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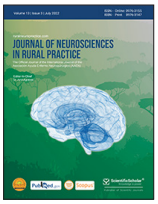

Original Article

Outcomes in pituitary adenoma causing acromegaly following endoscopic endonasal transsphenoidal surgery

Rajesh Chhabra[1], Ashwani Kumar[2], R. S. Virk[3], Pinaki Dutta[4], Chirag Ahuja[5], Manju Mohanty[1], Sivashanmugam Dhandapani[1]

[1]Department of Neurosurgery, Post Graduate Institute of Medical Education and Research, [2]Department of Neurosurgery, Government Medical College and Hospital, Departments of [3]Otorhinolaryngology, [4]Endocrinology and [5]Neuroradiology, Post Graduate Institute of Medical Education and Research, Chandigarh, India.

ABSTRACT

Objectives: The objectives of the study were to study the analysis of outcomes after endoscopic endonasal transsphenoidal surgery (EETSS) in acromegaly in terms of surgical complications, clinical improvement, endocrinological remission, achievement of prognostically critical growth hormone (GH) level, and requirement of additional treatment.

Materials and Methods: The study included 28 acromegaly patients, who underwent EETSS. A 2010 consensus criterion was used for defining remission. Assessment of prognostically critical GH level (random value <2.5 ng/ml), the extent of resection and additional treatment, was done at post-operative week (POW) 12.

Results: All adenomas were macroadenomas; with a mean volume of 16.34 cm^3 (range, 0.4–99 cm^3). Most adenomas had high-grade extensions. Most common suprasellar, infrasellar, anterior, and posterior extension grades were 3 (n = 13), 1 (n = 16), 1 (n = 14), and 0 (n = 20), respectively. Knosp Grade 3 was common on both sides (right, n = 9 and left, n = 8). One patient had already been operated on with EETSS, 1.5 years back from current surgery. Sixteen patients were on hormonal support, preoperatively. Four patients died during follow-up. Post-operative common complications were diabetes insipidus (DI, n = 18), cerebrospinal fluid rhinorrhea (n = 10), surgical site hematoma (n = 3), meningitis (n = 3), hydrocephalus (n = 2), and syndrome of inappropriate antidiuretic hormone (n = 1). The mean hospital stay was 11.62 days and 12.17 months were the mean follow-up period. At 12 POW, no improvement was seen in body enlargement and visual complaints, but all other complaints improved significantly except perspiration. Adenomas were decreased in all extensions except posterior and mean adenoma volume was reduced from 16.34 cm^3 to 2.92 cm^3 after surgery. Sub-total resection (STR, n = 10), near-total resection (NTR, n = 7), gross-total resection (GTR, n = 5), and partial resection (PR, n = 2) were achieved. Endocrinological remission and prognostically critical GH levels were attained in 29.17% (n = 7) and 66.67% (n = 16), respectively. NTR, GTR, STR, and PR were associated with 57.14%, 40%, 10%, and 0% endocrinological remission, respectively. Additional treatment was required in a total of 17 patients, three in GTR, nine in STR, three in NTR, and two in PR. Ten were treated with Gamma Knife radiosurgery along with medical treatment and seven with medical treatment alone.

Conclusion: A successful EETSS can reduce adenoma volume to achieve clinical improvement, endocrinologic remission, and prognostically critical GH level with some complications related to surgery. Pre-operative larger volume and higher extension grades affect these outcomes adversely.

Keywords: Pituitary adenoma, Acromegaly, Endoscopic endonasal transsphenoidal surgery

INTRODUCTION

Acromegaly is a persistent progressive multisystem disorder, most commonly due to pituitary adenoma, with mortality double that of the general population.[1,2] Only <5% of cases arise due to other conditions such as growth hormone (GH)-releasing hormone-secreting hypothalamic or neuroendocrine tumor, ectopic GH-secreting tumors, familial acromegaly, and multiple endocrine neoplasia type 1.[3-6] As acromegaly is a clinical syndrome, a patient may present at any stage of progression.

