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A follow-up study on outcomes of endoscopic transsphenoidal approach for acromegaly

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ABSTRACT

Objective: A thorough follow-up study in which the same clinic presents the change in the surgical outcomes of acromegaly over the years, is still lacking in the endoscopic era. In this study, we intended to evaluate the clinical characteristics, radiological features, surgical and late remission rates of newly diagnosed acromegaly patients treated in our clinic between 2014 and 2019 in order to delineate the surgical remission status according to radiological, microscopic, and hormonal features. As a follow-up to our initial report, we also aimed to display the change of surgical remission rates over time in a tertiary center.

Methods: A total of newly diagnosed 106 patients with acromegaly, who underwent endoscopic endonasal transsphenoidal approach (EETSA) in the last five years were retrospectively analyzed and presented in this study. Medical records were reviewed in clinical, biochemical, pathological, and radiological aspects to assess the relationship of preoperative patient characteristics with surgical remissions.

Results: The percentages of the giant pituitary adenomas (≥4 cm), adenomas with suprasellar extension and adenomas with surgically proven invasion of the cavernous sinus in the present series were 13%, 34%, and 20%, respectively. Gross total resection was achieved in 80% of the patients. Surgical remission and late remission rates were 66% and 86%, respectively. Nine (9.4%) patients in our current report had postoperative transient diabetes insipidus. The mean follow-up period in this series was 36.1 ± 18.1 (range 12–59) months.

Conclusion: The presented surgical results are considerably better than our published initial series of acromegaly patients operated in the same clinic between 2007 and 2014. The improvement in surgical remission rate support a positive surgical volume - remission rate relationship for acromegaly in the era of endoscopic endonasal skull base approaches. One possible factor for better results may be the increasing surgical experience in EETSA, which follows a trend toward gradual improvement of long-term late remissions via a multidisciplinary approach.

1. Introduction

Acromegaly is a subtle endocrine disease characterized by the overproduction of growth hormone (GH) and insulin-like growth factor-1 (IGF-1). It is commonly caused by a pituitary tumor, causing excessive production of GH [1–3]. The surgical treatment for patients with acromegaly mainly aimed to optimize hormone levels, eliminate clinical findings, and improve long-term morbidity and mortality by achieving

Abbreviations: GH, Growth Hormone; IGF-1, Insulin-like Growth Factor-1; PRL, Prolactin; TSH, Thyroid-Stimulating Hormone; f-T3, free T3; f-T4, free T4; ACTH, Adrenocorticotropic Hormone; FSH, Follicle-Stimulating Hormone; LH, Luteinizing hormone; Ki-67 LI, Ki-67 Labeling Index; PIT-1, Pituitary Specific Transcription Factor-1; OGTT, Oral Glucose Tolerance Test; MRI, Magnetic Resonance Imaging; GTR, Gross Total Resection; DI, Diabetes Insipidus; WHO, World Health Organization; SRS, Stereotactic Radiosurgery; EETSA, Endoscopic Endonasal Transsphenoidal Approach; CSF, Cerebrospinal Fluid; CSI, Cavernous Sinus Invasion; CI, Confidence Interval.

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total resection of the pituitary adenoma. Although surgical resection of the pituitary adenoma is the primary treatment option, multimodal management of acromegaly requires a multidisciplinary approach [4,5]. In this vein, adjuvant medical treatment and stereotactic radiosurgery (SRS) should be considered in patients with acromegaly who are unsuitable for surgery or with invasive adenomas not controlled by surgery [6].

Transsphenoidal surgical route is the gold standard for the resection of pituitary adenomas, and accordingly, endoscopic endonasal technique for the surgical treatment of acromegaly has been established and widely used among neurosurgical community [7,8]. The endoscopic endonasal transsphenoidal approach (EETSA) is more advantageous over conventional microsurgery, such as obtaining a wider view of the sellar/parasellar region and improving the exposure to visualize surgical areas [9–11]. Although overall surgical results via EETSA have been extensively reported for acromegaly, a thorough follow-up study in which the same clinic presents the change in the surgical results over the years, is still lacking in the endoscopic era. In this study, we intended to evaluate the clinical characteristics, radiological features, surgical and late remission rates of newly diagnosed acromegaly patients treated in our clinic within the last five years in order to delineate the surgical remission status according to radiological, microscopic, and hormonal features. As a follow-up to our initial report, we also aimed to display the change of surgical remission rates over time in a tertiary clinic.

