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Technical Notes & Surgical Techniques

Surgical considerations in the endoscopic endonasal transphenoidal approach for giant pituitary adenomas: A single surgeons' experience over a decade

Patrick Lekgwara (FC Neurosurgery (SA)) (Professor)[a],
Adrian Kelly (MMed Neurosurgery cum laude (SMU), FC Neurosurgery (SA)) (Dr.)[a,b,*],
Aftab Younus (FC Orthopedics (SA)) (Dr.)[c]

[a] Department of Neurosurgery, Dr George Mukhari Academic Hospital, Sefako Makgatho Health Sciences University, Pretoria, South Africa
[b] Department of Neurosurgery, 3rd floor Sciences Building, Sefako Makgatho Health Sciences University, Garankuwa, Pretoria, South Africa
[c] Department of Orthopedics, Helen Joseph Hospital, University of the Witwatersrand, Johannesburg, South Africa

A B S T R A C T

Aim: To determine the significance of patient demographics; presenting symptoms and examination findings; pre-operative hormonal status; tumor characteristics and postoperative extent of resection on outcome in all patients whom underwent an endoscopic endonasal transphenoidal resection of a giant pituitary adenoma.

Methods: From 01 January 2005–31 December 2016 sixty-two patients with giant pituitary adenomas were operated by a single surgeon via an endoscopic endonasal transphenoidal approach in our Department. We performed a retrospective chart review of these cases specifically recording patient age; gender; presenting Glasgow coma score and visual acuity; tumor size specifically recording height, width and anteroposterior measurements; whether complete/partial resection was achieved; post-operative cerebrospinal fluid leak and presence of diabetes insipidus; and Glasgow Outcome Score (GOS) at discharge.

Results: Of the variables considered significance was demonstrated between the pre-operative examination finding of absence of perception of light and GOS ($p = 0.002$). Significance was also demonstrated with regards pre-operative tumor size measured in any of the three dimensions namely tumor height ($p = 0.03$), tumor width ($p = 0.01$) and especially the pre-operative tumoral antero-posterior measurement ($p = 0.006$). None of the other variables considered demonstrated significance in terms of outcome.

Conclusion: The pre-operative examination finding of no perception of light and the diagnosis of a giant pituitary adenoma measured in any dimension but especially antero-posteriorally are specific prognostic variables that demonstrate significance in predicting outcome in patients with giant pituitary adenomas being considered for the endoscopic endonasal transphenoidal approach.

1. Introduction

As a group pituitary adenomas are the third most common primary intracranial neoplasm accounting for between 10 and 25% of cases of intracranial tumors [1]. Despite being largely benign in nature and thereby lacking invasiveness, their relentless growth and local mass effect does carry with it significant morbidity and mortality related to visual and endocrinological impairment, as well as due to pressure on critical structures [2]. As such they are a common problem referred to the Department of Neurosurgery at Dr. George Mukhari Academic Hospital and require meticulous medical and surgical management for optimal patient outcome. These are often late referrals with imaging revealing tumors of considerable size often extending beyond the boundaries of the pituitary fossa with significant intracranial extension. Those pituitary adenomas measuring greater than 4 cm in any dimension are termed giant pituitary adenomas and carry with them a unique set of surgical considerations [3].

In terms of the optimal surgical approach for giant pituitary adenomas the transcranial approach has and is still utilized and although still applicable as an adjunct in certain cases carries with it significant complications as well as inability to access the intrasellar component of the tumor [4]. The operating microscope utilizing an endonasal transphenoidal approach has intrinsic limitations in terms of visualization and extend of tumor resection [4]. More recently a world-wide shift towards the endoscopic endonasal transphenoidal approach which has considerable advantages over the formal approaches, these will be elaborated below [5].

The Neurosurgical Unit at Dr. George Mukhari Academic Hospital

* Corresponding author at: Department of Neurosurgery, Dr George Mukhari Academic Hospital, Sefako Makgatho Health Sciences University, Pretoria, South Africa.
E-mail address: adriankelly1000@yahoo.co.uk (A. Kelly).

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has been fortunate in terms of being a center specializing in the adoption of this endoscopic endonasal transphenoidal approach by a single surgeons' special interest. This experience now spans over a decade and between 2005 and 2016 sixty two of these cases have specifically involved the management of giant pituitary adenomas by the endoscopic endonasal transphenoidal approach.

