ABSTRACT

Background: Endoscopic transsphenoidal excision has revolutionized the surgical management of pituitary macroadenoma. There have been several retrospective studies on the factors determining the visual outcome after surgical excision of pituitary adenoma, but very few prospective studies were published in this context. This is a prospective study of the factors predicting visual outcome following endoscopic transsphenoidal excision of pituitary adenoma. Various factors like age, duration of visual symptoms, the volume of the tumour, suprasellar extension, parasellar extension, type of adenoma, pituitary apoplexy, completion of excision, fundoscopic changes, and preoperative visual deficits were studied.

Methods: Single centre prospective observational study done between November 2016 to December 2018. Thirty patients with pituitary macroadenoma who underwent trans nasal endoscopic excision were studied with preoperative and postoperative visual impairment scores (VIS). The visual outcome was categorized as a good outcome if more than 5% improvement in VIS and as worse otherwise. Various predictors that may influence the outcome were statistically compared.

Results: 83.3% of patients (n=25) showed improvement in their vision at 6months follow-ups. Overall visual outcome (considering both parameters, visual acuity and visual field together) was dependent on suprasellar extension (P=0.01), completion of excision (P=0.004), and primary optic atrophy (P=0.018). On subgroup analysis, recovery in visual acuity was significantly determined by the preoperative tumour volume (P=0.041), suprasellar extension (P=0.006), completion of excision (P=0.003), and primary optic atrophy (P=0.013). The improvement in the field of vision depended on the severity of preoperative field defects (P=0.04) and completion of excision (P=0.01). Conclusions: The factors predicting the early visual outcome were the suprasellar extension, completion of excision, preoperative field deficits, and primary optic atrophy. This study highlights the importance of early and proper intervention in pituitary adenomas managed surgically to procure the desired result.

KEYWORDS Pituitary neoplasms, Suprasellar extension, Transsphenoidal approach, Visual outcome, Endoscopic surgery
determining the early visual outcome is important as it gives the operating surgeon a better understanding of the expected outcome and can counsel the patient appropriately. Because of these reasons, this study has a high significance in this era of medicolegal uncertainties. Most of the published series on this context are retrospective studies. In contrast, we have studied the visual outcome of 60 eyes in patients with pituitary adenoma with suprasellar extension prospectively, which adds to the power of this study[5].

Methods

Study Design
Single centre prospective observational study of patients who underwent endoscopic transnasal transsphenoidal excision (TEE) of pituitary adenoma between November 2016 and December 2018 in the Department of Neurosurgery, Government Medical College Kozhikode, Kerala, India. The inclusion criteria were as follows: 1. all patients with radiologically proven pituitary adenoma causing visual impairment who were operated on with TEE irrespective of the suprasellar and parasellar extensions. 2. Postoperatively histopathological confirmation of pituitary adenoma. All patients not fulfilling the inclusion criteria and losing the 6 months clinical follow-up were excluded. Also, other pathologies like diabetic retinopathy and hypertensive retinopathy were excluded from the patients in whom vision was affected. The institutional review board of Government medical college Kozhikode approved the study. All patients underwent detailed neurological, ophthalmological, endocrinological, and radiological assessments before and after surgery.

Ophthalmological Assessment
Ophthalmological evaluation, including the visual acuity, visual field charting, and the fundus examination of each patient, was evaluated by the Department of Ophthalmology, Government Medical College Kozhikode. Visual acuity was measured using Snellen’s chart at 6 meters. The visual field was assessed using Humphrey’s automated perimetry. Fundoscopic examinations of all patients were done to rule out optic atrophy. The acuity and the field of vision were scored by the guidelines of the German ophthalmological society, and a visual impairment score (VIS) was calculated for each subject. The VIS score varied from ‘0’ to ‘100’. In addition, pre-operative VIS for visual acuity (PreVISVA) as well as the preoperative VIS for the visual field (PreVISVF) were separately noted.