Early institution of treatment leads to decreased disability and mortality risks in acromegaly patients,[7] as some morbidities can become irreversible with disease progression. Normalization of GH and insulin-like growth factor-1 (IGF-1) levels by reducing tumor volume, leading to symptom regression and management of acromegaly complications, is the primary goals of acromegaly treatment.[8] All patients should be managed at a tertiary care center as acromegaly is a multisystem disorder requiring a multidisciplinary approach.[9,10]

***Corresponding author:** Ashwani Kumar, Department of Neurosurgery, Government Medical College and Hospital, Chandigarh, India.
gautamashwani6@gmail.com

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Surgical adenomectomy, medical management, and stereotactic radiosurgery or external beam radiotherapy (EBRT) can be done to achieve disease remission. Medical treatment is mainly used to reduce surgical risk from comorbidities, as primary treatment in patients with cavernous sinus invasion without chiasmal compression that cannot be resected completely or in poor surgical candidates.[11] Stereotactic radiosurgery or EBRT is used only when other treatment options are impossible in an acromegaly patient like absolute contraindication of surgery or a patient refuses surgery with failure or contraindication or intolerance of medical treatment.[11] Both medical and stereotactic radiosurgery can be used for residual disease.

Surgical adenomectomy has become the first line of treatment.[12-14] Endoscopic transsphenoidal route is the preferred route as a wide-angled panoramic view is helpful to reach supra and parasellar lesions.[1,15-19] Although this route has benefits of better vision and minimal invasion, many patient-related and procedure-related factors affect post-operative outcomes. As gel foam and fat used for packaging may mimic adenoma on contrast-enhanced magnetic resonance imaging (CEMRI), imaging in the post-operative period to assess for residual adenoma should be done at least 12 weeks later surgical procedure to permit the disappearance of gel foam and fat packing.[20] In certain patients, the visual field deficits keep on improving as long as 1 year after surgery.[21] IGF-1 levels relate with comorbidities better than glucose-suppressed GH levels, thus, more predictive than nadir GH for anticipating insulin sensitivity and symptom score after surgery.[22,23]

The data concerning the outcomes endoscopic endonasal transsphenoidal surgery (EETSS) among Indian patients for GH-secreting pituitary adenomas are sparse. We conducted this study to assess post-operative outcomes of EETSS for pituitary adenoma causing acromegaly considering clinical improvement, endocrinological remission, and achievement of prognostically GH level as primary endpoints.

MATERIALS AND METHODS

This prospective, retrospective, and non-randomized study was conducted at a tertiary care hospital. Ethical committee clearance was taken. The diagnosis was made based on the following diagnostic criteria: Typical physical appearance or presence of two or more comorbidities including fatigue, recent-onset diabetes mellitus (DM), arthralgias, carpal tunnel syndrome, recent-onset or intractable hypertension, cardiac morbidity, sleep apnea syndrome, visual disturbances, excessive perspiration, colon polyposis, headache and increasing jaw malocclusion; elevated or equivocal IGF-1 considering age and sex, insufficient GH suppression following documented hyperglycemia during oral glucose load (i.e., absence of lowest serum GH level <1 ng/ml during every 30 min assay of GH within 2 h of 75 g of glucose load after documenting hyperglycemia), and presence of pituitary adenoma on CEMRI.[8] A total of 28 patients operated on between January 2016 and August 2019 were included: Fourteen patients were assessed retrospectively and 14 prospectively. The inclusion criterion was patients with pituitary adenoma causing acromegaly who underwent EETSS by a surgical team consisting of the same neurosurgeon and otorhinolaryngologist, in the department of neurosurgery. Exclusion criteria included patients who fulfilled the diagnostic criteria, but, who underwent some other surgery or medical management, refused to give consent, and who was found unfit for general anesthesia. A well-explained written consent was taken from all patients. Data were collected from hospital records and outpatient department follow-ups for retrospectively studied patients. Patients were managed routinely as per the clinical indication.

The same hormonal assay was maintained throughout the study. Endocrinological remission was considered if the patient had <1 ng/ml random GH and age/sex-adjusted normalization of IGF-1 level (2010 consensus criteria).[24] Patients, who failed to achieve remission, were evaluated for prognostically critical GH level, that is, <2.5 ng/ml, at 12 weeks; attainment of which is the most important parameter associated with reduced mortality rates.[25]