2. Methods

2.1. Study design and patient population

A total of 767 patients underwent 851 EETSA for pituitary adenomas between October 2007 and December 2019 in our department. Among them, 255 (33.2%) patients were diagnosed with acromegaly. In 2016, we published treatment results and remission rates of our initial 103 patients with acromegaly operated using the EETSA between 2007 and 2014 [4]. In this study, we aimed to review our subsequent surgical results in newly diagnosed 106 patients with acromegaly, operated between 2014 and 2019. Two patients with a previous history of transsphenoidal surgery and nine patients with insufficient endocrinological follow-up data were excluded from the study and a total of 95 newly diagnosed patients with a follow-up of at least 1 year were included. None of the patients had a previous endocrinological or surgical treatment history. Medical records were reviewed in clinical, biochemical, pathological, and radiological aspects. Treatment outcomes with early and late remission rates and complications were reported. This study was conducted in accordance with the Declaration of Helsinki. Informed consent form was obtained from all patients.

2.2. Biochemical and endocrinological assessment

Baseline GH, IGF-1, PRL, TSH, fT3, fT4, cortisol, ACTH, FSH, and LH levels were measured using immunoassay methods. Hormone levels at postoperative 24-h, 3-month, 6-month, and most recent visits were measured to evaluate hormone insufficiency and remission status. The endocrinological background and, if present, any previous medical treatments of patients were also recorded.

The Endocrine Society guidelines and experts' consensus and age- and sex-adjusted IGF-1 levels combined with nadir GH during an oral glucose tolerance test (OGTT) were used to diagnose and rule out acromegaly [12–14]. Acromegaly was diagnosed with increased IGF-1 level when compared with their normal values for age and sex and/or insuppressible GH levels during the 75 g OGTT.

All patients with acromegaly were referred to the Endocrinology Department within the pre- and postoperative periods. Comprehensive clinical and biochemical examinations were performed in the preoperative period for selective deficiencies of pituitary hormones. Early or surgical remission was achieved if GH levels during the administration of 75 g OGTT were <1 ng/mL, and if age and sex-adjusted IGF-1 levels were in reference ranges at 3 months postoperatively. The medication was terminated immediately following the surgery in patients receiving preoperative medical treatment, and assessment for early remission was performed at 6 months postoperatively.

"Late remission" was defined as the presence of normal IGF-1 and random GH or GH after the administration of OGTT <1 μg/l, in addition to the absence of any residual tumors in dynamic contrast-enhanced sellar magnetic resonance imaging (MRI) during the patients' last follow-up visit. Adjuvant medical therapy was administered to patients who could not achieve early remission. In patients who did not achieve remission with appropriate surgical and medical treatments, reoperation, and/or stereotactic radiosurgery (SRS) was considered depending on the presence, size, and extension of the residual pituitary adenoma on sellar MRI. Clinical findings of patients were also considered when evaluating the remission status of patients. Recurrence is defined as GH and/or IGF-1 levels higher than the normal limits after remission. Comprehensive clinical and biochemical examinations were performed for postoperative hormone deficiencies. Patients were followed up at the 3rd month, 6th month, and annually with outpatient visits.

2.3. Neuroimaging examination

All patients underwent preoperative paranasal sinus and cranial computed tomography, in addition to sellar magnetic resonance imaging (MRI). Intraoperative neuronavigation was used to ensure the location of the sella turcica and tumor borders, as well as to locate critical vascular and neural structures to prevent complications.

The diameters of all adenomas were measured using preoperative MRI, and their dimensions were calculated. Supra- and parasellar extensions of pituitary macroadenomas in patients with acromegaly with a diameter of ≥4 cm were considered as giant pituitary adenomas. Suprasellar extension was evaluated through the sellar MRI in regard to the tumor's relation to the planum sphenoidale in the sagittal plane. Cavernous sinus invasion was evaluated according to Knosp classification [15]. Cavernous sinus invasion was considered positive only in patients with Knosp Grades 3 and 4 [16]. In all patients, the amount of resection was initially confirmed by early postoperative sella MRI within 24 h. Sellar MRI was repeated at postoperative 3rd month, and then every 6 months until 2 years thereafter, for recurrence. No tumor on postoperative MRI was considered gross total resection (GTR).

2.4. Pathological assessment

Somatotropic pituitary adenomas originate from the PIT-1 lineage. Histologically, they may be densely or sparsely granulated [17]. Tissues obtained from pituitary adenomas in this study were subjected to immunohistochemical examinations using antibodies for all pituitary hormones after the routine pathological preparations. In addition, cellular proliferation markers such as Ki-67 labeling index (LI) and p53 and mitosis count were investigated. Ki-67 LI of ≥3% was considered positive; p53 and mitosis of ≥1% were considered positive. Immunoreactivity of each specimen was evaluated by a senior pathologist using a multi-head digital light microscope.

