and 39% (7, 10, 11, 27, 37, 39). Prior studies have also reported a low rate of new permanent DI (2–7%) (7, 10, 11, 27, 37, 39, 40). In our series, 5% of patients experienced new postoperative DI, 5% of patients required corticosteroid replacement beyond 2 months, and no patient experienced new hypothyroidism. Although new hypogonadism occurred in 29% of male patients who had normal testosterone levels preoperatively, 41% of those with preoperative hypogonadism (seven of 17) experienced normalization of their testosterone levels after surgery. Of the 13 women younger than 50 yr who had not undergone menopause, six were amenorrheic before surgery and five (83.33%) regained regular menses after surgery.

Conclusion

Our results demonstrate that the endoscopic method is an acceptable surgical approach to GH-secreting tumors. The endoscopic approach is associated with a high rate of remission based on the 2010 criteria. Preoperative variables including Knosp score and IGF-I and GH levels are independent predictors of outcome. Additionally, a postoperative d 1 or 2 morning GH level less than 2.5 ng/ml is a strong predictor of remission.

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