Impact of Experience on Outcomes After Endoscopic Transsphenoidal Surgery for Acromegaly

Abhijit Goyal-Honavar[1], Sauradeep Sarkar[1], Hesarghatta Shyamasunder Asha[2], Nitin Kapoor[2], Regi Thomas[3], Rajesh Balakrishnan[4], Geeta Chacko[5], Ari G. Chacko[1]

■ OBJECTIVE: **Acromegaly is a syndrome of metabolic alterations secondary to increased growth hormone levels from a somatotroph pituitary adenoma. A multidisciplinary approach beginning with surgery, followed by adjuvant radiation or medical therapy for residual disease, is considered standard of care. Several factors affect the likelihood of remission after surgery, but the impact of surgical experience on remission rates has not been adequately assessed.**

■ METHODS: **Retrospective review of 203 patients, divided into 2 eras (era 1, 102 patients; era 2, 101 patients) of patients who underwent transsphenoidal surgery for acromegaly by a single surgeon over 11 years, was performed, determining the effect of surgical experience on rates of remission and various complications. Remission was defined according to the 2014 Endocrine Society Clinical Practice Guideline.**

■ RESULTS: **The rate of surgical remission was 40.6% (62.9% among noninvasive adenomas). Rates of surgical remission significantly improved in the latter half of this cohort (31.2% in the first half vs. 50% in the second half), despite other factors being comparable. On multivariate analysis, surgeon experience, cavernous sinus invasion, and preoperative growth hormone levels affected the rates of surgical remission. Rates of cerebrospinal fluid leak and hypopituitarism were lower in the second half, whereas resolution of acromegaly-associated comorbidities was increased.**

■ CONCLUSIONS: **We report, in this large single-surgeon review of endoscopically operated acromegaly cases, increased rates of surgical remission and reduced complications with increasing surgeon experience. The overall experience of the treating team in dealing with perioperative and intraoperative factors also contributes to improved outcomes.**

INTRODUCTION

Acromegaly results from an excess of growth hormone (GH), most commonly from a somatotroph pituitary adenoma, and is associated with significant metabolic alterations negatively affecting quality of life.[1,2] Treatment is directed at rapid normalization of GH levels, which is usually effected with surgical resection, followed by radiation or medical therapy if there is residual disease.[3-5] Endoscopic transsphenoidal surgery offers several advantages over microscopic surgery and is equally safe and effective.[6]

With a constant exchange of ideas among the global consortium, surgeons are continuously upgrading their skills, their proficiency keeping pace with technological advancement. Hence, it is of value to assess if further advances in the endoscopic

Key words
- Acromegaly
- Complications
- Endoscopic surgery
- Remission
- Surgeon experience

Abbreviations and Acronyms
CSF: Cerebrospinal fluid
FSH: Follicle-stimulating hormone
GH: Growth hormone
ICA: Internal carotid artery
IGF-1: Insulin-like growth factor 1
LH: Luteinizing hormone
MRI: Magnetic resonance imaging
ROC: Receiver operating characteristic
TSH: Thyroid-stimulating hormone

From the Departments of [1]Neurosurgery, [2]Endocrinology, [3]Otorhinolaryngology, [4]Radiation Oncology, and [5]Pathology, Christian Medical College, Vellore, Tamil Nadu, India

To whom correspondence should be addressed: Ari G. Chacko, M.Ch. [E-mail: arichacko@cmcvellore.ac.in]

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techniques and surgeon experience translate to improved surgical outcomes.

Data that exist on this subject are limited in their scope. We reported data comparing outcomes and complications of endoscopic and microscopic surgery but did not look at the impact of surgeon experience on outcomes.[6] Hence, the aim of this retrospective study was to analyze a large single-surgeon cohort to assess the impact of experience on endocrinologic outcomes and surgical complications in patients undergoing endoscopic transsphenoidal surgery for acromegaly.

METHODS

Patients and Division into Cohorts

Between June 2008 and August 2019, 599 patients with pituitary adenomas, 233 (38.9%) of which were GH secreting, were treated at the neurosurgical service of the Christian Medical College, Vellore. We excluded surgeries performed between October 2015 and September 2017, during which time the senior surgeon was practicing at another center, where he operated on 20 patients with pituitary adenomas, 3 of which were somatotroph adenomas. The surgeon did not receive any clinical or laboratory-based training during this period. We included all patients operated on via the endoscopic transsphenoidal route with at least 3 months follow-up to allow for formal assessment of endocrinologic remission. Thirty patients were excluded for the following reasons: previous operation ($n = 18$), inadequate follow-up ($n = 5$), and operated on via transcranial route ($n = 7$). This surgical cohort finally comprised 203 patients, with a median follow-up of almost 3 years (35.3 months; range, 6–123 months). To analyze the impact of surgeon experience on outcome, we divided the cohort evenly into 2 eras: era 1 (102 patients, January 2008–June 2014) and era 2 (101 patients, July 2014–April 2019).