2.5. Surgical procedure

EETSA was performed following the binostril technique in all patients. Endoscopic lenses with 0° (including 30° and 45° angles) were used during the procedures. A vascularized nasoseptal flap was routinely prepared for large and giant macroadenomas because of the risk of postoperative cerebrospinal fluid (CSF). Intraoperative Doppler probe was routinely used to determine the vascular anatomy of the intra-parasellar region before the dural opening. During macroadenoma resection, suctioning and curettage were initiated from the inferior side of the tumor and then continued with both lateral sides and lastly to the

superior side. This technique prevented the premature folding of the collapsed suprasellar cisterns in most patients. An angled endoscope with 30° or 45° was used to explore the non-visualized parts of the suprasellar extension and/or tumor within the cavernous sinus.

2.6. Statistical analysis

Results were presented as numbers and percentages for categorical variables and as mean ± standard deviation, median, and minimum–maximum for continuous variables. Comparison of categorical variables between groups was performed using Chi-square or Fisher exact test. The normality of distribution for continuous variables was confirmed with the Kolmogorov–Smirnov test. To compare independent continuous variables between the two groups, the Student's *t*-test or Mann–Whitney *U* test was used depending on whether statistical hypotheses were fulfilled or not. Multivariate logistic regression analysis was performed to determine the effects of possible risk factors. Thus, based on the univariate analysis, any variable significantly related with death risk and those with a result of $p < 0.25$ were drawn into the analysis. Age was included as a biological factor in the model. The statistical level of significance for all tests was considered 0.05. Statistical analysis was performed using the IBM SPSS ver. 19 package program.

3. Results

Demographic, radiological, pathological, and preoperative hormonal characteristics of 95 patients with acromegaly are shown in Table 1. Among them, 56 (58.9%) were female and 39 (41.1%) were male, with a mean age of 43.4 ± 12.4 (range 16–79) years. All patients had typical clinical signs of acromegaly and mean preoperative GH level of 31.3 ± 21.2 (range 2–76) ng/mL, and the mean preoperative IGF-1 level was 657.3 ± 333.7 (range 238–1600) ng/mL. Four patients had preoperative hypocortisolism, and two had hypothyroidism. PRL level elevated in 33 patients: 27 of them had mild hyperprolactinemia, suggesting the stalk effect of the adenoma, and all of had macro- or giant adenomas. Postoperative PRL levels returned to normal limits without the need for additional treatment in all, except for 5 patients.

Sellar MRIs revealed 69 (72.6%) patients had pituitary macroadenomas, and 12 (12.6%) of them were giant adenomas (≥4 cm) (Fig. 1). Suprasellar extension was detected in 32 (33.6%) patients. Preoperative sellar MRIs revealed Knosp Grade 3 or 4 cavernous sinus invasion in 19 (20%) patients.

According to immunohistochemical examinations, Ki-67 LI was ≥3% in 33.6% of patients and p53 was ≥1% in 47.3% of patients. High mitotic index (≥2 mitosis detected in 10× high power fields) was detected in 23.1% of patients. However, 86 (91.6%) of 95 patients underwent surgery primarily, and 9 patients underwent initial medical treatment (octreotide) to alleviate their clinical symptoms preoperatively.

Table 1
Demographic, radiological and preoperative hormonal characteristics of 95 patients with acromegaly.

	Patients with acromegaly (95)
Demographical features	
Age, (years)* (Range)	43.4 ± 12.4 (16–79)
Female/Male, (n,%)	56 (58.9%) / 39 (41.1%)
Radiological features	
Size, (n,%)	
Macroadenoma / (Giant)	69 (72.6%) / 12 (12.6%)
Microadenoma	26 (27.4%)
Suprasellar extension +, (n,%)	32 (33.6%)
CSI +, (n,%)	19 (20%)
Preoperative hormonal features	
GH, (ng/mL)* (Range)	31.3 ± 21.2 (2–76)
IGF-1, (ng/mL)* (Range)	657.3 ± 333.7 (238–1600)
Pathological features	
Ki-67 +, (n,%)	32 (33.6%)
P53 +, (n,%)	45 (47.3%)
Mitosis +, (n,%)	22 (23.1%)

* Data was expressed as mean ± standard deviation.

Postoperative hormonal status, resection rates, remission status, complications, and follow-up periods are shown in Table 2. Early surgical remission was achieved in 63 (66.3%) patients at the postoperative 3rd month evaluation. Thus, our surgical remission rate for 95 patients was 66.3%. Three of 63 patients who were categorized in the early remission group were found to have recurrent disease during follow-up. Two of these patients had no apparent tumor detected in sellar MRI, and remission was achieved with additional medical treatment alone. The remaining patient was reoperated and has been followed up in remission after the second operation.