2. Materials and methods

This was a retrospective chart review of all consecutive patients presenting with a giant pituitary adenoma whom underwent an endoscopic endonasal transphenoidal resection by a single surgeon at the Department of Neurosurgery at Dr. George Mukhari Academic Hospital located in Pretoria, Gauteng, South Africa. The study period was from 01 January 2005–31 December 2016. Ethics approval for the study was granted by the Medical Research Ethics Committee of Sefako Makgatho Health Sciences University, reference number SMUREC/M/99/2018:IR.

A total of sixty-two patients whom presented to the Neurosurgical Department at our institution over the study period with a diagnosis of giant pituitary adenomas went for endoscopic endonasal transphenoidal resection. We performed a retrospective chart review of these cases specifically recording patient age; gender; presenting Glasgow Coma Score and visual acuity; tumor size specifically recording height, width and anteroposterior measurements; whether complete/partial resection was achieved; presence of a post-operative cerebrospinal fluid leak and diabetes insipidus, and Glasgow Outcome Score (GOS) at discharge. Once these variables were recorded univariate analysis was used to determine the significance of each in terms of GOS at discharge.

3. Results

The mean age of subjects was 46.7 (± 14.4) years and the minimum age was 18 years and maximum age was 78 years. No statistical significance was demonstrated between subject age and GOS ($p = 0.51$). With regards gender 50% (31) of subjects were male and 50% (31) subjects were female. Presenting symptoms in 90.5% (56) of subjects were headaches and 6.5% (4) subjects presented with seizures. Only 3% (2) subjects presented with neither headaches nor seizures. The mean length of symptoms prior to presentation was 36 (+/− 21) months. No statistical significance was demonstrated between length of symptoms preceding presentation and GOS ($p = 0.43$).

Table of presenting symptoms ($n = 62$):

Visual acuity abnormalities	92% (57)
Headache	90.5% (56)
Seizures	6.5% (4)
Neither headaches nor seizures	3% (2)

With regards neurological examination at presentation 92% (57) subjects were fully conscious GCS 15/15 and 5% (4) subjects were confused GCS 14/15 and 3% (1) subject was GCS 13/15. No statistical significance was demonstrated between presenting level of consciousness and GOS ($p = 0.09$).

Table of presenting Glasgow coma score ($n = 62$):

GCS 15/15	92% (57)
GCS 14/15	5% (4)
GCS 13/15	3% (1)

Visual acuity abnormalities were present in 92% (57) of subjects and were absent in 8% (5) subjects. No significance was demonstrated between the presence of visual acuity abnormalities and GOS ($p = 0.37$). Ophalmoplegia was present in 20% (12) subjects and was absent in 80% (50) subjects. In those subjects with opthalmoplegia a cranial nerve III opthalmoplegia was demonstrated in 58% (7) subjects and a cranial nerve VI was demonstrated in 42% (5) subjects. Looking more closely at the visual acuity in the 90% (57) subjects whom presented with abnormalities, in 28% (16) subjects there was no perception of light bilaterally and in 18% (10) subjects there was no perception of light unilaterally. In 54% (31) subjects visual acuity was reduced but perception of light was preserved. Statistical significance was demonstrated between the pre-operative examination finding of no perception of light and GOS ($p = 0.002$).

Table of pre-operative visual acuity ($n = 62$):

Reduced visual acuity but preserved perception of light	54% (31)
No perception of light bilaterally	28% (16)
No perception of light unilaterally	18% (10)
No visual acuity abnormality	8% (5)

Considering tumor size the mean tumor height in the most favorable GOS group was 31.3 mm and the mean tumor height in the most unfavorable GOS group was 57.4 mm. Significance was demonstrated between mean tumor height and GOS between these outcome groups ($p = 0.03$). With regards tumor width the mean tumor width in the most favorable GOS group was 24.6 mm and the mean tumor width in the most unfavorable tumor group was 44.8 mm. Significance was demonstrated between mean tumor width and GOS between these two groups ($p = 0.01$). When considering the mean tumor antero-posterior measurement in the most favorable GOS outcome group of 25.1 mm and the mean tumor width in the most unfavorable GOS group of 51.8 mm, significance was also demonstrated between these two groups and GOS, almost being highly significant reflected by the strength of the p value ($p = 0.006$).

Table of mean tumor size (millimetres) and Outcome group ($n = 62$):

	Most favorable outcome group	Least favorable outcome group
Height (p = 0.03)	31.3	57.4
Width (p = 0.01)	24.6	44.8
Antero-posterior (p = 0.006)	25.1	51.8

Considering the type of surgical procedure performed in 94% (55) subjects a purely endoscopic endonasal transphenoidal procedure was performed and in 6% (7) of subjects an endoscopic endonasal transphenoidal and staged transcranial microscopic procedure was performed.