Pre-operative workup included history taking and complete clinical assessment. Routine pre-operative investigations, as per hospital protocols, were done. A hormonal analysis of the patients considering pituitary functions was done. Ear, nose, and throat (ENT) examination for the status of nasal turbinates, nasal mucosa, size of the adenoid tissue, and sinonasal polyp was done to assess the feasibility of the endonasal route. Visual acuity and visual field evaluation were done. Radiological investigations including magnetic resonance imaging (MRI) sella and non-contrast computed tomography (NCCT) sella and paranasal sinuses were done. Adenomas were defined according to their size (microadenoma: <1 cm maximum dimension and macroadenoma: ≥1 cm maximum dimension) and SIPAP (MRI-based classification system for pituitary adenomas) classification[26] (including suprasellar: 0–4, infrasellar: 0–2, parasellar: Right and left Knosp's Grades 0–4, anterior: 0–1, and posterior: 0–1).[27]

Intraoperatively, middle turbinate was preserved and lateralized, the posterior septum was excised, no vascularized flap was raised, and no neuronavigation was used. The intraoperative assessment was done for variables including the extension of the tumor, ease of resection, and arachnoid violation. Arachnoid was breached in 17 patients and sellar floor reconstruction was done with fat and fascia (harvested from the thigh) and fibrin glue.

In patients in whom arachnoid was violated, the sellar floor was reconstructed using autologous tissue (fat and fascia harvested from the thigh) and fibrin glue.

Routine post-operative neurosurgical evaluation and management of complications were done. The biochemical and hormonal assessment was done on post-operative day (POD) 1 and post-operative week (POW) 1, 6, 12, and 24. Visual acuity and visual field assessment were also done at 12-week postoperatively. CEMRI was done to assess resection at POW 12 and defined as gross-total resection (GTR), near-total resection (NTR), sub-total resection (STR), and partial resection (PR), as per Edson *et al*. (2016).[28]

Based on remission and CEMRI findings, patients were also assessed at POW 12 for the need for additional treatment. Additional treatment was given as per indication and the patient's decision.

The outcome measures were clinical improvement, surgical complications, the extent of resection, achievement of endocrinological remission and prognostically critical GH level, and requirement of additional treatment.

Statistical analysis

The final data were compiled and presented as number (*n*) and percentage (%) for categorical variables and "mean with standard deviation (mean ± SD) and median with interquartile range (25^{th}–75^{th} percentiles)" for quantitative variables. Kolmogorov–Smirnov test was used to determine the data normality. Quantitative variables were assessed using t-test (independent and paired) and Wilcoxon signed-rank test. Chi-square test/Fisher's exact test and McNemar's test were used to analyze qualitative data. $P \leq 0.05$ was treated as statistically significant. The complete statistical analysis was done using "Statistical Package for the Social Sciences software, IBM manufacturer, Chicago, USA, version 21.0."

RESULTS

Pre-operative variables

There were eight women and 20 men and 41.79 years was the mean age (range, 19–62 years). Among 28 patients, five patients were smokers, 11 patients were hypertensive, 10 patients had DM, and three patients were suffering from some cardiac disease. Mean body mass index (BMI) was 26.82 kg/m^2 (range; 20.8–38.1), with 17 patients having high BMI. The patients presented with the mean duration of symptoms of 45.86 months (range, 2 months–16 years) and body enlargement (*n* = 24), hoarseness of voice (22 patients), headache (*n* = 21), visual complaints (*n* = 14), sleep-related problems (*n* = 12), joint pain (*n* = 8), perspiration (*n* = 5), secondary amenorrhea (*n* = 4), oligomenorrhea (*n* = 2), galactorrhea (*n* = 2), and skin pigmentation (*n* = 2) were common complaints. All patients had multiple complaints. One patient was bilaterally blind and one patient had unilateral blindness. Visual field defect was present as bitemporal hemianopia in 12 patients. All patients had nasal mucosa and turbinates hypertrophy. The nasal polyp was present in one patient and adenoid tissue hypertrophy was present in three patients. Sixteen patients were on hormonal support; 13 were on cortisol, seven were on thyroxine, and four were on insulin support, and

Table 1: Pre-operative variables*.

Age (years)	
Mean	41.79
Range	19–62
Sex (M/F)	8/20
Duration of symptoms (months)	
Mean	45.86
Range	2–180
Smoker (*n*†)	5
Hypertensive (*n*†)	11
DM (*n*†)	10
Cardiac morbidity (*n*†)	3
ENT examination (*n*†)	
Nasal mucosa hypertrophy	28
Nasal turbinate hypertrophy	28
Adenoid hypertrophy	3
Nasal polyp	1
Prior treatment (*n*†)	
No treatment	27
Medical treatment	0
Surgery	1
Radiation treatment	0

*Total patients – 28, †*n*: No. of patients, ENT: Ear, nose, and throat

Table 2: Outcomes*.