Preoperative Assessment

Data collected retrospectively included relevant history, clinical examination, and assessment of all hormonal axes (insulin-like growth factor 1 [IGF-1], serum GH, serum 8 AM cortisol, free T4, thyrotropin/thyroid-stimulating hormone [TSH], prolactin, follicle-stimulating hormone [FSH], luteinizing hormone [LH], and testosterone). We used a selective perioperative steroid protocol, administering steroids only in those patients with an impaired preoperative hypothalamopituitary adrenal axis or if the surgeon was unable to preserve the normal adenohypophysis.[7] We defined hypogonadism in men as low age-adjusted serum testosterone values (<265 ng/dL between 20 and 49 years of age and <212 ng/dL >50 years of age) and in women as amenorrhea with inappropriately low FSH and LH values.[8] Central hypothyroidism was defined as serum T4 values <4.5 μg/dL with an inadequate TSH response. Patients were evaluated for derangement of metabolic parameters, including complete fasting lipid profile, plasma glucose (fasting and postprandial) and hemoglobin A1c.

All patients underwent preoperative radiologic evaluation, comprising contrast magnetic resonance imaging (MRI), as well as direct coronal computed tomography imaging with bone windows. The maximum anteroposterior, transverse, and craniocaudal diameters were measured. Macroadenomas were defined as those with a maximum tumor diameter >10 mm, and giant adenomas as those exceeding 40 mm; invasion of the cavernous sinus(es) was defined as Knosp grades 3A, 3B, and 4.[9]

Surgical Approach and Techniques

All patients in this report were operated on via the endoscopic transsphenoidal route by the senior author (A.G.C.). Although several surgeons in our department operate on pituitary adenomas, all functional adenomas were referred to our unit enabling subspecialization. In the later era, a lumbar subarachnoid catheter was placed before positioning to drain cerebrospinal fluid (CSF) during tumor removal to reduce the incidence of intraoperative CSF leak.[10] We have always used a binarial approach, with the endoscope held by the first assistant in the right nostril. Although we initially performed a posterior septectomy without a middle turbinectomy, in the later cohort, we included a right middle turbinectomy, which enabled wider access into the sphenoid sinus and a rescue flap longitudinal mucosal incision for harvesting a pedicled nasoseptal flap in the event of a CSF leak.[11] Also in the later cohort, wide drilling of the sellar floor exposing the edges of both cavernous sinuses and the medial opticocarotid recesses permitted an excellent view of the medial cavernous components of the tumor and facilitated dissection in the superior cavernous space with angled endoscopes. We were not aggressive with tumor lateral to the internal carotid artery (ICA) and did not excise the cavernous sinus wall.

Pathologic Analysis

All tumor samples were subjected to immunohistochemical staining with a complete profile of hormonal markers, including GH, prolactin, TSH, adrenocorticotropic hormone, LH, FSH, alpha subunit of glycoprotein. The tumors were classified based on immunohistochemistry by a neuropathologist (G.C.). Adenomas expressing GH were further stained for cytokeratin; sparsely granulated adenomas showed staining of the perinuclear fibrous bodies, whereas densely granulated adenomas showed diffuse cytoplasmic staining. The MIB-1 labeling of the tumors was also assessed.

Postoperative Complications

We documented the rate of postoperative complications including CSF leak, postoperative hemorrhage, meningitis, diabetes insipidus, and hypopituitarism. Postoperative hypopituitarism was defined as new-onset central hypothyroidism, hypocortisolism, or hypogonadism requiring substitution therapy that persisted at follow-up and was stratified according to the appropriate hormonal axis. Diabetes insipidus was diagnosed if the urine output exceeded 300 mL/hour for 3 consecutive hours or >6 L/day, or if the serum Na^+ level was more than 145 mEq/L with a urine specific gravity <1.003.[12] Postoperative hyponatremia was defined as serum sodium level <130 mEq/L.