Endocrinological Assessment
Prolactin, growth hormone levels, insulin-like growth factor 1, thyroid-stimulating hormone, free T3, free T4, early morning serum cortisol, follicle-stimulating hormone, and luteinizing hormone were assessed preoperatively and after surgery, at discharge from the hospital, and three months follow up.

Neuroradiological Assessment
All the patients were evaluated with 1.5T magnetic resonance imaging (MRI) brain (plain and contrast) pre-operatively and 3 months post-surgery. Diameters of the lesion were measured in craniocaudal (CC), anteroposterior (AP), and transverse (TR) dimensions and the volume was calculated using the De Chiro and Nelson formula \[\text{volume} = (CC \times AP \times TR \times \pi / 6)\]. In the craniocaudal direction, the suprasellar extension (SSE) was measured. A line was drawn on the midsagittal image from the tuberculum sellae to the upper end of the dorsum sellae to define the sellar roof. The maximal SSE perpendicular to that line was measured on the mid-sagittal section. Also, the parasellar extension into the cavernous sinus was noted. Contrast-enhanced CT of paranasal sinuses was also taken for preoperative planning. MRI brain was repeated at 3 months follow-up to assess the completion of excision. Completion of excision was graded as near-total excision if the contrast-enhancing tumour residual volume is less than 15%, partial excision if the residual volume is 15-50% and decompression if it is more than 50%.

Surgical Approach
The senior authors performed standard binaural trans-sphenoidal endoscopic resection of pituitary adenoma. We used zero-degree as well as 30-degree endoscopes. The dura was repaired using fascia lata and fat graft reinforced with fibrin glue. A vascularised nasoseptal flap was not used in any of our cases.

Follow-up and Visual Outcome
All subjects were assessed ophthalmologically at 6 months post-surgery, and their VIS was reassessed (PostVIS). All those patients with betterment in the VIS of more than 5% from the preoperative value were considered an improvement and were grouped as a good outcome. Those patients whose VIS deteriorated, remained the same, or if the improvement was less than 5% after surgery, were grouped as a bad outcome. Similarly, the outcome for visual acuity and field were determined separately by comparing the change in visual impairment score for visual acuity (VISVA) and visual impairment score for the visual field (VISVF) after surgery.

Statistical Analysis
Data were entered in Excel and analyzed using SPSS software (version 22.0 [IBM Corp., Armonk, New York, USA]). Kolmogorov Smirnov test was used to assess whether our data was normally distributed. Means, median and standard deviations were computed for continuous variables. A comparison of categorical variables between the two was performed using the Chi-square test. The Independent samples T-test performed a comparison of continuous variables between the two groups. Continuous data which were not normally distributed were analyzed using the Mann-Whitney U test. Wilcoxon signed-rank test was used to compare paired nonparametric data. P <0.05 was considered significant.

Results
Between November 2016 and December 2018, 30 patients who satisfied the inclusion criteria were studied. Among them, 17 were males, and 13 were females. The mean age of our study population was 47.7±11.8 years. The most common symptom besides visual impairment was headache (65%). The most common type of adenoma was non-functioning macroadenoma (70%). Prolactinoma (16%) was the most common functioning pituitary adenoma, followed by GH secreting adenoma (10%) (Table1). Seven patients (23%) presented with pituitary apoplexy. The mean duration of visual symptoms was 7.3 ± 5.3 months. The mean largest diameter of the lesion was 2.6 ± 0.41cm. The mean volume of the lesion was 10.15 ± 4.63cc. Mean suprasellar extension (SSE) was 1.6 ± 0.32cm. Parasellar extension was noted in 17 patients (56.6%). The most common fundus abnormality noted was temporal pallor, which was present in 8 patients (26.6%),
followed by optic atrophy in 2 patients (6.7%). Post-operative MRI revealed near-total excision of the adenoma in 26 cases (86.8%), partial excision in two (6.6%), and mere decompression in the rest (6.6%).