Resection (*n*†)	
GTR	5
NTR	7
STR	10
PR	2
Remission (*n*†)	7
Prognostically critical GH (*n*†)	16
Clinical improvement (in terms of number of patients)	All except body enlargement, visual complaints, and perspiration
Hospital stay (days)	
Mean	11.62
Range	6–21
Duration of follow-up (months)	
Mean	12.17
Range	2–32
Additional treatment (*n*†)	
No treatment	7
Medical treatment only	17
Surgery	0
Gamma Knife radiosurgery	10

*Total patients – 24, †*n*: Number of patients, GTR: Gross-total resection, NTR: Near-total resection, STR: Sub-total resection, PR: Partial resection, GH: Growth hormone

among them, seven patients were on combined hormonal support. One patient received prior treatment (EETSS) for adenoma, around 1.5 years back from the current surgery [Table 1].

Mean GH level was 32.83 ng/ml (range, 5.72–89.8 ng/ml) and IGF-1 levels were raised in all patients compared to normal values according to age and sex. All adenomas were macroadenomas with mean volume of 16.34 cm^3 (range, 0.42–99 cm^3). Most adenomas had high-grade extensions. The most common suprasellar, infrasellar, anterior, and posterior extension grades were 3 (n = 13), 1 (n = 16), 1 (n = 14), and 0 (n = 20), respectively. Knosp Grade 3 was common on both sides (right, n = 9 and left, n = 8). One patient had obstructive hydrocephalus. All patients had sellar-type sphenoid sinus and there was no calcification of adenoma on pre-operative NCCT.

Table 3: Complications*.

CSF rhinorrhea ($n^{\dagger}$)	10
Operative site hematoma ($n^{\dagger}$)	3
Hydrocephalus ($n^{\dagger}$)	2
Infection ($n^{\dagger}$)	3
DI ($n^{\dagger}$)	
Transient	17
Permanent	1
SIADH ($n^{\dagger}$)	1
Mortality ($n^{\dagger}$)	4

*Total patients – 28, $^{\dagger}n$: No. of patients, CSF: Cerebrospinal fluid, DI: Diabetes insipidus

Outcomes

Mean duration of hospital stay was 11.62 days (6–21 days). The mean follow-up time was 12.17 months (2–32 months) [Table 2].

Mortality

Four patients died during the follow-up period and their death was the cause of attrition. The individual case findings and causes of death are shown in Supplementary file 1. These four patients were excluded from paired data analysis as their post-operative data were not available.

Complications and their management

The most common complication was diabetes insipidus (DI, n = 18), transient in 17, and became permanent in one patient requiring long-term Pitressin support. The next common complication was cerebrospinal fluid (CSF) rhinorrhea (n = 10) for which diversion (lumbar drain) was required in one patient. A total of three CSF diversions were done, the other two CSF diversions by ventriculoperitoneal shunt (VP shunt) were performed for the late development of meningitis-induced hydrocephalus. Another patient who developed meningitis was managed with antibiotics. Three patients developed operative site hematoma, which required observation only. Only one patient developed syndrome of inappropriate antidiuretic hormone (SIADH) and was managed [Table 3].

Table 4: Clinical improvement*†.

Variable	Pre-operative	Post-operative (12 weeks)	Change (S/NS)
BMI (kg/m^2)			
Mean	26.82	24.68	S
Range	20.8–38.1	19.5–31.1	
No. of patients with high BMI ($n^{\ddagger}$)	17	12	NS
Symptoms ($n^{\ddagger}$)			
Headache	21	2	S
Visual complaints	14	14	NS
Joint pain	8	0	S
Sleep-related problems	12	1	S
Body enlargement	24	24	NS
Perspiration	5	1	NS
Hoarseness of voice	22	1	S
Others (menstrual disturbances, skin pigmentation, and galactorrhea)	10	4	S
Visual field ($n^{\ddagger}$)			
Normal	10	10	NS
Bitemporal hemianopia	12	12	NS
Blindness			
Unilateral	1	1	NS
Bilateral	1	1	NS

*Total patients – 24, †At POW 12, $^{\ddagger}n$: No. of patients, BMI: Body mass index

Table 5: Endocrinological and radiological changes*.