Early remission was not achieved in 32 (33.7%) patients who underwent surgery, and all of them received medical treatment following the surgery. Octreotide treatment was initially prescribed to all 32 patients who did not achieve early remission, and cabergoline treatment was prescribed to 10 of patients with postoperative IGF-1 levels of 2 times higher than the normal limits. Three patients were administered pegvisomant due to partial or no response to octreotide treatment and impaired glucose metabolism. Of 32 patients who did not achieve early remission, 19 had GH and IGF-1 levels within normal limits at the last follow-up, indicating that late remission was achieved with the help of medical treatment. With these results, late remission was achieved in 82 (86.3%) patients during the last follow-up visit. Thus, the overall remission rate for 95 patients is 86.3% in this case series.

A total of 13 (13.7%) patients had neither early nor late remission following EETSA and medical therapy. SRS was performed without delay in 10 of these patients; however, remission was not achieved within the follow-up period. The remaining 3 patients were reoperated, 1 of whom had late remission after 1 year with added postoperative medical treatment and the other two had persistent hormone elevation and additional SRS was performed; however, remission was still not achieved. The detailed treatment flow chart of patients with acromegaly is shown in Table 3.

The mean GH and IGF-1 levels were 1.8 ± 1.2 (range 0.1–10.3) ng/mL and 236.3 ± 112.1 (range 84–755) ng/mL, respectively, during the last follow-up visit. Early postoperative radiological examinations within 24 h revealed that 76 (80%) of 95 patients had GTR. The mean follow-up period was 36.1 ± 18.1 (range 12–59) months, with a follow-up period of at least 1 year.

No patients in this series had postoperative CSF leak. In addition, no patients had major complications such as arterial and/or cranial nerve injury. Although no patients had postoperative panhypopituitarism, transient DI occurred in 9.4% of patients and the DI was persistent in only one of these patients, requiring a long-term vasopressin treatment.

3.1. Remission status according to radiological, microscopic, and hormonal features

The relationship between early and late remission status and various patient characteristics is shown in Table 4. Both early (41.7%) and late remission (70%) rates were significantly lower in patients younger than 35 years as compared to other age groups. Although remission rates were higher (92.3%) in microadenomas, both early (41.7%) and late remission (58.3%) rates were low for giant adenomas. Moreover, differences in remission rates were statistically significant in patients with suprasellar extension and in those with cavernous sinus invasion (CSI). High mitotic index (≥2 mitosis detected in 10× high power fields), as well as a positivity of other pathological microscopic markers, was found to have had no significant effect on remission rates. Significantly higher remission rates were observed in patients with GTR compared to subtotal resection.

Effects of pre- and postoperative hormone values on early and late remissions are also shown in Table 4. According to multivariate analysis