**Visual outcome**

At 6 months follow-up, there were 25 patients (83.3%) with more than 5% improvement in their VIS and were grouped as a good outcome; the rest were considered poor. The median PreVIS (preoperative visual impairment score) and PostVIS (postoperative visual impairment score) were 82 (48.5,87) and 34 (22.7,60) respectively. There was a significant improvement in scores between the PreVIS and PostVIS (P < 0.01) (tre 1). There was a statistically significant correlation between PreVIS (severity of visual impairment) and duration of visual impairment, lesion size, or SSE. On univariate analysis, SSE (P=0.01) and incomplete excision (P=0.006) was significantly associated with poor early visual outcome. (Table 2)

![Figure 1 Whisker and box plot showing the comparison of preoperative and post operative visual impairment scores](image)

Mean preoperative visual acuity was 0.26 ± 0.24 on the right side and 0.24 ± 0.19 on the left side. Mean postoperative sensitivity was 0.48 ± 0.33 on the right side and 0.43 ± 0.3 on the left side. There was a statistically significant improvement in postoperative visual acuities (P < 0.01). 24 patients in our study population had an improvement in visual acuities, while 6 had no improvement. While considering various factors determining the betterment of visual acuity, the SSE (P=0.006) and volume of the lesion (P=0.04) were considered statistically significant (Table 2).

**Visual field defects**

Visual field defects before and after surgery in our study are given in table 3. The median PreVISVF (preoperative VIS for visual field) was 22 (18,22), and that for PostVISVF (postoperative VIS for visual field) was 14(8,22). There was a statistically significant improvement in VISVF after surgery (P<0.001). At 6 months follow-up VISVF improved in 17 patients (56.6%), remained the same in 9 (30%), and worsened in 4 (13.4%). Hence 17 patients had a good outcome for their field deficits while the remaining 13 were on the other hand. On univariate analysis, PreVISVF (P=0.04) and the completion of excision (P=0.04) were the factors predicting visual field improvement. To study the pattern of field improvement, we analyzed all eyes with complete blindness as well as tunnel vision (n=9). At 6 months follow-up, there was an improvement in nasal fields in 88% (n=8). Also, we tried to understand the recovery of patients with temporal field defects. Out of the 21 eyes with improvement in their temporal field defects, all had betterment in the inferior quadrant first (100%, n=21), followed by the superior quadrant (66.6%, n=13).

30% of the patients had fundus abnormalities secondary to the adenoma. The significant fundus change was temporal pallor(26%), and primary optic atrophy was present in 4% of cases. We found no association between fundus abnormalities and visual outcome (P=0.17). However, in the subgroup analysis, there was a statistically significant association between optic atrophy and poor outcome for visual acuity (P=0.013) as well as overall visual outcome (P=0.018).

The median SSE of our study population was 1.5cm (1.3, 2.0). SSE was significantly associated with overall visual outcome (P=0.006). The receiver operating characteristic (ROC) curve was plotted between the SSE and visual outcome. The area under the curve was 0.86, and the best cut-off for SSE beyond which the patient had a bad prognosis was 1.95cm, with a sensitivity of 80% and specificity of 84%. On the other hand, parasellar extension was not significantly associated with visual outcomes.

**Discussion**

The popularity of trans nasal endoscopic pituitary surgeries has increased since its introduction in the early 1990s[6]. Better panoramic visualization and a safer trans nasal corridor have helped endoscopic surgery evolve as the gold standard procedure for sellar and suprasellar pathologies. Utilizing the present high-resolution endoscopes, the surgeon can efficiently decompress the optic apparatus preserving and protecting the parasellar vital structures[7].

The visual improvement after transsphenoidal decompression of the optic apparatus occurs in various phases, the early and late phases. The early phase commences from ten minutes after proper decompressive surgery to around 6 months. This early phase is divided into a fast phase lasting for the first few days and a slow phase lasting for 4-6 months. The early fast phase of recovery is due to the restoration of signal conduction along the axons of ganglion cells. The early slow phase is due to impaired axonal transport and remyelination re-establishment. There is also the third phase of the chronic improvement of vision which may last for months, and the actual cause for this phase is not known[8][9][10]. We have studied the early visual recovery since our follow-up period was 6 months.