Variable	Pre-operative	Post-operative (12 weeks)	Change (S/NS)
GH (ng/ml)			
Mean	32.83	3.68	S
Range	5.72–89.8	0.1–11.8	
Adenoma volume			
Mean	16.34	2.92	S
Range	0.42–99	0–30.9	
Hydrocephalus ($n^{\dagger}$)	1	1	NS
Extension ($n^{\dagger}$)			
Suprasellar			
Total	24	12	S
Grade			
0	0	12	S
1	1	10	S
2	9	2	S
3	13	0	S
4	1	0	S
Infrasellar			
Total	17	1	S
Grade			
0	7	23	S
1	16	1	S
2	1	0	S
Anterior			
Total	14	0	S
Grade			
0	10	24	S
1	14	0	S
Posterior			
Total	4	0	NS
Grade			
0	20	24	NS
1	4	0	NS
Knosp parasellar			
Total			
Rt	23	14	S
Lt	22	12	S
Grade			
0			
Rt	1	10	S
Lt	2	12	S
1			
Rt	5	8	S
Lt	6	4	S
2			
Rt	6	3	S
Lt	6	4	S
3			
Rt	9	1	S
Lt	8	2	S
4			
Rt	3	2	S
Lt	2	2	S

*Total patients – 24, $^{\dagger}n$: No. of patients, GH: Growth hormone

Table 6: Types of resection*.

Outcome	GTR	NTR	STR	PR
Patients ($n^{\dagger}$)	5	7	10	2
Duration of hospital stay (days)				
Mean	9.6	11.57	11.4	10.5
Range				
Endocrine remission ($n^{\dagger}$)	2	4	1	0
Prognostically critical GH levels achievement ($n^{\dagger}$)	4	6	6	0
Additional treatment ($n^{\dagger}$)				
No treatment	2	4	1	0
Medical treatment only	3	3	9	2
Surgery	0	0	0	0
Gamma Knife radiosurgery	0	2	6	2

*Total patients – 24, $^{\dagger}n$: No. of patients, GTR: Gross-total resection, NTR: Near-total resection, STR: Sub-total resection, PR: Partial resection, GH: Growth hormone

Clinical improvement

This was assessed at 3-month follow-up. Visual complaint and body enlargement remained persistent in all patients and joint pain improved in all patients. Headache (n = 2), sleep-related problems (n = 1), perspiration (n = 1), hoarseness of voice (n = 1), and other complaints including menstrual problems, galactorrhea, and skin pigmentation (n = 4) were persistent. Improvements in all symptoms except perspiration were statistically significant. Although all patients had complaints, only three patients were with multiple complaints. Mean BMI was decreased to 24.68 kg/m^2, ranging from 19.5 to 31.1, with only 12 patients having high BMI. This post-operative change in mean BMI was statistically significant, but the number of patients with high BMI did not change significantly. Visual field defects did not improve, but an increase in defects was not seen [Table 4].

Twenty-two patients were on hormonal support, including cortisol (n = 22), thyroxine (n = 13), and insulin (n = 4) support, and out of 22 total, 14 patients were on combined hormonal support. Hypocortisolism developed in a significant number of patients. One patient, who was taking insulin preoperatively, did not need insulin after resection and one patient who was not on insulin preoperatively, needed insulin after resection.

Endocrine and radiological evaluation

Evaluation was done at POW 12. Adenoma volume was reduced to 2.92 cm^3 (range, 0–30.9 cm^3) and 12 were macroadenoma. The mean of decrease in volumes was 13.42 cm^3 ranging from 0.22 to 68.1 cm^3. This reduction in adenoma volume was statistically significant. All extensions were decreased significantly except posterior. The most common suprasellar extension was Grade 0 (n = 12) followed by Grade 1 (n = 10). Twenty-three patients

had Grade 0 infrasellar extension postoperatively. No patient had anterior and posterior extension after surgical resection. Grade 0 extension was the most common type on both right (n = 10) and left (n = 12) sides. Mean GH level was 3.68 ng/ml (range, 0.1–11.8 ng/ml) at POW 12 and mean IGF-1 levels were normal in all patients as per age/sex [Table 5].