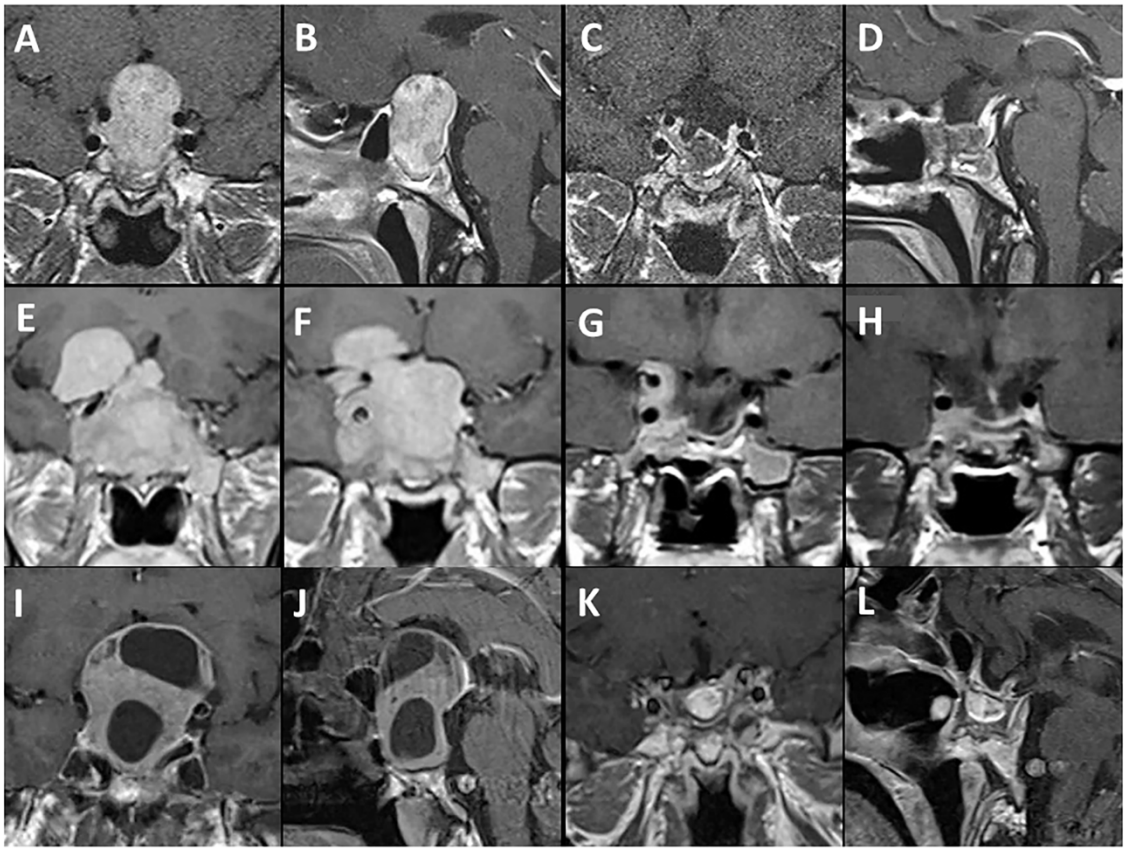


Fig. 1. Preoperative (**A** and **B**) and postoperative (**C** and **D**) contrast enhanced T1-weighted MR images obtained in a 30 years old female patient who underwent gross total resection of a macroadenoma with suprasellar extension. Preoperative (**E** and **F**) and postoperative (**G** and **H**) contrast enhanced T1-weighted coronal plane MR images obtained in a 51 years old male patient who underwent resection of a giant adenoma with frontotemporal extension and right carotid artery encasement. Preoperative (**I** and *J*) and postoperative (**K** and **L**) contrast enhanced T1-weighted MR images obtained in a 47 years old male patient who underwent gross total resection of a giant adenoma with intracranial extension.

Table 2
Outcomes of 95 patients with acromegaly.

	Patients with acromegaly (n = 95)
Postoperative hormonal features	
Mean First 24 h GH* (Range)	3.1 ± 1.8 (0.1–16.4)
Mean First 24 h IGF-1* (Range)	437.9 ± 283.7 (147–1427)
Mean 3. Month GH* (Range)	4.6 ± 4.6 (0.1–16)
Mean 3. Month IGF-1* (Range)	298.6 ± 205.2 (79–1400)
Mean Last visit GH* (Range)	1.8 ± 1.2 (0.1–10.3)
Mean Last visit IGF-1* (Range)	236.3 ± 112.1 (84–755)
Resection Rate	
GTR, (n,%)	76 (80%)
STR, (n,%)	19 (20%)
Treatment Outcome	
Early Remission, (n,%)	63 (66.3%)
Late Remission, (n,%)	82 (86.3%)
Complications	
Diabetes insipidus, (n,%)	9 (9.4%)
Follow-up (months)* (Range)	36.1 ± 18.1 (12–59)

* Data was expressed as mean ± standard deviation.

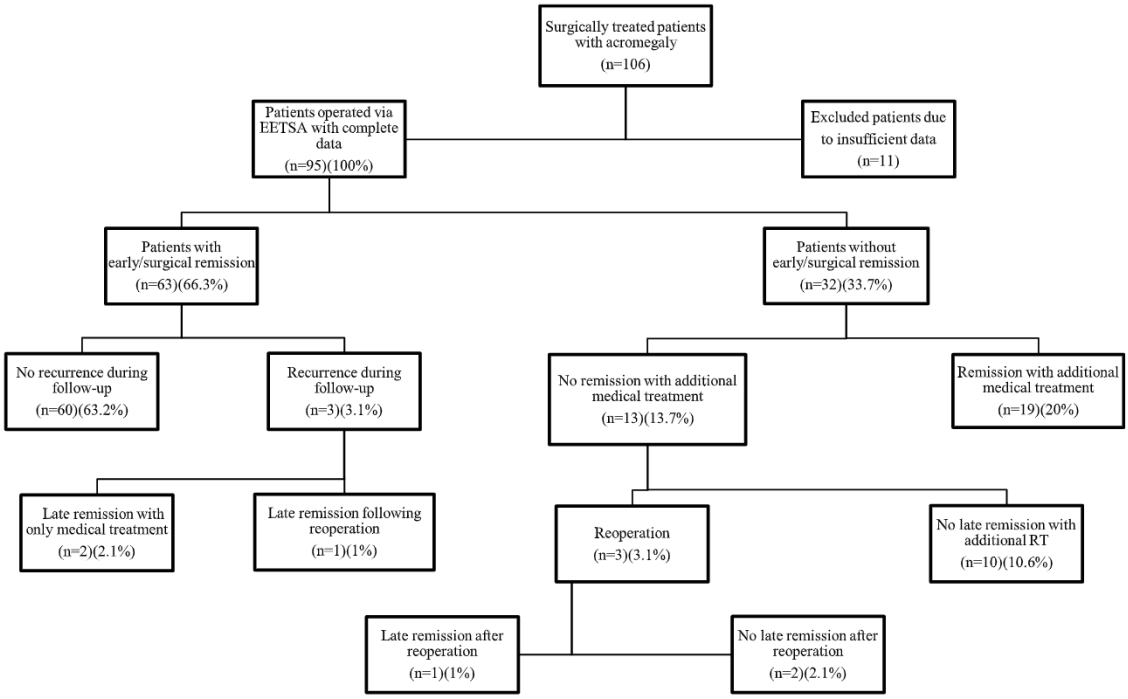
results, the preoperative GH value (odds ratio (OR) 0.953, 95% confidence interval (CI) 0.918–0.990, $p = 0.012$), and the amount of resection (OR 8.910, 95% CI 2.610–30.417, $p < 0.001$) are the most salient predictors of late remission. (Table 5).