Assessment of Remission

The random serum GH level was measured the morning after surgery and the serum GH level after an oral glucose tolerance test was measured on the seventh postoperative day. The first postoperative follow-up was at 3 months after surgery and annually thereafter, with measurements of GH and IGF-1 values, and other

hormonal axes. Patients' diabetes mellitus and hypertension were also evaluated, for adjustments of medications. Surgical remission was assessed at the first follow-up visit or before initiation of any adjuvant therapy. We defined remission as normal age-adjusted IGF-1 values as per reference values from our laboratory in conjunction with normal GH (a random GH value <1 ng/mL or nadir GH value <0.4 ng/mL after suppression with oral glucose if the random GH exceeded 1 ng/mL), in keeping with the 2014 Endocrine Society Clinical Practice Guideline.[13]

Postoperative Imaging

Broadly, postoperative MRI was reserved for those in whom biochemical features indicated residual disease, including some patients who had increased postoperative day 1 and day 7 serum GH levels but were in remission at 3 months follow-up without adjuvant therapy. Patients who achieved remission and those with mildly increased GH levels (<5 ng/mL) in whom adjuvant radiotherapy was not planned did not undergo routine postoperative MRI scans, because normalization of GH/IGF-1 levels is a good marker of radiologic remission.[14,15] Thus, postoperative imaging studies were performed in 155 patients (76%). This imaging included either hyperacute postoperative MRI (performed 6–8 hours after surgery) in patients with large macroadenomas or MRI at follow-up in patients with residual disease who consented to radiation therapy.

Management of Residual Disease

For patients with residual tumor accessible in the sella, re-surgery was offered and those who were unwilling for surgery were given radiation therapy. Patients with obvious tumor in the cavernous sinus were advised early adjuvant radiotherapy (conventional, fractionated stereotactic radiation therapy or stereotactic radiosurgery). In patients in whom the GH/IGF-1 values were not sufficient to declare remission, yet low enough (<5 ng/mL) that patients were content with the improvement in acromegalic features with better control of comorbidities, we used medical therapy (cabergoline in most cases because of financial constraints).

Statistical Analyses

Data were entered into an electronic database via Microsoft Access (Microsoft, Redmond, Washington, USA), and analyzed with SPSS version 24 (IBM Corp., Armonk, New York, USA). Descriptive statistics were applied for all variables of interest, for the entire cohort, as well as stratified by the era and occurrence of remission. Categorical variables were analyzed with the χ^2 test and continuous variables such as age and serum GH levels were analyzed with the Student t test. The unpaired t test was used to compare continuous variables among temporally distributed patient groups, such as tumor size across the 2 eras, whereas the paired t test compared means of variables of the same patients preoperatively and postoperatively. The Mann-Whitney U test was used to assess the difference in median values of nonparametrically distributed variables, such as duration of symptoms. A cutoff for surgical experience required to improve the rate of remission was arrived at using receiver operating characteristic (ROC) curve analysis. We used the Youden method, using the point with the highest sensitivity and specificity to predict an improved rate of remission. We assessed factors that could predict surgical remission using multiple regression analysis, including age, gender, preoperative GH level, tumor size, cavernous sinus invasion, surgical era, and sparsely granulated histology. A P value <0.05 was considered significant.

RESULTS

Preoperative Patient and Tumor Characteristics

The median time to diagnosis (36 months), demographic features, incidence of various clinical features, and comorbid conditions did not differ significantly between the 2 eras (Table 1).

The mean GH values were comparable across eras (48.6 vs. 37.5 ng/mL; P = 0.181). The mean tumor diameter of adenomas in both eras was similar (24.3 vs. 22.8 mm; P = 0.924), as was the proportion of macroadenomas and giant adenomas. Overall, cavernous sinus invasion was noted in 98 adenomas (49.5%) on preoperative imaging, but the rates of invasion were similar in the 2 eras (52.9% vs. 43.5%; P = 0.181). Of the 98 invasive adenomas, 65 (66.3%) showed Knosp grades 3B or 4.

Remission of Disease and Adjuvant Therapy

One patient died in the immediate postoperative period. The patients were followed up for a median period of 35.3 months. All patients reported varying degrees of acromegaly regression and achieved better control of their blood glucose levels and blood pressure. At 3 months follow-up, 82 patients achieved surgical remission (40.6%), with increasing rates of surgical remission from era 1 to 2 among the entire cohort (31.2% vs. 50%; P = 0.007), as well as among noninvasive adenomas (50% vs. 73.6%; P = 0.012). The rate of surgical remission among adenomas that invaded the cavernous sinus did not significantly change (14.8% in era 1 vs. 18.6% in era 2; P = 0.617) (Table 2). Overall, 120 patients did not achieve surgical remission. Of these patients, 13 did not receive any adjuvant therapy because their postoperative GH levels, although not in remission, were <5 ng/mL and were associated with significant clinical improvement. The remaining 107 patients received adjuvant therapy. Five patients were reoperated on for residual tumor; 1 did not require any adjuvant therapy, whereas 3 required cabergoline and 1 underwent stereotactic radiosurgery and was put on cabergoline therapy. Figure 1 summarizes our outcomes across various forms of adjuvant therapy. Overall, our remission rate improved significantly from 40.2% in era 1 to 55% in era 2 (P = 0.035).