Out of 24 patients in whom we could assess resection status at 12 weeks by CEMRI, we achieved STR (n = 10) in the maximum number of patients followed by NTR (n = 7). GTR was achieved in five patients and PR in two patients. Endocrinological remission was achieved in a total of 29.17% of patients (n = 7). All patients who achieved remission had IGF-1 levels normal as per their age/sex. About 40% of patients with GTR (n = 2), 57.14% with NTR (n = 4), 10% with STR (n = 1), and no patient with PR fulfilled the criteria of endocrinological remission. The highest remission rate was observed with NTR. Out of 17 patients who could not achieve remission, nine patients achieved prognostically critical GH levels [Table 6].

Additional treatment

Additional treatment was needed in 17 patients. Three patients with GTR who could not achieve remission were given medical treatment. Two PR, nine STR, and thee NTR patients needed additional treatment. All refused repeat surgery, but 10 patients who gave consent for Gamma Knife radiosurgery were treated with the same along with medical treatment. The remaining four patients who did not give consent for surgery and Gamma Knife radiosurgery both were given medical treatment only. Out of 17 patients, 10 were treated with Gamma Knife radiosurgery along with medical treatment and seven were treated with medical treatment alone [Table 6].

DISCUSSION

Worldwide literature supports that endoscopic transsphenoidal surgery has a good safety profile with <2% morbidity and <0.1% mortality which can be attributed to almost complete resection of the tumor. In this study, we have attempted

Table 7: Comparison with available literature

Parameter		Hofstetter *et al.* (2010)[29]	Jane *et al.* (2011)[30]	Shin *et al.* (2012)[31]	Hazer *et al.* (2013)[32]	Fathalla *et al.* (2014)[33]	Yildirim *et al.* (2014)[34]	Anik *et al.* (2017)[35]	Babu *et al.* (2017)[36]	Taghvaei *et al.* (2018)[37]	Current study
Type of study†		P	R	R	R	P	R	R	R	P	B
Duration of study (years)		6.3	5.4	12.3	6.3	NA	4.3	18	8	3.3	3.5
Number of patients		24	60	53	214	20	56	401	58	68	28
Follow-up period (months)		23	21.84	30	33.3	11	18	13-182	64	20.97	12.17
Surgical team‡		M	M	M	S	S	M	M	S	M	S
Male: female ratio		1.18	1.22	1.3	0.98	0.82	0.44	0.89	1	1.13	0.4
Mean age (years)		50.7	48	43.7	41.9	42	42.3	42.04	48.6	39.35	41.79
Adenoma type (macro/ micro)		4/19	46/14	45/6	163.51	18/2	51/5	294/107	37/21	52/16	28/0
Pre-operative Knosp grade	0-2 (%)	NA	75	71.53	NA	30	67.86	78.55	81.03	85.29	32.14
	3-4 (%)	NA	25	28.5	NA	70	32.14	21.45	18.97	14.70	67.86
Mean hospital stay (days)		NA	2.32	3.6	NA	NA	NA	NA	2.24	NA	11.62
Remission rate (%)		46	69.7	50.9	62.6	35	66.1	68.1	69	63.2	29.17
Prognostically critical GH achievement rate (%)		NA	NA	62.3	75.7	NA	74.6	79.1	NA	67.61	66.67
Mortality rate (%)		0	0	0	0	0	0	NA	0	0	14.29
Type of resection (n*/%)	GTR	17/70.83	NA	42/79.24	NA	10/50	NA	NA	NA	61/89.71	5/20.83
	NTR	0	NA	11/20.75	NA	0	NA	NA	NA	7/10.3	7/29.17
	STR	7/29.17	NA	0	NA	10/50	NA	NA	NA	0	10/41.47
	PR	0	NA	0	NA	0	NA	NA	NA	0	2/8.33
Additional treatment (surgery and radiosurgery)(n*)		5	11	12	NA	6	19	19	12	NA	10