Considering extent of resection complete resection was achieved in 50% (31) subjects and partial resection was achieved in 50% (31) subjects. No statistical significance was demonstrated between partial/complete removal and GOS ($p = 0.13$). In the partially resected group 32% (10) subjects were re-operated and 68% (21) subjects were not re-operated.

With regards post-operative complications 94% (58) subjects did not experience a cerebrospinal fluid leak and 6% (4) subjects did experience a cerebrospinal fluid leak. Post-operatively 86% (53) subject's experienced transient diabetes insipidus, 9% (6) subjects experienced no diabetes insipidus and 5% (3) subjects exhibited permanent diabetes insipidus. No statistical significance was however demonstrated between the development of these complications and GOS ($p = 0.47$).

Considering outcome at discharge 48% (30) subjects resumed normal life, 27% (17) subjects had moderate disability but were independent, 11% (7) subjects were severely disabled, 4% (2) subjects were in a persistently vegetative state and 10% (6) subjects had demised.

Table of post-operative outcome ($n = 62$):

Resumed normal life	48% (30)
Moderate disability but independent	27% (17)
Severely disabled	11% (7)
Persistently vegetative state	4% (2)
Demised	10% (6)

4. Discussion

While the first record of transphenoidal surgery can in fact be traced back to as early as 1907 by pioneers such as Hermann Schloffer and later Harvey Cushing, the transphenoidal approach was only truly popularized by Jules Hardy in the 1960's with the advent of the operating microscope [5]. While the endoscope was also introduced around this time it was largely abandoned due to limitations in technology inhibiting its useful application [5]. Only in the last two decades has the huge advances in 3-D endoscopic color visualization seen the pendulum swing back to the use of the endoscope which is quickly replacing its microscopic predecessor in the operating room [5].

Besides the controversies surrounding the optimal surgical approach as either transcranial; microscopic transphenoidal or endoscopic transphenoidal, a fundamental understanding must begin by firstly defining two cornerstone treatment strategies in the management of giant pituitary adenomas [6]. The first aims to achieve complete removal in a single surgery by either a single or combined surgical approach [6], while the latter involves staged surgery [7]. While staged surgery avoids the complications of the transcranial approaches it does carry with it the disadvantage of possible intra-tumoral hemorrhage or re-growth of residual tumor in the interim before the next surgery [7]. In our study considering re-operation in the partially resected group of 50% (31) subjects, 32% (10) subjects were re-operated utilizing a staged approach and 68% (21) subjects were not re-operated. The reasons for not re-operating in the partially resected group included residual tumor that demonstrated no growth, was inaccessible as well as in asymptomatic patients.

While in pituitary adenomas without significant suprasellar nor lateral extension the endoscopic and microscopic approaches have similar outcomes in terms of extent of resection and complications, it is in giant pituitary adenomas that the endoscopic approach has clear advantages [5]. Wide panoramic view employing superior fiber optic illumination, angled endoscopes giving the surgeon the ability to see around corners as well as the extended approaches which enable the surgeon direct access to the anterior and posterior as well as lateral extensions of these tumors, has seen the endoscopic transphenoidal approach becoming popularized [4]. These advantages translate into increased resection percentages and decreased complications as compared to the microscopic approach [4,8].

The debate has hence evolved where in the consideration of specifically giant pituitary adenomas with significant suprasellar and lateral extensions what we really should be comparing is the transcranial approaches versus the endoscopic transphenoidal approach to deal with the suprasellar, anterior, posterior, and lateral extensions of these tumors [5]. The microscopic approach has little applicability to manage these extensions [5]. In our study 100% (62) of the giant pituitary adenomas were managed initially by an endoscopic endonasal transphenoidal approach and a staged approach was planned as either repeat endoscopic endonasal transphenoidally in tumors that descended or transcranially in tumors that did not descend. In the partially resected group of 50% (31) subjects, 32% (10) subjects were re-operated and 68% (21) subjects were not re-operated. In the re-operated group of 10 subjects 30% (3) had a repeat endoscopic endonasal approach performed and 70% (7) had a transcranial microscopic approach performed as the staged procedure.