Postoperative MRI was done in 155 patients; among the 99 whose image showed evidence of residual tumor, the most common site of tumor residue was the cavernous sinus (64.3%), followed by the sella (25.7%), suprasellar (5.9%), and clivus (3.9%).

Factors Affecting Rates of Remission

Patients who achieved surgical remission were significantly older (39.5 vs. 35.6 years; P = 0.015) and were more likely to be male (56.1% vs. 40.8%; P = 0.034) compared with those who were not in remission. In addition, patients with smaller adenomas (maximum tumor diameter 18.6 mm vs. 26.9 mm; P < 0.001) that were not invasive into the cavernous sinuses (19.5% vs. 67.5%; P < 0.001) and produced lesser preoperative elevation of GH levels (15.9 vs. 40 ng/mL; P < 0.001) were more likely to go into surgical remission, as shown in Table 3.

Table 1. Baseline Preoperative Characteristics in 203 Patients with Acromegaly

Variable	Overall (N = 203)	Era 1 (N = 102)	Era 2 (N = 101)	*P* Value (Era 1 vs. 2)
Clinical characteristics				
Age (years)	37.1 ± 11.1	36.6 ± 10.9	37.6 ± 11.1	0.512
Male sex	88 (44.9)	50 (49)	45 (44.6)	0.524
Incidentally detected	8 (4.1)	2 (1.9)	6 (5.9)	0.145
Duration of symptoms (months), median (interquartile range)	36 (18–60)	36 (12–60)	36 (18–60)	0.898
Body mass index (kg/m^2)	26.2 ± 3.5	26.1 ± 3.4	26.2 ± 3.9	1
Diabetes mellitus	72 (35.5)	33 (32.4)	39 (38.6)	0.351
Hypertension	75 (36.9)	35 (34.3)	40 (39.6)	0.434
Biochemical characteristics				
Mean basal growth hormone value (ng/mL)	43.1 ± 36.1	48.6 ± 43.2	37.5 ± 33.13	0.181
Hypothyroidism	31 (15.3)	20 (19.6)	11 (10.9)	0.084
Hypocortisolism	15 (7.6)	9 (8.8)	6 (5.9)	0.432
Hypogonadism	45 (23)	16 (15.7)	29 (28.7)	0.025
Radiologic characteristics				
Macroadenomas	168 (82.8)	84 (82.4)	84 (83.2)	0.877
Giant adenomas	18 (8.9)	7 (6.9)	9 (8.9)	0.588
Mean diameter (mm)	23.4 ± 10.8	24.3 ± 10.8	22.8 ± 11.3	0.924
Cavernous sinus invasion	98 (49.5)	54 (52.9)	44 (43.5)	0.181
Knosp 3B	19 (9.4)	7 (6.9)	12 (11.9)	0.219
Knosp 4	46 (22.7)	28 (27.5)	18 (17.8)	0.101
Histologic features				
Sparsely granulated	128 (63.1)	69 (67.6)	59 (58.4)	0.144
MIB index >3	127 (62.6)	58 (56.9)	69 (68.3)	0.129

Values are number (%) except where indicated otherwise.

Univariate analysis showed that patients with preoperative basal GH values <40 ng/mL, adenoma size <20 mm, noninvasive tumors, and surgery in era 2 had significantly better rates of surgical remission. The multivariate analysis incorporating the same variables showed that only preoperative GH levels, invasion of the cavernous sinuses, and surgery in era 2 remained significant (Table 4).

Improvement in Metabolic Parameters

Of 72 patients who were on oral antidiabetic agents (OADs), 27 (37.5%) experienced reduction in the number of agents required to control their blood glucose level at 12 weeks follow-up; 20 (27.7%) discontinued their medication entirely and among 28 patients who were preoperatively on insulin, it was stopped during their immediate postoperative period in 21 (75%). The mean reduction in hemoglobin A1c values 3 months after surgery was 1.4% (95% confidence interval, 1.05–1.87; $P < 0.001$). Seventy-five patients required antihypertensive medications preoperatively; the requirement for antihypertensive medication reduced in 15 patients (20%) and 10 of them (13.3%) were taken off their medication altogether. Levels of serum cholesterol normalized in 36 of 108 patients (33.3%) by 12 weeks postoperatively. Overall, 48 patients of 118 (40.6%) with an acromegaly-associated comorbidity experienced resolution after surgery, which was significantly more likely in era 2 compared with era 1 (52.5% vs. 28.8%; $P = 0.009$).