We had an overall improvement in vision of 83.3%, while improvement in visual acuity was seen at 87% and that for the visual field was 57%. Betterment in the visual acuity (87%) was greater than in the visual field (57%). This visual outcome was comparable with the many previously published studies. We have measured both acuity and field of vision using the VIS, a tool devised by the German ophthalmological society for quantitative assessment of vision, and a statistical tool to assess the outcome effectively[11].

We found that the improvement in visual acuity and the overall visual prognosis was significantly associated with the SSE and completion of excision. Greater the SSE, there will be greater compression on the chiasma. Since the chiasma is supplied by vessels from the inferior aspect, there can be a greater stretch on them, causing ischemic injury. A recent study by Luomaranta et al. has also emphasized SSE as a predictor of visual outcome; they have also tried to identify the cut-off for SSE beyond which the patient had a deficit of around 9.5mm[12]. In this study,
### Table 1 Clinical characteristics of our study group

| Characteristics                        | Number (%) | mean±SD  |
|----------------------------------------|------------|----------|
| Age (years)                            |            | 47.7±11.87 |
| Gender                                 | Male       | 17 (56.7%) |
|                                        | Female     | 13 (43.3%) |
| Type of the adenoma                    | FPA        | 21 (70%)  |
|                                        | Prolactinoma | 5 (16.7%) |
|                                        | Growth Hormone Adenoma | 3 (10%) |
|                                        | Cushing’s Adenoma | 1 (3.3%) |
| Duration of visual symptoms            | Less than 2 months | 5 (16.7%) |
|                                        | 2-6 months | 12 (40%) |
|                                        | 6-12 months | 10 (33.3%) |
|                                        | More than 12 months | 3 (10%) |
| Apoplexy                               | Present    | 7 (23.3%) |
|                                        | Absent     | 23 (76.7%) |
| Fundus Changes                         | Normal     | 20 (66.7%) |
|                                        | Temporal Pallor | 8 (26.7%) |
|                                        | Optic Atrophy | 2 (6.7%) |
| Volume (cc)                            |            | 10.15±4.63 |
| Parasellar extension                   | Present    | 17 (56.7%) |
|                                        | Absent     | 13 (43.3%) |
| Suprasellar extension (cms)            |            | 1.61±0.32 |
| Completion of excision                 | Near total | 26 (86.7%) |
|                                        | Subtotal   | 2 (6.7%)  |
|                                        | Decompression | 2 (6.7%)  |

FPA- Functional pituitary adenoma, NFPA- Non-functional pituitary adenoma.

### Table 2 Various predictive factors studied and their influence on visual outcome

| Factors                        | Visual Acuity  | P  | Visual Field     | P  | Overall Visual Outcome | P  |
|-------------------------------|----------------|----|----------------|----|------------------------|----|
| Age                           | 49.2±10.7      | 0.2| 48.4±10.18      | 0.6| 48.76±10.6             | 0.3|
| Duration of visual symptoms   | 1.29±0.9       | 0.4| 6.6±5.6         | 0.34| 7.04±5.2               | 0.5|
| Volume (cc)                   | 9.3±3.9        | 0.041| 9.34±3.5       | 0.05| 9.42±3.9               | 0.08|
| Type of adenoma               | FPA-6          | 0.48| FPA-5           | 0.9| FPA-6-19               | 0.12|
| SSE (cm)                      | 1.52±0.3       | 0.006| 1.54±0.32      | 0.13| 1.53±0.28              | 0.01|
| PSE                           | 54%            | 0.5| 64.7%           | 0.3| 60%                    | 0.86|
| Apoplexy                      | 30%            | 0.6| 25%             | 0.3| 28%                    | 0.67|
| Fundus Changes                | 41%            | 0.3| 23.5%           | 0.1| 60%                    | 0.17|
| Incomplete Excision           | 4%             | 0.003| 0%              | 0.01| 4%                     | 0.004|
| PreVIS                        | 70.2±25.6      | 0.3| 66.94±29        | 0.98| 68.72±26.18            | 0.6|
| PreVISVA                      | 48.04±22       | 0.41| 40.4±23.48      | 0.12| 46.7±22.6             | 0.8|
| PreVISVF                      | 22.6±13.5      | 0.46| 27.18±11.5      | 0.04| 22.4±13.2             | 0.7|