Current thinking is that unless there are specific instances namely 1. Fibrous consistency 2. Dumbbell tumor with a central constriction limiting access of the endoscope to the suprasellar or lateral extensions and 3. Tumors with large suprasellar components that do not descend, the endoscopic transphenoidal and extended approaches are replacing the transcranial approaches as a first line surgical approach [9]. More recently advances in the experience and understanding of the extended approaches as well as surgical adjuncts being applied to the endoscopic transphenoidal approach such as image guidance; specialized transphenoidal instruments, micro Doppler pencil probes and neurophysiological monitoring, have seen these classical limitations being challenged [5].

Besides the superiority in the degree of resection that the endoscope facilitates regarding suprasellar and lateral extension, a further advantage has been noted regarding large adenomas that invade the cavernous sinus [10,11]. As a principle cavernous sinus invasion has traditionally been noted to be an independent predictor of unfavorable outcome limiting the extent of resection [12]. Several authors have however researched this point and have noted a higher resection rate with the endoscope versus the microscopic approach facilitated by the panoramic view and angled endoscopes enabling visualization of the medial wall of the cavernous sinus [11,12]. In our study lateral extension assessed as tumor width was associated with a poorer outcome ($p = 0.01$) and we support the literature that this carries with it a poorer prognosis.

Reduced nasal complications from avoidance of nasal packing in the endoscopic transphenoidal approach translating into increased patient comfort, avoidance of the septal fistula and saddle nose deformity-classically associated with the microscopic approaches is a further established advantage of the endoscopic transphenoidal approach and is clearly established in the literature [13,14].

The endoscopic transphenoidal approach does however have its own set of limitations other than the tumor characteristics, as given above, that may favor a transcranial approach. Firstly it is associated with a steep learning curve and many studies note an increased complication rate during a surgeons' early experience with this technique [15]. In fact this is a valid point of reluctance put forward by many surgeons who consider this learning curve associated complication rate unacceptable [15]. Our study recognized the steep learning curve associated with this approach as supported by patient outcome where although 92% (57) subjects were fully conscious GCS 15/15 at presentation, at discharge 11% (7) subjects were severely disabled, 4% (2) subjects were in a persistently vegetative state and 10% (6) subjects had demised. In total 25% (16) subjects had an adverse outcome post the procedure, most of which occurred earlier in the study period associated with the surgeons early learning curve.

A recent landmark study comprising a comprehensive systematic review conducted by Komotar from 1995 to 2010 directly compared the surgical outcomes related to the transcranial; microscopic transphenoidal and endoscopic transphenoidal approaches- specifically regarding giant pituitary adenomas [4]. This study comprised an impressive meta-analysis of 478 patients [4]. The first outcome measure was the extent of resection measured in terms of whether gross total resection was achieved [4]. The endoscopic transphenoidal group had a gross total resection rate of 47% compared to transcranial approach 10% and the microscopic transphenoidal approach 30% [4]. In our study a similar extent of resection was achieved where gross total resection was achieved in 50% (31) subjects. The second outcome measure of this study was improved visual outcome and here the endoscopic transphenoidal approach demonstrated an impressive advantage over the other approaches where it was noted that visual improvement occurred in 91% of subjects while in the transcranial group only 40% of subjects experienced visual improvement and in the microscopic transphenoidal group only 35% of subjects experienced visual improvement [4]. In our study none of the subjects with no perception of light pre-operatively experienced visual improvement post-operatively.

In looking more closely at the endoscopic transphenoidal approach itself, a further consideration is whether a uninarial or binarial approach is used [16]. This is specifically dealt with in a paper that

considered 218 operations where a uninarial technique is advocated as both adequate and in fact desirable [16]. In this paper gross total resection was achieved in 90% of cases with an extremely low incidence of nasal complications of 1.4% [16]. Neuronavigation and lateral fluoroscopy were considered essential adjuncts routinely used in this study [16].

With the increased popularity of the endoscopic transphenoidal approach, several papers have attempting to detail specific factors that should be considered pre-operatively to be associated with a less than expected outcome.

A recent paper considered specific tumor characteristics and challenged what has been advocated as suitable to the endoscopic transphenoidal approach, 1. Large tumors 2. Cavernous sinus invasion 3. Intracranial extension and 4. Irregular configuration were found to be statistically significantly associated with a suboptimal degree of resection compared to cases in which these tumor factors were not present [17]. If on subsequent imaging this large suprasellar or lateral extension does not descend into the sella, a transcranial approach is advocated as an adjunct staged to deal with these large suprasellar and lateral extensions [17]. While cited in the above paper as limitations of the effectiveness of the endoscopic endonasal transphenoidal approach these findings are in fact controversial. Cappabianca, a world expert on the approach, challenges this by stating that if the tumor is removed correctly during the procedure, the tumor almost always collapses into the sella and very rarely will a transcranial approach be needed [18]. In this paper the endoscopic endonasal transphenoidal approach is considered a valid alternative to the transcranial route for the management of giant pituitary adenomas [18].