Visual Outcomes and Complications

Of 34 patients with preoperative impairment of visual acuity or visual fields, 28 improved after surgery. Of 18 patients in the first era, 14 noticed improved vision, compared with 14 of 16 patients in the second ($P = 0.436$). There were 3 instances of transient decrease in vision in the cohort (1 in era 1 and 1 in era 2), recovering to preoperative levels by the time of discharge or first follow-up.

The rates of postoperative hypopituitarism were significantly lower in era 2 (23.5% in era 1 vs. 11.9% in era 2; $P = 0.044$), and although the rate of intraoperative CSF leak was lower in era 2 (21.6% vs. 13.9% in era 1), this did not reach statistical significance ($P = 0.151$). There was one mortality, which occurred in a

Table 2. Complications and Endocrine Outcomes

Variable	Overall (N = 203), n (%)	Era 1 (N = 102), n (%)	Era 2 (N = 101), n (%)	*P* Value (Era 1 vs. 2)
Postoperative period				
Intraoperative CSF leak	36 (17.7)	22 (21.6)	14 (13.9)	0.151
Postoperative CSF leak	2 (1)	1	1	0.481
Meningitis	1 (0.5)	1 (1)	0	—
Endocrine outcomes				
Diabetes insipidus	23 (11.3)	11 (10.8)	12 (11.9)	0.805
Hypopituitarism	36 (17.7)	24 (23.5)	12 (11.9)	0.044
Hypothyroidism	14/172 (8.1)	8/82 (9.8)	6/90 (6.7)	0.592
Hypocortisolism	31/188 (16.5)	21/93 (22.6)	10/95 (10.5)	0.031
Recovered pituitary function	20/72 (27.8)	8/35 (22.9)	12/36 (33.3)	0.334
Resolution of acromegaly-associated comorbidity	48/118 (40.7)	17/59 (28.8)	31/59 (52.5)	0.009
Adjuvant therapy				
Adjuvant radiation only	12 (6.6)	8 (7.8)	4 (4)	0.240
Cabergoline therapy only	40 (19.7)	18 (17.6)	22 (21.7)	0.370
Combined radiation and cabergoline	55 (27.6)	37 (36.3)	18 (17.8)	0.003
Reoperated	5 (2.5)	3 (3)	2(2)	0.991
Remission rates				
Overall (inclusive of adjuvant therapy)	96 of 202* (47.5)	41 (40.2)	55/100* (55)	0.035
Surgical remission (Total)	82 of 202* (40.6)	32/102 (31.2)	50/100* (50)	0.007
Noninvasive adenomas	66 of 105 (62.9)	24/48 (50)	42/57 (73.6)	0.012
Invasive adenomas	16 of 97 (16.5)	8/54 (14.8)	8/43 (18.6)	0.617

CSF, cerebrospinal fluid.
*1 patient died in the immediate postoperative period.

22-year-old woman operated on in era 2 who underwent subtotal resection of an invasive tumor that had extended into the suprasellar subarachnoid space across the aperture of the diaphragma sellae. On the third day after surgery, this patient developed rapidly progressive neurologic deterioration, with imaging showing subarachnoid hemorrhage and diffuse brain edema. Despite treatment with steroids and nimodipine, she died of worsening vasospasm and hypothalamic dysfunction.

ROC Curve Analysis

On using ROC curve analysis to determine a cutoff of surgical experience that significantly affected rates of remission, the Youden method yielded a threshold of 102 surgeries (sensitivity, 0.720; specificity, 0.675; area under the curve, 0.721). This result also corresponded to the median value of this cohort and the division point between the 2 eras.