4. Discussion

In the present study, our surgical results in newly diagnosed subsequent 106 patients with acromegaly were reviewed to analyze the surgical remission status according to clinical, radiological, microscopic, and hormonal features. The clinical and radiological outcomes, in line with endocrinologic data, were also evaluated to present the late remission rate of our acromegaly patients. Gross total resection could be achieved in four out of five patients and the surgical remission rate was 66%. The presented surgical remission rates were considerably better than those in our published initial series of acromegaly patients operated in the same clinic between 2007 and 2014 (51.5% vs 66%) [4]. This is the first follow-up study of a tertiary center demonstrating the change and improvement of surgical remission rates for acromegaly in the endoscopic era. At this point, it is legitimate to suggest that no major advances occurred in the endoscopic surgical technique and intraoperative supportive equipments within a relatively short time frame in between our two reports. The improvement in surgical remission rate in our clinic over a decade support a positive surgical volume - remission rate relationship for acromegaly in the era of endoscopic endonasal skull base approaches. We speculate that one possible factor for better surgical results may be the increasing surgical experience on EETSA.

The average age and the female/male ratio of our previous and current series were comparable (Table 6).Nearly 70% of the cases were macroadenomas in both of our series(68% in previous vs. 73% in current) and the rate of giant adenomas is also similar (12.3% vs. 12.6%). Likewise, the percentages of cases with suprasellar extension (24.7% vs. 33.6%) and CSI (%27 vs. %20) were congruent in our previous and current acromegaly series. In conclusion, no significant statistical difference was found in terms of demographic profile and radiological characteristics between two case series (Table 6). Importantly, GTR increased 18 percent (62% vs. 80%) and early remission rate improved 14 percent (51% vs. 66%) in the current study, which were both

Table 3
Treatment flow chart of acromegaly patients.



statistically significant ($p < 0.005$ and $p = 0.033$) (Table 6).

The striking significant rises in GTR and - intimately related - early remission rates in the current study clearly reflects the importance of achieving successful maturation during endoscopic endonasal surgery. In this regard, the role of the surgical learning curve in reducing the risk of major intraoperative complications during endoscopic skull base surgery has been repeatedly underlined by previous studies [18–20]. The majority of the operations in our clinic were performed by the same surgeon and it seems reasonable to assume that an increase in endoscopic surgical experience has a positive effect on the treatment outcome.

The primary goal of treatment in acromegaly is to normalize the patient's GH and IGF-1 levels to achieve remission and improve patients' clinical findings [21]. According to current treatment guidelines, transsphenoidal surgery is the widely accepted first-line treatment for acromegaly [6,12]. Medical therapy is the second-line treatment strategy for the management of acromegaly and may be implemented for patients unsuitable for surgery or those who did not achieve surgical remission. Some patients still fail to reach remission, resulting in the need for radiotherapy via SRS or conventional techniques. Therefore, a well-balanced multidisciplinary treatment concept in acromegaly should only be applied by a fully collaborative pituitary center [4,6].

The percentage of giant pituitary adenomas in our acromegaly series is relatively high, constituting 13% of patients, and the surgical remission rate is 70% when giant adenomas were excluded from the calculation. The literature review displays remission rates between 65% and 75% in the series published using 2000 criteria for remission and between 60% and 80% in the series using 2010 consensus criteria for acromegaly [21–29]. Surgical remission rates using endoscopic approaches seem to be slightly better than those of microsurgery [30–35]. Compared with the literature, similar rates of surgical remission were obtained in this study; however, our late remission rates were significantly higher than those listed in the literature (87%).