Our study supports the above in that suprasellar extension measured as pre-operative tumor height ($p = 0.03$), lateral extension measured as pre-operative tumor width ($p = 0.01$), and especially antero-posterior measurement ($p = 0.006$) are associated with an adverse outcome in the endoscopic endonasal transphenoidal approach to giant pituitary adenomas. We propose that increased growth but especially antero-posterior growth towards the brainstem causes the development of vascular anastomoses between the enlarging pituitary tumor and the brainstem which cause possible venous infarcts of the brainstem with intra-operative collapse of the tumor explaining why this particular measurement is especially significant as a prognostic pre-operative variable.

The influence of tumor size on vision and visual outcome which was specifically considered in a 2015 paper that considered this specific issue in 78 patients whom underwent endoscopic endonasal transphenoidal resection of pituitary macro adenomas, of which 81% were giant pituitary adenomas [19]. Factors evaluated by this paper were 1. Pituitary adenoma size; 2. Pre-operative visual impairment scale; 3. Vertical size; 4. Severe optic atrophy; 5. Sagittal displacement 6. Coronal displacement; 7. Suprasellar extension and 8. Infrasellar extension [19]. Here multivariate analysis noted the only factor significantly related to the visual impairment scale was increasing size of the tumor-which predicted decreased improvement [19]. This supports the finding by Komotar, above, by noting significant improvement can in fact occur with the endoscopic endonasal transphenoidal approach despite the pre-operative visual impairment scale [19]. Visual field deficits are noted to improve most dramatically while deficits in acuity, although they often do improve, rarely return to normal [19]. Our study again supports tumor size as a predictive outcome variable in all dimensions and supports the poor return of visual acuity post operatively.

In terms of complications several papers state intracranial hemorrhage to be the most serious complication of endoscopic endonasal surgery [3,5,9,17,20]. This leads to diffuse vasospasm of arteries in the subarachnoid space and is associated with significant morbidity and mortality [20]. The peri-operative mortality rate in the endoscopic endonasal approach for giant pituitary adenomas is recorded in a 2016 paper to be 7.1% [21]. As the most serious complication this was addressed in a paper published in 2016 which on autopsy noted the source of hemorrhage to commonly be either residual tumor of secondary to collapse of the diaphragm sella to which several arterial perforators may be adhered [20].

Besides post-operative hemorrhage which is the most serious complication, perhaps the most common operative complication associated with this surgery, especially in the extended approaches commonly required in these giant adenoma cases, is a post-operative cerebrospinal fluid leak which has an incidence between 10 and 20% [20,21]. This may be managed conservatively with placement of a lumbar drain and bedrest [9], or immediate operative re-exploration and closure of the leak [21]. In our study 94% (58) subjects did not experience a cerebrospinal fluid leak and 6% (4) subjects did experience a cerebrospinal fluid leak. The discrepancy between our low cerebrospinal fluid leak rate and the higher rate proposed in the literature can be explained by our limited utilization of the extended approaches. We prefer to leave residual tumor as reflected by our gross total resection rate in 50% (31) of subjects and stage the approach for another day. By adopting this approach we have experienced a cerebrospinal fluid leak considerably lower than that proposed.

Other specific complications and their incidence related to the endoscopic endonasal transphenoidal approach, as put forward in a 2014 paper, are sinusitis (13%); syndrome of inappropriate antidiuretic hormone SIADH (4%); transient diabetes insipidus DI (53%); permanent diabetes insipidus DI (3.5%); epistaxis (2.4%) and hydrocephalus requiring shunt procedure (2.7%) [9]. In our study we had a considerably higher rate of transient diabetes insipidus than that put forward in the literature where 86% (53) subjects experienced this complication, although in only 5% (3) subjects did this become permanent in line with the literature.

5. Conclusion

In our study the pre-operative examination finding of no perception of light and the diagnosis of a giant pituitary adenoma measured in any dimension but especially antero-posteriorally are specific prognostic variables that demonstrate significance in predicting outcome.

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Conflict of interests

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