DISCUSSION

Improving Outcomes with Increasing Surgical Experience

Tumor size, invasiveness, duration of acromegaly, and preoperative GH levels are important predictors of surgical outcomes.[6,16-22] This report of 203 somatotroph adenomas shows the effect of a surgeon experience on endocrinologic outcomes and complications with endoscopic endonasal surgery over a 11-year period. The rates of surgical remission of acromegaly improved from 31.2% in era 1 to 50% in patients operated in era 2 despite other factors determining remission being the same. ROC curve analysis in this study showed that cumulative experience gained after 102 transsphenoidal operations resulted in improved outcomes in subsequent patients. This finding is consistent with previous suggestions that experience with 100 acromegaly surgeries in a center performing 25–50 acromegaly surgeries a year is sufficient to improve rates of remission.[23] A few older studies[19,24] have reported improved remission rates from 58.5% to 72.6% after a cutoff of 108 surgeries but are limited by the fact that they did not compare tumor characteristics such as size and invasiveness on either side of this cutoff nor did they assess the effect of experience on postoperative complications.[19]

We found that other endocrinologic outcomes such as postoperative hypopituitarism and resolution of acromegaly-associated comorbidities were better with increasing experience. Specifically, 27.7% of patients were able to discontinue their oral antidiabetic

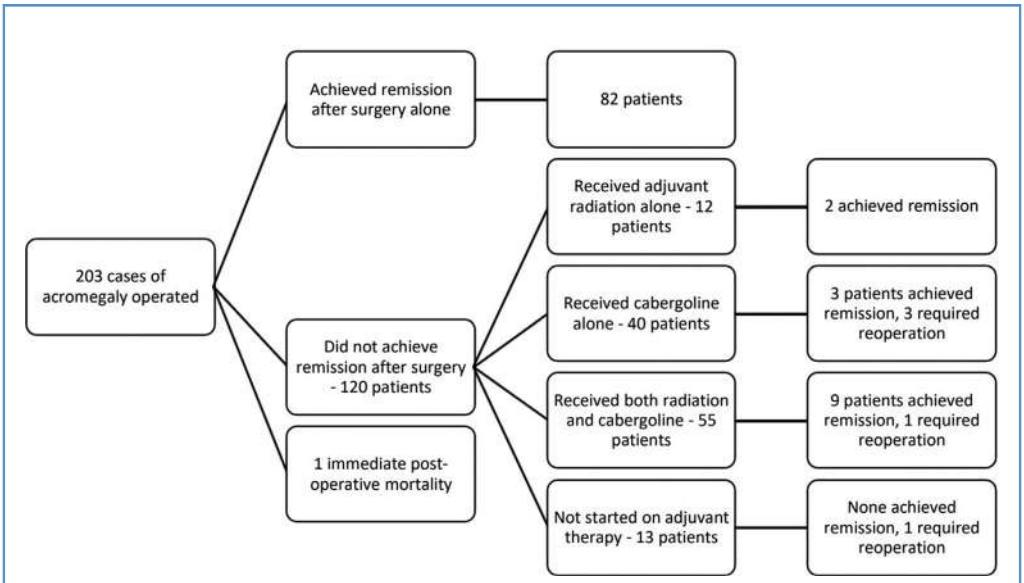

Figure 1. Summary of Follow-Up Data of 203 Patients with Acromegaly.

agents, a proportion comparable to recent experience from other centers.[25]

Although the rates of postoperative CSF leak were lower in the later cohort, this was not statistically significant. The results of our multivariate analysis indicated that predictors of remission were preoperative GH levels, cavernous sinus invasion, and increased surgeon's experience. Lower preoperative GH levels have almost universally been reported to predict remission, as have the rates of cavernous sinus invasion.[17-19,26] One group of investigators reported that higher grades of acromegalic features and the presence of acromegaly-associated comorbidities negatively affected remission rates.[17]

The higher overall rates of remission reported by Hazer et al.[19] compared with our cohort (62.6% vs. 47.5%) was mainly because our patient population had a higher proportion of large adenomas (23.8% of their adenomas were microadenomas vs. 9.6% of our cohort) and invasive adenomas (25.2% of their GH adenomas invaded the cavernous sinus, vs. 49.5% of our cohort.) Experience at our center involves adenomas that are larger and more invasive than most modern series examining remission in acromegaly.[16,18,20,21] Knosp 3 adenomas are not a homogenous group; Micko et al.[9] reported a significantly higher rate of intraoperative cavernous sinus invasion among Knosp 3B adenomas, compared with those graded as Knosp 3A (70.6% vs.

Table 3. Comparison of Surgical Remission and Nonremission Patient Groups

Variable	Remission (N = 82)	Nonremission (N = 120)	*P* Value
Age (years)	39.5 ± 11.6	35.6 ± 10.3	0.015
Male sex	46 (56.1)	49 (40.8)	0.034
Acromegaly-associated comorbidity (Diabetes mellitus/Hypertension/Obstructive Sleep Apnea)	33 (40.2)	58 (48.3)	0.257
Mean adenoma size (mm)	18.6 ± 9.5	26.9 ± 10.9	<0.001
Invasive adenomas	16 (19.5)	81 (67.5)	<0.001
Preoperative GH levels (ng/mL) (interquartile range)	15.9 (8.1—30.8)	40 (20—73.15)	<0.001
Residue present at first postoperative magnetic resonance imaging	13/45 (35.1)	86/110 (78.2)	<0.001
Sparsely granulated	47 (57.3)	80 (66.7)	0.177
MIB-1 index	3.1 ± 1.9	3.5 ± 2.1	0.180
GH + prolactin staining	41 (50)	50 (41.7)	0.243

Values are number (%) except where indicated otherwise.
GH, growth hormone.