*n: No of patients, †Type of study: P- prospective, R- retrospective, B- both, ‡Surgical team: S- single, M- multiple, GTR: Gross-total resection, NTR: Near-total resection, STR: Sub-total resection, PR: Partial resection, GH: Growth hormone

to assess outcomes following EETSS in pituitary adenoma causing acromegaly. The study included 28 patients operated on by a single surgical team. Resection of the tumor and complete cure with better survival remains the primary objective of a surgeon while dealing with cases of pituitary adenoma. For achieving this with minimal complications, the surgeon's experience is an important factor, especially in acromegaly patients as compared to other pituitary adenomas. This is because acromegaly-associated pituitary adenoma has the unique feature of tumor behavior and vascular and bone remodeling.[29] Considering this, we included all patients operated on by a single surgical team in our institute. Both neurosurgeons and otorhinolaryngologist were senior experienced surgeons in this field. Although this eliminated the confounding factor of surgeon's experience but constrained the inclusion of patients in our study leading to small sample size. Moreover, in the prospective group, four patients died postoperatively which led to the limitation of their post-operative data for comparison with pre-operative variables, leading to further limitation of paired comparison of data.

We compared our study with similar studies; available in the literature, which used the same criteria to define remission [Table 7].[30-37] All studies which included patients operated by a single surgical team could study fewer patients like our study except Hazer *et al*. (2013)[29] study which included 214 patients as this was a longer duration study of around 6.3 years. The most common resection in our study was STR, while in others, it was GTR. The remission rate in these studies ranged from 35% to 69.5%, but the remission rate in our study was 29.17%, much lower than others. This may be due to more percentage of patients with Knosp Grades 3 and 4 as compared with other studies, as we can see in Fathalla *et al*. (2014)[33] study, which had more number of patients (70%) with higher Knosp grades, also had a lower remission rate of 35%. It means that different characteristics of adenoma in our study were responsible for the lower remission rate. Prognostically critical GH achievement rates ranged from 62.35 to 79.1%, while in our study, it was 66.67%, comparable to others. The mortality rate in our study was 14.29 and in others, no mortality occurred. Some degree of post-operative hypopituitarism was observed in all studies including ours. The longest mean duration of hospital stay 11.62 days was seen in our study.

CONCLUSION

A successful EETSS can reduce adenoma volume to achieve endocrinologic remission with some surgery-related complications. Even if remission and GTR are not achieved after surgery, achievement of prognostically critical GH level leads to decreased disease-related mortality. The relief from the mass effects of adenoma and decreased GH from the pre-operative level also leads to significant clinical improvement after surgery. Furthermore, as seen in our study, pre-operative larger volume and high-grade tumor extensions affect post-operative remission rates adversely.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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SUPPLEMENTARY FILE 1

Case 1

A 48-year-old female patient died 2 months after surgery. During the hospital stay, she developed transient DI which was managed. She also developed the right middle cerebral artery (MCA) and left anterior cerebral artery (ACA) territory infarct on POD 6. She was discharged from our hospital with Glasgow Outcome Score (GOS) 3, after 21 days of surgery. She did not come for any follow-up visits. Through telephonic inquiry, the authors came to know that she died at home due to some respiratory problems.

Case 2

Another mortality was of a 62-year-old female patient on POD-10 during the hospital stay. She developed transient DI and transient CSF rhinorrhea during the post-operative period. On POD-7, she developed massive hematemesis followed by hypotension and deteriorated to E1VTM1 from E4V5M6. The source of bleeding could not be traced in the upper gastrointestinal endoscopy and contrast-enhanced computed tomography (CECT) abdomen and the patient succumbed to death.

Case 3

Death of another 35-year-old female patient was due to sudden cardiac arrest on POD-0.

Case 4

The last mortality was of a 26-year-old female patient, around 2.5 months after surgery. She developed transient DI and transient CSF rhinorrhea during her hospital stay. She was discharged on POD-17 with GOS-5. She did not come for routine follow-up. After around 2 months of surgery, she was admitted to the emergency with Glasgow Coma Score (GCS) E3V4M6 and raised intracranial pressure (ICP) features. Meningitis along with hydrocephalus was diagnosed on workup. Antibiotics were started immediately and the ventriculoperitoneal (VP) shunt was done after 2 weeks. She deteriorated to E1VTM1 on POD-3 of shunt surgery and resuscitation was done. NCCT showed dense intraventricular hemorrhage (IVH). External ventricular drain (EVD) was inserted. Computed tomography (CT) angiography of cerebral vessels showed a ruptured basilar top aneurysm. The patient could not be revived and died on POD-7 of shunt surgery.

Autopsy of the patients who died in hospital could not be done as their attendants refused. Patients who died were excluded from paired data analysis as their post-operative data were not available.