The rate of pituitary macroadenomas in other acromegaly series operated using EETSA is similar to ours (76%–79%); however, percentages of giant adenomas in those series are not specifically mentioned [23–25]. Almost all giant pituitary adenomas correspond to grade D according to the modified Hardy classification, usually extending to supra- and parasellar regions, third ventricle, sometimes extending to the brain stem. In our study, late remission of giant pituitary adenomas in patients with acromegaly is significantly lower than those of macroadenomas (58.3%). Moreover, the overall acromegaly remission rate is 92% when calculated excluding giant pituitary adenomas.

Nishioka et al. reported that remission was negatively correlated with CSI positivity in acromegaly [26]. The exact definition of CSI with an MRI-based classification remains ambiguous, since its objective endoscopic verification by the surgeon may not always be possible [36]. The reported CSI rates for acromegaly ranged from 50% to 75%, and remission rates in patients with CSI ranged from 33% to 41% [24,25,37,38]. The peroperatively verified true CSI rate in our series is only 20%. Therefore, intraoperative thorough endoscopic evaluation of the medial wall separates the compression of the cavernous sinus medial wall by the tumor from that of the true invasion. In a recent study, Cardinal et al. achieved high GTR and remission rates in a series of acromegaly patients with a relatively low percentage of CSI (13%) [29]. Compared to the literature, lower CSI rates may be one of the underlying causes of high overall remission rates in their series [29].In the current study,the remission rate is significantly higher in patients without (91%) than in those with CSI (68%) and, GTR could be achieved in nearly half of the patients (47%) with CSI.

The definition of "atypical pituitary adenoma" has been removed in the 2017 WHO Classification of Tumours of Endocrine Organs due to failure to standardize the definition and failure to predict the recurrence adequately [39,40]. Concomitantly, a high mitotic index (≥2 mitosis detected in 10× high power fields) and a positivity of other pathological microscopic markers did not significantly affect remission rates in this study.

Table 4
The relationship between early and late remission status and variables of the patients.

Variables	Total	Early remission	*p* value	Late remission	*p* value
Age			0013		0032
< 35	24	417%		708%	
35–55	56	750%		929%	
> 55	15	733%		867%	
Sex			0411		0687
Male	39	615%		846%	
Female	56	696%		875%	
Size			0045		0010
Micro	26	769%		923%	
Macro	57	667%		895%	
Giant	12	417%		583%	
Suprasellar extension			0016		0004
No	32	746%		937%	
Yes	63	500%		719%	
CSI			0051		0021
No	76	711%		908%	
Yes	19	474%		684%	
Ki-67			0308		0306
Negative	63	698%		889%	
Positive	32	594%		813%	
P53			0423		0615
Negative	50	700%		880%	
Positive	45	622%		844%	
Mitosis			0833		0490
No	73	658%		877%	
Yes	22	682%		818%	
Preoperative GH			0005		0058
<4.5	45	822%		933%	
4.5–30	42	548%		810%	
>30	8	375%		750%	
Preoperative IGF-1			0213		0414
<625	55	727%		891%	
625–825	17	647%		765%	
>825	23	522%		870%	
GH 24. h			<0001		<0001
<2.5	74	824%		973%	
≥2.5	21	9,5%		476%	
IGF-1 24. h			0005		0027
<350	49	796%		939%	
≥350	46	522%		783%	
GH 3. month			<0001		<0001
<2.5	78	782%		936%	
≥2.5	17	118%		529%	
IGF-1 3. month			<0001		0002
<350	66	833%		939%	
≥350	29	276%		690%	
GH last visit			<0001		<0001
<2.5	83	747%		95.2%	
≥2.5	12	8,3%		250%	
IGF-1 last visit			<0001		<0001
<350	83	747%		940%	
≥350	12	8,3%		333%	
Resection			<0001		<0001
Subtotal	19	263%		474%	
Total	76	763%		961%	

Table 5
Multivariate analysis of remission predictors.*

Variables	OR (95% CI, *p* value)
Preoperative GH level	0.953 (95% CI 0.918–0.990, $p = 0.012$)
GTR rate	8.910 (95% CI 2.610–30.417, $p < 0.001$)

OR: odds ratio, CI: confidence interval, GH: growth hormone, GTR: gross total resection.

* In order to avoid distortion of significance, nine patients who received the preoperative octreotide were excluded from statistical analysis.

Table 6
Comparison the demographical, hormonal and radiological features and treatment outcomes of two studies.