Table 4. Regression Analysis of Factors Predicting Surgical Remission

	Univariate Analysis			Multivariate Analysis		
Variable	**OR**	***P* Value**	**95% CI**	**OR**	***P* Value**	**95% CI**
Age <36 years	0.674	0.097	0.422–1.075	1.025	0.923	0.619–1.698
Male gender	1.246	0.348	0.787–1.974	1.125	0.628	0.699–1.810
Preoperative growth hormone level ≤40 ng/mL	4.317	<0.001	1.978–9.423	3.215	0.004	1.441–7.175
Adenoma size >20 mm	0.332	<0.001	0.199–0.552	0.611	0.099	0.340–1.097
Cavernous sinus invasion present	0.182	<0.001	0.101–0.328	0.547	<0.001	0.235–1.270
Era 2 versus 1	6.035	<0.001	3.253–11.197	5.081	<0.001	2.721–9.487
Sparsely granulated adenoma	0.636	0.056	0.400–1.011	0.717	0.176	0.337–1.440
MIB index >3	0.672	0.112	0.412–1.097	1.064	0.815	0.631–1.795

OR, odds ratio; CI, confidence interval.

26.5%), with consequently lower rates of gross total resection and remission. This distinction is of great significance to our report, because a third of our adenomas (65/203) were classified as Knosp 3B or 4. In a recent series, Asha et al.[17] reported an overall primary surgical remission rate of 73%, in a cohort with a high incidence of cavernous sinus invasion (49/81 patients). Among those with intraoperative evidence of cavernous sinus extension, remission was achieved in 26.5% of patients.

Surgical Techniques and Adjuncts Improving Outcomes

Several operative and perioperative factors that govern the safety and efficacy of endoscopic transsphenoidal surgery progressively evolve at any center treating pituitary tumors. Thus, the overall positive impact on patient outcomes with experience represents the composite impact of continual efforts in all these dimensions and not just with on-table technical expertise alone. Over the years, better understanding of the endoscopic anatomy of the anterior skull base has translated into more aggressive drilling of the sellar floor, exposing the medial opticocarotid recesses and the anterior genu of the ICA to effectively deal with large suprasellar extensions and invasive adenomas.[27] Through these maneuvers, lateral displacement of the ICA with the shaft of the instruments used for tumor removal enables safe access to the superior compartment of cavernous sinus behind the anterior genu of the ICA. We do not venture lateral to the ICA on principle, and no cases of ICA injury were recorded in this series. Our poor surgical remission rates in invasive tumors are a reflection of the large number of Knosp 3B and 4 adenomas in our series as well as our conservative strategy. Aggressive techniques in the pursuit of tumors extending into the cavernous sinus, such as excision of the medial wall of the cavernous sinus, have been reported from dedicated skull base centers, with good remission rates.[28,29] These investigators clearly state that such techniques were applied for Knosp 1–3 tumors alone with isolated attachment to or invasion of the medial wall of the cavernous sinus and were not recommended in tumors with extensive invasion of the cavernous sinuses.[28,29] Despite the use of such techniques, adherence of adenoma tissue to vital structures such as the ICA and cranial nerves, invasiveness, and fibrous consistency are factors that prevent complete resection, which are noted in more than half of Knosp 4 adenomas.[29,30] These aggressive maneuvers can result in devastating complications such as profuse cavernous bleeding, ICA injuries, and oculomotor nerve palsies.[31,32] The unnecessary exposure of patients with Knosp 3 or 4 invasive tumors to these neurovascular injuries is not defensible when these patients nonetheless require stereotactic radiosurgery to achieve remission. This sentiment is echoed by Knosp et al.,[30] who reported that their rate of remission was 0% in Knosp 3B and 4 adenomas compared with 88% in Knosp 1 adenomas.[9]

Re-surgery for residual or recurrent tumors, in an attempt to improve response to adjuvant therapy, seems to provide comparable remission rates to those undergoing primary surgery (46.8% vs. 56.4%).[26] As expected, significantly fewer adenomas invading the cavernous sinus (14.7%) achieve remission despite re-surgery,[26] and therefore, our policy is to proceed with the goal of reducing tumor size sufficiently for a safe delivery of stereotactic radiosurgery, avoiding the morbidity of repeat transsphenoidal surgery. We have also incorporated the use of neuronavigation and intraoperative Doppler sonography, particularly in patients undergoing reoperation for recurrent or residual tumors.