FPA- Functional pituitary adenoma, NFPA- Non-functional pituitary adenoma, PreVIS- preoperative visual impairment score, PreVISVA- preoperative visual impairment score for visual acuity, PreVISVF- preoperative visual impairment score for visual field.
we analyzed our results. We found a cut-off (1.95cm) for SSE, beyond which the patient had a worse prognosis after surgical resection. To the best of our knowledge, we could not find another study that found out the probable cut-off value of SSE that determines the early visual outcome. Another study by van Essen et al. had contradictory findings where they found that patients with higher SSE had higher odds of greater visual recovery[13]. They speculate the reason for this unexpected result is that the patients with a higher degree of chiasmal compression might have benefited more from decompression than those without SSE.

Our study achieved near-total adenoma excision for 86.6% of patients, comparable with the previously published data from meta-analyses. We had a significant association between incomplete excision and poor visual outcome (P=0.004). Among our patients who had incomplete excision, two had prolactinomas. These subjects had progressive deterioration of their vision while on dopamine agonist treatment and proceeded with TEE. Because of the dopamine agonist treatment, the consistency of the adenoma was firm too hard, preventing the complete excision[14]. While another patient who had subtotal excision developed Stevens-Johnson Syndrome associated with iritis as a consequence of drug allergy in the post-operative period producing deterioration of vision[15]. The poor visual outcome due to incomplete tumour excision can be attributed to persistent compression on the optic apparatus by the residual tumour tissue; also postoperative oedema will worsen the deficits.

The outcome for visual acuity was significantly affected by the tumour volume (P=0.041). In our study group, all adenomas had SSE, and there was a positive correlation between the tumour volume and SSE (r=0.4, P=0.04). Hence there would be a corresponding increase in SSE with increased tumour volume in our study population, resulting in increased pressure on the optic chiasma. R.W. Ho et al., in their retrospective study, have stressed the importance of preoperative tumour volume in visual recovery[16]. In their retrospective analysis of 201 patients, Yu et al. also found small tumour volume associated with favourable postoperative visual outcomes[17].

Visual field recovery was significantly associated with the severity of preoperative visual field deficits (P=0.04) and the completion of excision (P=0.01). Very few studies looked into the recovery of the visual field as a separate entity following TEE. We had a 56% improvement in visual fields at 6 months follow-up. Our results were in concordance with the study by Gnanalingham et al. They studied 41 patients retrospectively and had an overall 60% improvement in the field of vision. Also, they observed that the severity of preoperative field deficits significantly affected the postoperative recovery of the same[18]. J. Lee et al. retrospectively studied 50 patients and demonstrated similar results[19]. Primary optic atrophic changes were associated with poor outcomes. Many previous studies had a similar observation. They proposed that retrograde axonal degeneration due to long-standing compression on optic chiasma resulted in poor postoperative visual recovery[20][21].

Conclusion
Betterment in the overall visual outcome and visual acuity was predicted by the suprasellar extension, completion of excision, and presence of atrophic changes in the optic disc. Suprasellar extension of more than 1.95cm was associated with poor early visual outcomes. Improvement of the visual field depended on the severity of the preoperative field deficits. Prolactinomas had more chance of incomplete excision, resulting in poorer visual recovery.

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Table 3 The visual field defects in our series

| Field defects  | Preoperative | Postoperative |
|---------------|--------------|--------------|
|               | Right eye    | Left eye     | Right Eye | Left Eye |
| Normal        | 5            | 5            | 8         | 6        |
| Central Scotoma | 3            | 3            | 7         | 7        |
| Quadrantanopia | 2            | 9            | 4         | 8        |
| Nasal defect  | 1            | 0            | 0         | 0        |
| Temporal defect | 14          | 15           | 11        | 9        |
| Tunnel Vision | 5            | 5            | 0         | 0        |
| Total Anopia  | 0            | 2            | 0         | 0        |
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