	Patients with acromegaly (n:103) (2007–2014)	Patients with acromegaly (n:95) (2014–2019)	*p* value
Demographical features			
Age (years)* (Range)	44.2 ± 11.5 (11–67)	43.4 ± 12.4 (16–79)	0.638
Female / Male, (*n*, %)	60 (58.3%) / 43 (41.7%)	56 (58.9%) / 39 (41.1%)	0.920
Hormonal features			
Preoperative GH (ng/mL)	15.7 ± 8.6	31.3 ± 21.2	<0.001
Preoperative IGF-1 (ng/mL)	688 ± 148	657.3 ± 333.7	0.393
Postoperative GH¥(ng/mL)	1.05 ± 0.87	1.8 ± 1.2	<0.001
Postoperative IGF-1¥(ng/mL)	232 ± 79.8	236.3 ± 112.1	0.754
Radiological features			
Size, (*n*,%)			
Microadenoma	31 (32%)	26 (27.4%)	0.196
Macroadenoma	66 (68%)	69 (72.6%)	0.486
Giant adenoma	12 (12.3%)	12 (12.6%)	0.914
Suprasellar extension (+)	24, (24.7%)	32 (33.6%)	0.146
CSI (+)	27, (27.8%)	19 (20%)	0.233
Treatment Outcome			
GTR, (*n*,%)	64 (62.1%)	76 (80%)	0.005
Early Remission, (*n*, %)	53, (51.5%)	63 (66.3%)	0.033
Late Remission, (*n*, %)	78, (75.2%)	82 (86.3%)	0.058

* Data was expressed as mean ± standard deviation.
¥ Last visit hormone values.

In this study, EETSA showed a significant decrease in GH and IGF-1 values at postoperative 48 h and 66% of patients had met early remission criteria at postoperative 3rd month. According to our multivariate analysis, preoperative GH values and GTR ratio were found as the best remission predictors. Similarly, Jane et al. reported that preoperative hormone (GH and IGF-1) values were predictors of remission [25]. Also, Starke et al. stated that lower preoperative GH levels and Knosp grades provides the best preoperative predictors of remission [32].

Classical results of the postoperative CSF leak rate in EETSA of pituitary macroadenomas are approximately 3% [41–43]. As a clinic that performed over 1100 endoscopic endonasal skull base surgical procedures in more than a decade, our postoperative CSF leak rate in pituitary pathologies is <1%. No patients in this series had postoperative CSF leak, which can be attributed to the generous use of vascularized septal flap in patients who need them, such as large and giant pituitary adenomas.

The commendable increase was seen on remission outcomes of patients with acromegaly treated in the same clinic over time. In our previous study [4], surgical remission rate was 51.5%, which improved to 66% in this study. Furthermore, late remission rate improved from 75% to 86%. Overall, late remission rate for acromegaly is 81% in 198 patients who were operated in our clinic during the 11-year period. The surgical experience plays a major role in developing a safe and accurate way to effectively perform tumor resection during endoscopic pituitary surgery, including surgical decisions on the extent of dural opening and finding/maintaining an extracapsular plane around the tumor. Thus, obtaining the best surgical outcomes and improving the remission rates predominantly depend on the surgical experience. More than 90% of the procedures in the present case series were performed by one of the senior authors (N.T.), and the same surgeon actively participated in surgeries of all remaining cases. So, our data suggests that an increasing

caseload could also improve the surgical outcomes in acromegaly.

One of the limitations in this study was the fact that 9 patients were treated with octreotide to reduce disease-related comorbidities during the preoperative period. Because of the late decrease in GH and IGF-1 levels due to the octreotide effect, postoperative remission status was decided using GH and IGF-1 levels at 6 months instead of 3 months postoperatively. Although this study has no too short-term follow-up data, further studies should be undertaken for the long-term remission results.

5. Conclusion

EETSA is a safe and effective method for the treatment of acromegaly. Increasing the surgical experience plays a critical role in achieving higher remission rates over time. Awareness of the predictive factors for long term remission may prove helpful to the surgeon in planning the treatment, and the amount of resection along with the preoperative GH values are salient remission predictors.

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CRediT authorship contribution statement

Seckin Aydin: Conceptualization, Methodology, Data curation, Writing - original draft, Writing - review & editing. **Baris Ozoner:** Conceptualization, Data curation, Formal analysis. **Serdar Sahin:** Methodology, Data curation. **Orkhan Alizada:** Methodology, Writing - original draft. **Nil Comunoglu:** Writing - review & editing, Validation. **Buge Oz:** Writing - review & editing, Validation. **Nurperi Gazioglu:** Supervision, Validation. **Pinar Kadioglu:** Supervision, Validation. **Necmettin Tanriover:** Conceptualization, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

All authors have no potential conflicts of interest to disclose.

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