Factors Reducing the Rates of Postoperative Complications

Our ability to discern the tumor pseudocapsule and normal adenohypophysis at surgery enables preservation of endocrine function[33-35]; however, this is also a skill that is progressively acquired with experience. The intraoperative drainage of CSF from a lumbar subarachnoid catheter[10,36] markedly reduced the turgor of the arachnoid pouch and is reflected in the reduction of our incidence of intraoperative CSF leak from 21% in era 1 to 13% in era 2. Because we rarely applied the expanded approaches for these tumors, our dural repair with fat held in place with a piece of septal bone/vomer proved effective, with postoperative

CSF leaks rarely occurring at a rate of 1%. This finding is on par with the rates of CSF leak reported in the literature, which tend to be around 2% in most series,[19,37] with rates as low as <1% in some series[17,24,26,38] and as high as 5% in series of invasive adenomas requiring more extensive approaches.[29]

Kasemsiri et al.[39] noted that an often-ignored disadvantage of endoscopic transsphenoidal surgery is "finding a willing co-surgeon with compatible personality, philosophy of treatment, skills, ethics, and professional vision." At our institution, frequent collaboration with an otolaryngorhinology team has resulted in their input at all 3 stages of management (preoperative assessment, intraoperative assistance, and postoperative care). Preoperative endoscopic assessment enables better planning of surgery because nasal infections can be identified and treated properly before surgery. The intraoperative assistance has allowed for an increase in professional support and an ever-increasing comfort level at surgery. Specifically, this collaboration has helped improve both the nasal exposure and the repair of CSF leaks with pedicled nasoseptal grafts when required. Meticulous postoperative endoscopic care results in better quality of life and earlier resolution of nasal symptoms.[40]

Acquiring technical proficiency with endoscopic surgical techniques may prove challenging to beginners. Despite its advantages of increased illumination, high-definition visualization, and wide-angled view, unfamiliarity with endoscopic surgery and the relative reduction in depth perception prolong the learning curve in many neurosurgeons, who have traditionally received extensive training in microsurgery.[41] This situation necessitates specialized training, perhaps in the form of a dedicated fellowship or exposure to cadaveric specimens, to gain knowledge of anatomy and maneuvering of instruments in a restricted space.

Improving Postoperative Care to Deliver Better Outcomes

An important and often overlooked factor that safeguards good patient outcome in pituitary surgery relates to postoperative care. Problems with fluid—electrolyte balance and hormonal deficiencies in the immediate postoperative period are best managed with a strict protocol-based treatment strategy.[7] Delayed hyponatremia is the most common cause of readmission after transsphenoidal surgery[42]; raising patient awareness through specialized nurse educators helps in early identification of this problem. Violation of protocols occurs frequently in clinical practice and the introduction of checklists is recommended to reduce errors.[43]

Limitations

Our study is limited by the retrospective nature of data collection. We excluded patients operated on during the 2 years that the senior surgeon (A.G.C.) was working at another hospital. During this period, he operated on 20 pituitary adenomas, 3 of which were somatotroph adenomas, and did not receive any fellowship or laboratory-based training in endoscopic skull base surgery. Therefore, it is unlikely that the learning curve would have been altered significantly by this 2-year hiatus.

CONCLUSIONS

This article describes the surgical outcomes in a large cohort of patients with acromegaly undergoing endonasal endoscopic surgery. Experience gained by a single surgeon significantly improves surgical remission rates and also reduces complications. These data support the discussion surrounding the establishment of pituitary centers of excellence, because subspecialization in this rare disease enables faster accrual of experience that translates to improved surgical outcomes in acromegaly.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Abhijit Goyal-Honavar: Conceptualization, Methodology, Formal analysis, Data curation, Writing - original draft. **Sauradeep Sarkar:** Data curation, Formal analysis, Writing - review & editing. **Hesarghatta Shyamasunder Asha:** Writing - review & editing. **Nitin Kapoor:** Writing - review & editing. **Regi Thomas:** Writing - review & editing. **Rajesh Balakrishnan:** Writing - review & editing. **Geeta Chacko:** Writing - review & editing. **Ari G. Chacko:** Conceptualization, Methodology, Writing - review & editing.

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